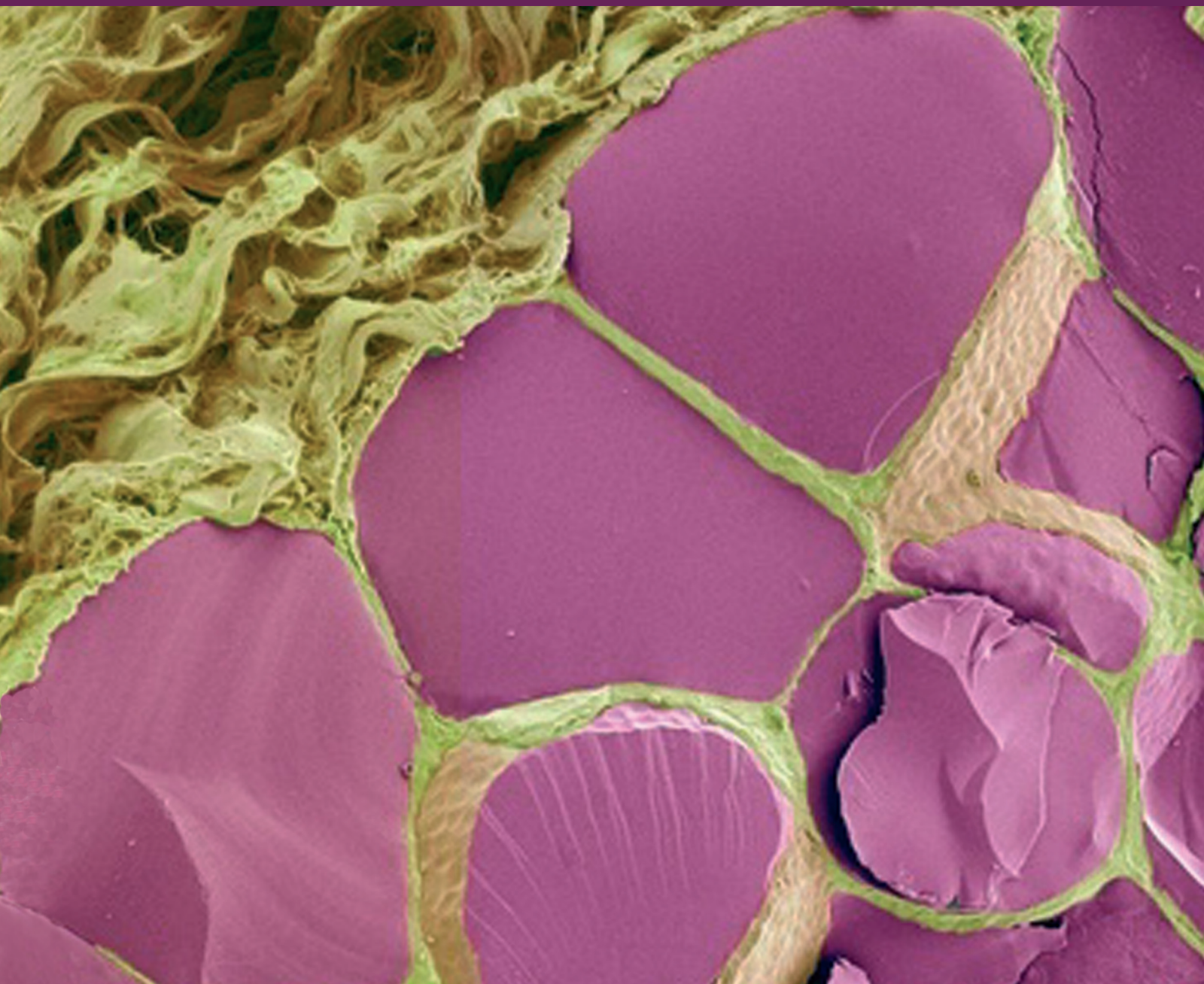


# Coordinating Care Aspects Related to Sexual Health in the Aging Male

Guest Editors: Antonio Aversa, Lorenzo Maria Donini, Roberto Bruzziches, Roberto LaCava, Francesco Mattace Raso, and Alan Sinclair





---

## **Coordinating Care Aspects Related to Sexual Health in the Aging Male**

## **Coordinating Care Aspects Related to Sexual Health in the Aging Male**

Guest Editors: Antonio Aversa, Lorenzo Maria Donini, Roberto Bruzziches, Roberto LaCava, Francesco Mattace Raso, and Alan Sinclair



---

Copyright © 2014 Hindawi Publishing Corporation. All rights reserved.

This is a special issue published in "International Journal of Endocrinology." All articles are open access articles distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

## Editorial Board

Anil K. Agarwal, USA  
John Ayuk, UK  
Amelie Bonnefond, France  
Donald W. Bowden, USA  
Shern L. Chew, UK  
Iacopo Chiodini, Italy  
Giuseppe D'Annunzio, Italy  
F. Xavier Donadeu, UK  
Maria L. Dufau, USA  
Kristin Eckardt, Germany  
Dariush Elahi, USA  
Katherine Esposito, Italy  
Oreste Gualillo, Spain  
Mahin Hashemipour, Iran

Andreas Höflich, Germany  
Michael Horowitz, Australia  
Khalid Hussain, UK  
Dario Iafusco, Italy  
Daniela Jezova, Slovakia  
Janaka Karalliedde, UK  
Mafgorzata Kotula-Balak, Poland  
Fernand Labrie, Canada  
Hyun C. Lee, Republic of Korea  
Mario Maggi, Italy  
Ludwik K. Malendowicz, Poland  
Matteo Monami, Italy  
Robert D. Murray, UK  
Faustino R. Pérez-López, Spain

Dario Pitocco, Italy  
Ursula Ploeckinger, Germany  
Andrew V. Schally, USA  
Alexander Schreiber, USA  
Muhammad Shahab, Pakistan  
Kazuhiro Shiizaki, Japan  
Kevin Sinchak, USA  
Ajai Kumar Srivastav, India  
Stuart Tobet, USA  
Jack R. Wall, Australia  
Matthew Watt, Australia  
Aimin Xu, Hong Kong  
Paul M. Yen, USA  
Naveed Younis, UK

## Contents

**Coordinating Care Aspects Related to Sexual Health in the Aging Male**, Antonio Aversa, Lorenzo Maria Donini, Roberto Bruzziches, Roberto LaCava, Francesco Mattace Raso, and Alan Sinclair  
Volume 2014, Article ID 653587, 3 pages

**Testosterone Deficiency, Cardiac Health, and Older Men**, G. Hackett, M. Kirby, and A. J. Sinclair  
Volume 2014, Article ID 143763, 10 pages

**Erectile Dysfunction in the Elderly: An Old Widespread Issue with Novel Treatment Perspectives**, Pietro Gareri, Alberto Castagna, Davide Francomano, Gregorio Cerminara, and Pasquale De Fazio  
Volume 2014, Article ID 878670, 15 pages

**Quality of Life and Sexual Health in the Aging of PCa Survivors**, Mauro Gacci, Elisabetta Baldi, Lara Tamburrino, Beatrice Detti, Lorenzo Livi, Cosimo De Nunzio, Andrea Tubaro, Stavros Gravas, Marco Carini, and Sergio Serni  
Volume 2014, Article ID 470592, 16 pages

**Effects of Long-Term Testosterone Therapy on Patients with “Diabesity”: Results of Observational Studies of Pooled Analyses in Obese Hypogonadal Men with Type 2 Diabetes**, Ahmad Haider, Aksam Yassin, Gheorghe Doros, and Farid Saad  
Volume 2014, Article ID 683515, 15 pages

**The Interplay between Magnesium and Testosterone in Modulating Physical Function in Men**, Marcello Maggio, Francesca De Vita, Fulvio Lauretani, Antonio Nouvenne, Tiziana Meschi, Andrea Ticinesi, Ligia J. Dominguez, Mario Barbagallo, Elisabetta Dall’Aglio, and Gian Paolo Ceda  
Volume 2014, Article ID 525249, 9 pages


**Health-Related Quality of Life and Quality of Sexual Life in Obese Subjects**, Eleonora Poggiogalle, Luca Di Lazzaro, Alessandro Pinto, Silvia Migliaccio, Andrea Lenzi, and Lorenzo M. Donini  
Volume 2014, Article ID 847871, 7 pages

**Benign Prostatic Hyperplasia: A New Metabolic Disease of the Aging Male and Its Correlation with Sexual Dysfunctions**, Giovanni Corona, Linda Vignozzi, Giulia Rastrelli, Francesco Lotti, Sarah Cipriani, and Mario Maggi  
Volume 2014, Article ID 329456, 14 pages

**Progressive Improvement of T-Scores in Men with Osteoporosis and Subnormal Serum Testosterone Levels upon Treatment with Testosterone over Six Years**, Ahmad Haider, Ulrich Meergans, Abdulmageed Traish, Farid Saad, Gheorghe Doros, Paul Lips, and Louis Gooren  
Volume 2014, Article ID 496948, 9 pages

**Effects of Five-Year Treatment with Testosterone Undecanoate on Metabolic and Hormonal Parameters in Aging Men with Metabolic Syndrome**, Davide Francomano, Andrea Lenzi, and Antonio Aversa  
Volume 2014, Article ID 527470, 9 pages

**Hormonal Modulation in Aging Patients with Erectile Dysfunction and Metabolic Syndrome**, Inês Campos Costa, Hugo Nogueira Carvalho, Luís Pacheco-Figueiredo, Inês Tomada, and Nuno Tomada  
Volume 2013, Article ID 107869, 7 pages



---

**Trunk Fat Negatively Influences Skeletal and Testicular Functions in Obese Men: Clinical Implications for the Aging Male**, Silvia Migliaccio, Davide Francomano, Roberto Bruzziches, Emanuela A. Greco, Rachele Fornari, Lorenzo M. Donini, Andrea Lenzi, and Antonio Aversa  
Volume 2013, Article ID 182753, 6 pages

## Editorial

# Coordinating Care Aspects Related to Sexual Health in the Aging Male

**Antonio Aversa,<sup>1</sup> Lorenzo Maria Donini,<sup>1</sup> Roberto Bruzziches,<sup>1</sup> Roberto LaCava,<sup>2</sup> Francesco Mattace Raso,<sup>3</sup> and Alan Sinclair<sup>4</sup>**

<sup>1</sup> Department of Experimental Medicine, Faculty of Medicine, Sapienza University of Rome, 00161 Rome, Italy

<sup>2</sup> Department of Territorial Geriatric Medicine, ASP Catanzaro, 88100 Catanzaro, Italy

<sup>3</sup> Department of Internal Medicine, Erasmus University Medical Center, 3015 CE Rotterdam, The Netherlands

<sup>4</sup> Bedfordshire and Hertfordshire Postgraduate Medical School, Birmingham B29 6JD, UK

Correspondence should be addressed to Antonio Aversa; [antonio.aversa@uniroma1.it](mailto:antonio.aversa@uniroma1.it)

Received 27 February 2014; Accepted 27 February 2014; Published 14 April 2014

Copyright © 2014 Antonio Aversa et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Global demographic changes demonstrate that the number of men aged 65 and older continues to increase dramatically. In order to attain a high level of health and well-being, important interventional areas such as diet, exercise, and sexuality may have important implications for older men.

Ageing males are at higher risk of several geriatric conditions, including falls from postural hypotension or balance and gait impairment, polypharmacy (more than three prescription medications), and use of sedative-hypnotic medications. These may be overshadowed by the development of prostate cancer, cardiovascular disease (CVD), depression, and obesity. It is known that obese men and women have a lower quality of life when compared with lean counterparts. In this issue, Poggiogalle et al. investigated the quality of life and more specifically the quality of sexual activity, in 95 obese men and women. Although the number of included patients was relatively small, the authors found an inverse association between body mass index and sexual activity in both men and women. In men, the results were mostly driven by erectile dysfunction and lack of sexual desire, whereas women reported a reduction of sexual disturbances with aging.

Aging men experience a gradual decline in serum testosterone (T), known as late onset hypogonadism (LOH), a condition that is often neglected by clinicians. It is estimated that hypogonadism affects between 19 and 40% of men over the age of 65. Consequently, understanding this phenomenon

and its relationship with changes in body composition in older males is important because of associated conditions such as the metabolic syndrome, type 2 diabetes mellitus or obesity, CVD, and chronic heart failure. Hackett et al. give an update on the risk/benefit ratio of T supplementation on cardiac function in older men. They conclude that men with low T usually present with troublesome symptoms, particularly ED, and require treatment to address those problems, as well as addressing cardiovascular prevention. A considerable body of evidence suggests that low T is associated with increased CVD and cancer mortality. A policy of taking little or no action for these men based on concerns of increased cardiovascular and cancer risk associated with physiological replacement would seem illogical. There is considerable evidence of modest cardiac and metabolic benefits that are shown to reduce cardiovascular risk, plus sexual, mood, and quality of life changes associated with restoring T levels. These may also provide benefits to particular subgroups of frail older men thus avoiding fears over prostate and cardiac risk that must be supported by larger clinical studies in such populations.

The risk/benefit ratio of T replacement therapy on different organs, alone or in combination with nutraceuticals, is also a matter of debate in the aging male. In particular, together with the role of nutritional status as key factor of successful aging, mineral assessment has received attention as an important determinant of physical performance. There



is evidence that magnesium exerts a positive influence on anabolic hormonal status, including testosterone, in men. Maggio et al. in their review summarize data from observational and intervention studies about the role of magnesium in testosterone bioactivity and the potential underlying mechanisms of this relationship in male subjects.

Gradual changes associated with male aging in the male reproductive system may include changes in testicular tissue, sperm production, and erectile function. Emerging data suggest that bone mass, energy metabolism, and reproduction may be coregulated by changes in body composition and visceral fat amount. It is now accepted that bone is an endocrine organ favouring whole-body glucose homeostasis and energy expenditure. These functions of bone are, in part, mediated by an osteoblast-specific secreted molecule, osteocalcin (OSCA). The potential relationship between circulating levels of OSCA and T with adipose tissue and bone mineral density in obese men has been evaluated by Migliaccio et al. in an original study carried out in an outpatient male clinic population. In their study, they propose for the first time the pivotal role of OSCA in the regulation of bone, metabolism, and reproductive functions.

Erectile dysfunction (ED) is a concern for many aging men. Erections occur less frequently as men age, and aging men often have less ability to experience repeated ejaculation. The underlying problem is likely to be due to medical reasons in about 90% of cases. Several medications (especially those used to treat hypertension and certain other conditions) may cause some men to be unable to develop or maintain enough of an erection for intercourse or to alter ejaculations. Gareri et al. presented an update in this area especially with regard to geriatric populations. Since data from pooled analyses are scarce, they found it difficult to recommend a specific optimal treatment for older men with comorbidities. However, they conclude that a Vardenafil orodispersible preparation is reported to have the fastest onset of action (pending the postmarketing data arriving soon from Avanafil, which is supposed to be as fast as ten minutes after assumption), while Tadalafil is reported to have the longer duration of action, with both representing a safe approach in an aged population. The novel longer-term use of phosphodiesterase type 5 inhibitors for other than ED conditions, that is, Sildenafil in pulmonary hypertension and Tadalafil in lower urinary tract symptoms (LUTS), appears to be promising ideas.

Benign prostate hyperplasia (BPH) may eventually interfere with urination and render older men more likely to have LUTS and/or prostatitis, especially in the presence of LOH. Pathogenic interconnections between BPH, inflammation, metabolic syndrome (MetS), and LOH are shown in the review by Corona et al. which highlights possible interventions to prevent their negative effect on men's health. BPH/LUTS represent a significant problem among aging men; they were historically considered as a normal consequence of the aging process and, as such, their negative effects on men's well-being were only dealt with through medical or surgical intervention. This view has been challenged in the last decade and now BPH/LUTS are seen more preventable than inexorable ailments of the

older male population. Evidence presented in this review indicates that several modifiable metabolic factors play a role in determining the progression of LUTS/BPH. MetS and its components, hypogonadism and prostate inflammation, are, in fact, emerging as medical conditions commonly associated with BPH/LUTS, which in turn can be viewed as a complex disorder that involves a metabolic component that may begin early in the life of the male, remain asymptomatic, but is likely to be detectable even in the early stages of the disease. The mechanisms underpinning the relationship between MetS and prostate inflammation are likely to be similar in young and old men but chronic exposure to elevated inflammation, along with low T/high estradiol levels, may contribute to BPH in the long term. Preventing the development of the disease even from the asymptomatic phase should be the basis for designing a resilient program of elder healthcare.

Prostate cancer (PCa) becomes more common as men age. It is one of the most frequent causes of cancer death in men. Bladder cancer also becomes more common with ageing. All these situations may severely impair sexual behaviour and hence the quality of life of these individuals. Several trials on androgens and PCa have recently focused on urinary continence, quality of life, and sexual function, suggesting a new point of view on the whole endocrine aspect of PCa. In their review, Gacci et al. confirm that any treatment for PCa can have a long-lasting negative impact on quality of life and sexual health. In particular, sexual health, urinary continence, and bowel function can be worsened after prostatectomy, radiotherapy, or hormone treatment, mostly in the older population. The current knowledge on the role of hormones, metabolic aspects, and primary treatments for PCa in the quality of life and sexual health of older PCa survivors is analyzed in this review.

This issue has provided many insights into the management of older men with hypogonadism, especially as far as its related complications regard, that is, obesity, diabetes, and osteoporosis. Long-term T treatment of diabetic obese men with low T levels produced important clinical benefits in men with this combined syndrome, "diabesity." Haider et al. collected and analyzed data from two observational, prospective, cumulative registry studies of 561 men with LOH receiving T therapy for up to 6 years. As far as we are aware, a unique aspect of this study is that it followed diabetic obese hypogonadal men for a period of 6 years, which is the longest reported duration of T treatment to date. Although the designs of the registry studies have some limitations, for example, they do not take into account behavioural and lifestyle changes, the authors conclude that T therapy of obese, diabetic men improves glycaemic control and lipid profiles and may prove useful in reducing the risk of CVD. In another original study, Haider et al. investigated the effects of normalizing serum testosterone on bone mineral density in 45 middle-aged to elderly men with osteoporosis, diagnosed with LOH. They demonstrated that T treatment not only improved their bone mineral density (from osteoporosis to osteopenia over six years of treatment), but also benefited their metabolic state, mood, and sexual functioning. Similarly, Francomano et al. show for the first time the results of a controlled, long-term study (60-month),

on the effects of T replacement therapy in hypogonadal men with MetS. The authors confirmed the beneficial effects of a long-acting T injection on anthropometric and metabolic parameters defined as a reduction of cardiovascular risk factors (lipid profile, blood pressure, insulin resistance, and HbA1c). Noteworthy, a significant improvement in bone mineral density in relation to a concomitant increase in the levels of serum vitamin D was firstly reported, which is explained by a possible direct effect of testosterone on renal expression of the 1-alpha-hydroxylase and on the reduction of fat mass independently from estradiol modifications. In addition, the add-on effects of T injections on circulating levels of pituitary hormones lead the authors to consider obesity as a “panhypopituitarism” condition determining a multiendocrine dysfunction. Last, but not least, the remarkable safety profiles of hormone replacement therapy on haematological and prostatic parameters were confirmed in all these studies.

As men approach older age with all their exuberance, they exit with physiological maturity. Let us just stop for a moment to meditate what are the physical and psychological impacts of such changes and what new complex mechanisms are going to change over the continuation of life. This is not the end of life itself, but it is a more complex interplay between maturity and wisdom. If an older man does not apply “*Virtute e Canoscenza*” he might be transformed into its opposite, that is, bewilderment and melancholy. This transmutation is the basis for the “alchemical” endocrinologist, who uses his tools to process the spirit and the senses. This issue provides new considerable progress in several important metabolic areas related to male sexual function and how this has such an important bearing on male health and well-being and the development of premature CVD in the aging male. We are beginning to be more objective about the benefits and risks of T therapy, seeing the complex relationship between MetS, obesity, and LUTS becoming unravelled, and gaining new insights into metabolic bone disease. This is an exciting time and at this current rate of enquiry this should prompt a further review in this area in three years!

Antonio Aversa  
Lorenzo Maria Donini  
Roberto Bruzziches  
Roberto LaCava  
Francesco Mattace Raso  
Alan Sinclair

## Review Article

# Testosterone Deficiency, Cardiac Health, and Older Men

G. Hackett,<sup>1,2</sup> M. Kirby,<sup>2,3</sup> and A. J. Sinclair<sup>2,4</sup>

<sup>1</sup> Heartlands Hospital, Bordesley Green East, Birmingham, B9 5SS, UK

<sup>2</sup> IDOP, University of Bedfordshire, Putteridge Bury Campus, Luton, Bedfordshire LU2 8LE, UK

<sup>3</sup> The Prostate Centre, 32 Wimpole Street, London W1G 8GT, UK

<sup>4</sup> The Luton & Dunstable Hospital, Lewsey Road, Luton, Bedfordshire LU4 0DZ, UK

Correspondence should be addressed to A. J. Sinclair; [sinclair.5@btinternet.com](mailto:sinclair.5@btinternet.com)

Received 26 November 2013; Revised 12 January 2014; Accepted 5 February 2014; Published 10 April 2014

Academic Editor: Antonio Aversa

Copyright © 2014 G. Hackett et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Low levels of testosterone are manifested by erectile dysfunction, reduced sexual desire, and loss of morning erections with increasing numbers of men are being diagnosed and require treatment. The prevalence rates of testosterone deficiency vary according to different studies but may be as high as 40% in populations of patients with type 2 diabetes. There is increasing evidence that testosterone deficiency is associated with increased cardiovascular and all-cause mortality. Screening for low testosterone is recommended in a number of high risk groups including those with type 2 diabetes and metabolic syndrome. There are recent data to suggest that testosterone replacement therapy may reduce cardiovascular mortality as well as improving multiple surrogate markers for cardiovascular events. Specific clinical trials of testosterone replacement therapy are needed in selected populations but in the meantime we must treat patients based on the best current evidence.

## 1. Introduction

The current ISSAM (International Society for Study of the Aging Male), EAU (European Association of Urology), and BSSM (British Society for Sexual Medicine Association) definition of Late Onset Hypogonadism [1, 2] is

*“A biochemical syndrome associated with advancing age and characterised by a deficiency in serum androgen levels with or without a decreased genomic sensitivity to androgens. It may result in significant alterations in the quality of life and adversely affect the function of multiple organ systems”.*

This state of hypogonadism causes a global decrease in energy and a decrease in the feeling of well-being. It also causes a change in sexual function and has other endocrine and metabolic repercussions. These can affect bones, muscles, and lipids, as well as cognitive function. Testosterone Deficiency Syndrome (TDS) or Late Onset Hypogonadism which is defined on the basis of clinical symptoms associated with abnormal testosterone levels. The European Male Aging Study [3] (EMAS) studied 3369 men aged 40–79 at 8

European centres and concluded that the 3 following cardinal symptoms were most likely to be related to low levels of testosterone.

*Erectile Dysfunction, Reduced Sexual Desire, and Loss of Morning Erections.* Other symptoms such as hot flushes, sweats and tiredness, loss of vitality, reduced shaving frequency, gynaecomastia, depressed mood, poor concentration, and sleep disturbance were regarded as less specific.

Recent guidelines suggest that a level of total testosterone of <8 nmol/L or free testosterone of less than 180 pmol/L requires testosterone replacement therapy and total testosterone of >12 nmol/L or free testosterone of >225 pmol/L does not. Between these levels a trial of therapy for a minimum of 6 months should be considered based on symptoms [1, 2]

## 2. Biochemical Assessment of Hypogonadism

Total testosterone should be measured between the hours of 7 and 11 am on 2 occasions at least 1 month apart and ideally be assessed by mass spectrometry (ID-GCMS). Equilibrium dialysis is currently the gold standard for free testosterone as

immunoassays based on analogue displacement are currently inaccurate [1, 2, 4].

The Endocrine society [4] recommends that men with the following conditions should be screened for low testosterone routinely:

- (i) type 2 diabetes,
- (ii) metabolic syndrome,
- (iii) moderate to severe chronic lung disease,
- (iv) osteoporosis,
- (v) HIV,
- (vi) history of infertility,
- (vii) treatment with steroids, opiates (even medically prescribed), and anticonvulsants,
- (viii) alcohol abuse.

### 3. Low Testosterone and Increased Mortality

There is increasing evidence from multiple long-term studies that TDS is associated with increased cardiovascular and all-cause mortality [5–13]. Two recent meta-analyses have looked at a large number of long-term studies linking low testosterone to increased cardiovascular and all-cause mortality [14, 15]. Araujo et al. [14] concluded that the evidence for a link between low testosterone and increased mortality was strong but concluded that most studies involved issues in cohort selection and choice. They concluded that a decrease of 2.1 standard deviations in total testosterone was associated with a 25% increase in mortality. Haring [15] et al. looked at the data in terms of several models and found that even after strict adjustment for comorbidities there was a consistent link between mortality risk and testosterone level throughout the studies but that this did not prove causation (Table 1).

The EMAS group [16] recently reported 4.3 year follow-up data on 2599 men aged 40–79 and concluded that men with a baseline TT of 8 nmol/L or less and sexual symptoms had a 3-fold increased mortality and a 5-fold increased risk of cancer death. These authors concluded that there is a small number of men with low testosterone at considerable risk of early death.

A recent 10 year study from Western Australia involving 3690 men followed up from 2001–2010 concluded that TT and FT levels in the normal range were associated with decreased all-cause and cardiovascular mortality, for the first time suggesting that both low and DHT are associated with all-cause mortality and higher levels of DHT reduced cardiovascular risk [17].

Six published studies usually involving small samples have shown that low TT and FT are associated with CAD and 4 have shown no association [18]. Four studies have shown inverse associations between low TT or FT (Table 2) and the severity of CAD [18]. One involved 803 men assessed by Gensini score, based on the location and number of stenotic coronary artery segments and degree of luminal narrowing [19]. Such studies do not establish whether low TT or FT is a cause or a consequence of CAD.

*3.1. Mortality Studies from High Risk Groups.* Malkin et al. [20] followed up 930 men referred with coronary artery disease for 6.9 years. The prevalence of hypogonadism was 24%, mortality rates were 21% versus 12% ( $P = 0.002$ ) for hypogonadal men versus eugonadal, and the study was halted early at 6.9 years. Only beta-blocker therapy and left ventricular failure were found to have a greater influence on survival.

Muraleedaran [21] et al. screened a primary care diabetic population of 587 patients and followed them up for 5.8 years. They found that 475 of men had normal TT levels, 22% were overtly hypogonadal ( $<8$  nmol/L), and 31% were in the borderline range. These percentages were in close agreement with earlier publications by Kapoor [22] et al. and Hackett et al. [23]. The mortality rate [21] over 5 years in the hypogonadal group was 17.2% versus 9% in the normal testosterone cohort. The effect of treatment with TRT reduced the mortality rate of treated cohort (8.4%) to that of the eugonadal group whereas the mortality for the untreated remained high at 19.2%, after adjustment for all confounding factors.

*3.2. Effect of Low Testosterone on Surrogate Markers for Cardiovascular Risk.* Decreases in serum total cholesterol (TC) have been noted as early as after 4 weeks [23] but most studies have reported a decrease after 3 months [24]. Greater reductions were seen in obese men [24] with metabolic syndrome. The MRFIT [25] study showed that hypogonadal men had slightly increased triglycerides and HDL, leading to the suggestion that TRT might be expected to lower triglycerides and HDL. A recently published 5-year registry involving 230 men treated with long acting testosterone showed highly significant reductions in TC, LDL, and triglycerides with increase in HDL, associated with significant reduction in weight, BMI, and visceral fat [26].

The decrease in serum triglycerides follows a similar pattern: after 4 weeks with decrease over 9 months [25] and maximum effect at 12 months [25]. The decrease in low-density lipoprotein cholesterol seems somewhat slower: after 3 months, after 40–44 weeks, or after 12 months [25].

Studies have found both an increase and decrease in HDL cholesterol [26–28] dependent on the presence of diabetes or the use of statins. TRT has also been shown to reduce fibrinogen to levels similar to fibrates. Low androgen levels are associated with an increase in inflammatory markers [24]. A decline was noted in IL6 and TNF-alpha within 16 weeks [27] and in another study after 16 weeks [24]. In the Moscow study, C-reactive protein was reduced by TRT at 30 weeks versus placebo [27].

Several of the above studies have shown reduction in waist circumference, visceral fat, and BMI [26–28]. Preliminary longer term studies suggest that considerable weight loss can be seen for up to 4 years. Placebo controlled studies in untreated hypertension are difficult to conduct for ethical reasons. In some studies, a decline in diastolic blood pressure has been observed, after 3–9 months [24, 26] and in systolic blood pressure [24, 26]. Maximum effects were observed after 12 months and up to 5 years [24, 26].

TABLE 1: Association of low testosterone levels with all-cause mortality by different cut-offs from recent studies.

| Cut-off for the definition of low total testosterone (TT) | MMAS; [8]<br>TT < 6.94 nmol/L<br>(200 ng/dL) | Wang; [31]<br>TT < 8.0 nmol/L<br>(230 ng/dL) | Rancho<br>Bernardo; [7]<br>TT < 8.36 nmol/L<br>(241 ng/dL) | Male veterans study;<br>[32]<br>TT < 8.7 nmol/L<br>(250 ng/dL) | HIM; [33]<br>TT < 10.41 nmol/L<br>(300 ng/dL) | EPIC; [6]<br>TT < 12.5 nmol/L<br>(360 ng/dL) | Age-specific cut-off<br><10th percentile |
|---|--|--|--|--|---|--|--|
| Low TT (n)  | 34   | 69   | 82   | 98   | 241   | 474  |  |
| Model 1   | 1.59 (0.83; 4.02)                            | 1.96 (0.93; 3.63)                            | 2.21 (1.26; 3.89)**  | 2.24 (1.41; 3.57)**  | 1.33 (0.93; 1.90)                             | 1.28 (0.95; 1.72)                            | 2.21 (1.40; 3.49)**                      |
| Model 2   | 2.12 (1.01; 4.46)*                           | 2.08 (1.12; 3.86)*                           | 2.33 (1.33; 4.12)**  | 2.10 (1.34; 3.29)**  | 1.28 (0.89; 1.84)                             | 1.20 (0.88; 1.62)                            | 2.26 (1.43; 3.59)**                      |
| Model 3   | 2.50 (1.18; 5.27)*                           | 2.24 (1.21; 4.17)*                           | 2.53 (1.43; 4.47)**  | 2.32 (1.38; 3.89)**  | 1.37 (0.95; 1.99)                             | 1.28 (1.93; 1.75)                            | 2.35 (1.47; 3.74)***                     |
| Model 4   | 2.68 (1.19; 6.04)*                           | 2.13 (1.06; 4.26)*                           | 2.56 (1.38; 4.76)**  | 1.92 (1.18; 3.14)**  | 1.11 (0.72; 1.69)                             | 1.10 (0.78; 1.56)                            | 2.25 (1.35; 3.75)**                      |

Model 1: adjusted for age. Model 2: adjusted for age, and WC. Model 3: adjusted for model 2, smoking (3 categories), high-risk alcohol use, and physical activity. Model 4: adjusted for model 3, renal insufficiency, and DHEAS. HR: hazard ratio; CI: 95% confidence interval; CVD: cardiovascular disease; WC: waist circumference; DHEAS: dehydroepiandrosterone sulfate.

\*  $P < 0.05$ .

\*\*  $P < 0.01$ .

\*\*\*  $P < 0.001$ .



TABLE 2: Association between testosterone level and severity of coronary artery disease.

| Study name                                | Subfraction of testosterone used for analysis | Method of measuring CAD severity   | Main findings   | Remarks   |
|---|---|--|---|---|
| Dobrzycki et al. [34]<br>(CCS, $n = 96$ ) | TT, FT, FAI                                   | Duke index*  | Inverse correlation between FT and CAD severity               | $r = -0.69, P = 0.048$                                    |
| Rosano et al. [35]<br>(CCS, $n = 129$ )   | TT  | Coronary artery score**  | Inverse correlation between TT and CAD severity               | $r = -0.52, P < 0.01$                                     |
| Li et al. [36]<br>(CCS, $n = 803$ )       | TT  | Genisi score***  | Inverse correlation between TT and CAD severity               | $r = -0.188, P < 0.001$                                   |
| Phillips et al. [37]<br>(CCS, $n = 55$ )  | TT, FT  | Visual estimation of coronary artery occlusion and calculation of mean percent occlusion**** | Inverse correlation between TT and FT levels and CAD severity | TT: $r = -0.43, P < 0.02$ ;<br>FT: $r = -0.62, P < 0.001$ |

CAD indicates coronary artery disease; CCS: case-control study; FAI: free androgen index; FT: free testosterone; TT: total testosterone.

\*Duke prognostic coronary artery index: a prognostic tool involving the extent and severity of atherosclerotic lesions in coronary arteries.

\*\*Coronary artery score: authors multiplied the degree of coronary artery obstruction by the number of stenoses.

\*\*\*Genisi score: calculated based on location and number of stenotic coronary artery segments, and degree of luminal narrowing.

\*\*\*\*Authors visually estimated the maximum percent reduction in luminal diameter of the left main, left anterior descending, left circumflex, and right coronary arteries. The mean of these 4 values was used to estimate CAD severity.

**3.3. Effects on Angina Threshold and Heart Failure.** Men with angiographically proven CAD (coronary artery disease) have significantly lower testosterone levels [29] compared to controls ( $P < 0.01$ ) and there was a significant inverse relationship between the degree of CAD and TT (total testosterone) levels ( $r = -0.52, P < 0.01$ ). Nearly 25% of men presenting for coronary angiography had testosterone levels in the low hypogonadal range and some 50% had a TT of less than 11 nmol/L [30].

Studies have shown pharmacological doses of testosterone to relax coronary arteries when injected intraluminally [39] and to produce modest but consistent improvement in exercise-induced angina and reverse associated ECG changes [40]. The mechanism of action is via blockade of calcium channels with effect of similar magnitude to nifedipine [40].

In men with chronic stable angina pectoris, the ischaemic threshold increased after 4 weeks of TRT and a recent study demonstrates improvement continuing beyond 12 months [39, 40]. Exercise capacity in men with chronic heart failure increased after 12 weeks [30], predominantly through the improvement in skeletal muscle performance.

Lower levels of endogenous testosterone have been shown to be associated with longer duration of the QTc interval and TRT has been shown to reverse this effect [41]. Carotid artery intimal thickness is associated with low endogenous testosterone suggesting an increased risk of atherosclerosis [31].

A trial of 209 elderly frail men [32] over 65 randomised to receive either placebo or 100 g of topical testosterone gel was terminated early as there were 23 cardiac events (2 deaths) in the 106 men in the testosterone group versus 5 in the placebo group, despite positive results in study end points. These events included myocardial infarction and dysrhythmias and hypertension. The authors conceded that there were more cardiovascular comorbidities in the active treatment group and that the starting dose and escalation were outside the product licence. The active treatment group had more severe CAD. The study involved rapid escalation up to 150 mg per

day, above the manufacturers recommended dose and many of the events were reported with inadequate validation.

**3.4. Testosterone, Insulin Resistance, and Type 2 Diabetes.** Studies have shown an inverse relationship between serum testosterone and fasting blood glucose and insulin levels [33]. Both hyperinsulinaemia and low testosterone have been shown to predict the development of type 2 diabetes (T2D) [42, 43]. Medications such as chronic analgesics, anticonvulsants, 5ARIs, and androgen ablation therapy are associated with increased risk of testosterone deficiency and insulin resistance [1, 2].

Hypogonadism is a common feature of the metabolic syndrome [42, 43]. Intraabdominal adiposity (IAA) drives the progression of multiple risk factors directly, through the secretion of excess free fatty acids, inflammatory adipokines, and decreased secretion of adiponectin [44]. The important contributions of IAA to dyslipidaemia and insulin resistance provide an indirect, though clinically important, link to the genesis and progression of atherosclerosis and cardiovascular disease [44]. The presence of excess IAA is an important determinant of cardiometabolic risk. The INTERHEART study [45] involving 29,972 participants examined the contributory factors involved in first AMI (acute myocardial infarction) and found IAA to be an important predictive factor and recommended waist circumference or hip-waist ratio as a standard measurement of cardiovascular risk. Women with T2D or metabolic syndrome characteristically have low SHBG and high free testosterone [6]. The precise interaction between insulin resistance, visceral adiposity, and hypogonadism is, as yet, unclear but the important mechanisms are through increased aromatase production, raised leptin levels, and increase in inflammatory kinins [46].

In obese males, levels of testosterone are reduced in proportion to degree of obesity. The first step in reducing visceral fat is diet and lifestyle change [46]. Patients should be advised to switch to a low glycaemic diet, providing

TABLE 3: Outcome of therapy with long acting TU in a population of men with type 2 diabetes and hypogonadism (BLAST) Hackett et al. IJCP Dec 2013 [38].

|                | HbA1c<br>(%)<br>>7.5 | Weight<br>(kg) | BMI<br>(kg/m <sup>2</sup> ) | WC<br>(cm)       | TC<br>(mmol/L) | EF<br>(TT < 8 nmol/L)   | AMS<br>(points) | HADS-D       | GEQ<br>(% imp)   |
|----------------|----------------------|----------------|-----------------------------|------------------|----------------|-------------------------|-----------------|--------------|------------------|
| 30 weeks       | -0.41                | -0.7           | -0.3                        | -2.5             | -0.25          | +3.0                    | -5.3            | -1.01        | 46               |
| <i>P</i> value | <b>0.007</b>         | 0.13           | <b>0.01</b>                 | <b>0.012</b>     | <b>0.025</b>   | <b>0.006</b>            | 0.095           | 0.64         | <b>&lt;0.001</b> |
| 82 weeks       | -0.89                | -2.7           | -1.00                       | -4.2             | -0.19          | +4.31<br>+9.57<br>PDE5I | -8.1            | -2.18        | 67-70            |
| <i>P</i> value | <b>0.009</b>         | <b>0.016</b>   | <b>0.019</b>                | <b>&lt;0.001</b> | <b>0.035</b>   | <b>0.003</b>            | <b>0.001</b>    | <b>0.001</b> | <b>0.0001</b>    |

carbohydrate that does not increase glucose levels that means reducing potatoes and bread and substituting natural rice and full corn. Men should be encouraged to combine aerobic exercise with strength training. As muscle increases, glucose will be burned more efficiently and insulin levels will fall. A minimum of 30 minutes exercise three times weekly should be advised [46].

Men with low testosterone levels show less diurnal variation compared with younger men with normal levels [1]. Testosterone increases levels of fast-twitch muscle fibres [46]. By increasing testosterone, levels of type 2 fibres increase and glucose burning improves. Weight loss will increase levels of testosterone and augment the effects of lifestyle and exercise advice [47].

Diabetes specialists have traditionally considered the fall in testosterone level as being a consequence of obesity but studies now clearly show that low testosterone leads to visceral obesity and metabolic syndrome and is also a consequence of obesity [4]. Large long-term studies have shown that baseline levels of testosterone predict the later development of type 2 diabetes [25, 42, 43]. In the case of MMAS [43], a baseline total testosterone of less than 10.4 nmol/L was associated with a greater than 4-fold incidence of type 2 diabetes over the next 9 years and NHANES-III followed up men from as young as 20 and found a similar 4 times greater prevalence independent of obesity or ethnicity [42]. Diabetes UK data 2010 [48] showed the prevalence of type 2 diabetes in men aged 35–44 to be doubled that of women despite men in that age group having lower levels of obesity and taking more exercise. This effect was even more marked in southern Asian men [48]. A study has recently commenced in Australia to establish whether treating young obese men with low testosterone will reduce the incidence of type 2 diabetes.

There is high level evidence that TRT improves insulin resistance, as measured by HOMA-IR [49–52], and reduces HbA1c [49] by approximately 0.7% by 18 months [53] and inflammatory markers (CRP, IL6, and TNF-alpha) in men with type 2 diabetes and metabolic syndrome [26–28]. There is also high level of evidence for reduction in total cholesterol, weight, BMI [26–28], and visceral fat (a significant marker for CV risk) and improvement of lean muscle mass. The BLAST study [53, 54] suggested that men with depression (23% of the cohort with diabetes) were markedly less responsive to testosterone and that improvement in metabolic parameters

required sustained levels of testosterone above 12 nmol/L [53, 54] (Table 3).

A recent 5 year registry of 255 men age 36–69 [26] treated with long acting TU has shown mean reductions in waist circumference of 8.5 cm, weight reduction of 15.5 kg, total cholesterol by 2.4 mmol/L, reduction in HDL, and triglycerides with HbA1c by 0.9% (7.06 to 6.16).

**3.5. The Effects of Testosterone Replacement Therapy on Cardiovascular Mortality.** A prospective recent study of 587 men with type 2 diabetes [21] involved 5.8 years follow-up. Low testosterone was defined as TT <10.4 nmol/L. Fifty-eight men were treated with testosterone for 2 years or more. The mortality rate was 20% in the untreated group and 9.1% in the normal group independent of comorbidities and therapies. Mortality was 8.6% in the treated group ( $P = 0.049$ ) (Figure 1).

A similar retrospective US study involved 1031 men with 372 on TRT. The cumulative mortality was 21% in the untreated group versus 10% ( $P = 0.001$ ) in the treated group with the greatest effect in younger men and those with type 2 diabetes [55]. In a recent paper of 145 patients with first ischaemic stroke and diabetes, 66% were found to be hypogonadal, and in the testosterone treated group 7% had a recurrence of stroke in 2 years versus 16.6% in the control group with 28% of the treated men returning to work versus 6% of the control group. There were significant improvements in lipid profile and HbA1c [56].

A recent retrospective US study of 8709 men [57] with baseline TT of 10.4 nmol undergoing coronary angiography involved follow-up for mean 840 days. In the cohort of 7486 patients not receiving testosterone therapy, 681 died, 420 had MIs, and 486 had strokes. Among 1223 patients receiving testosterone therapy, 67 died, 23 had MIs, and 33 had strokes. At first sight these results would closely agree with the findings in [21, 55], but a complex statistical analysis reversed the trend and concluded that there was a greater risk in the TRT group. There were concerns that 1132 patients experiencing events were excluded because they were prescribed TRT after the event when surely these should have been included in the untreated group, increasing the events by 70%.

The baseline TT was 1 nmol/L lower in the treated group and previous studies show that this may increase the mortality by up to 30%, yet this was not considered in the 50

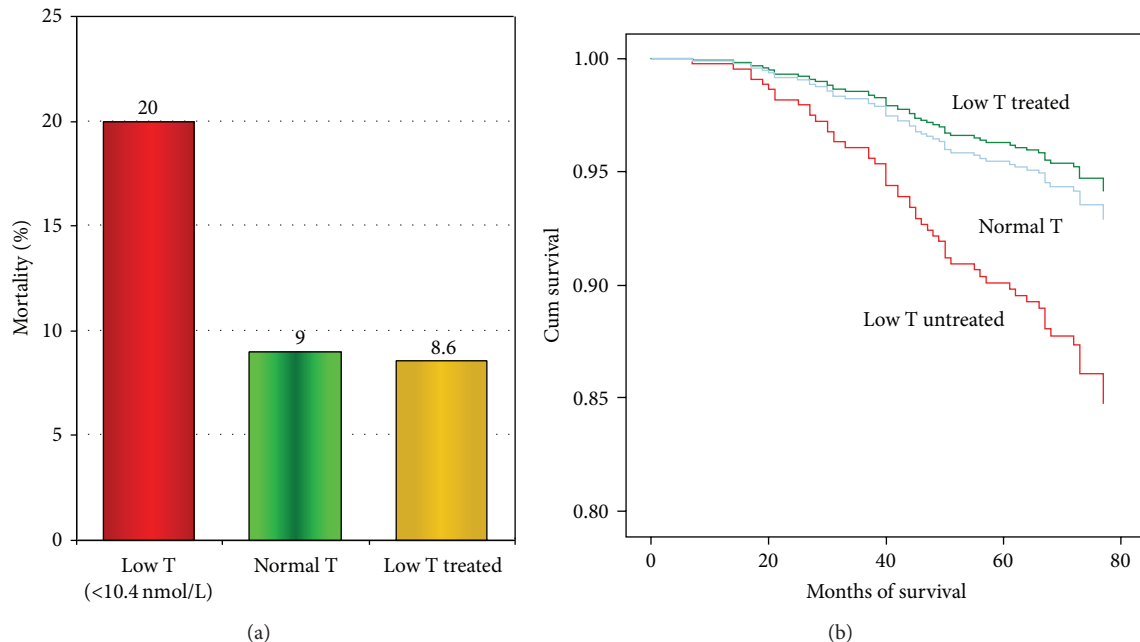


FIGURE 1: Low testosterone predicts increased mortality and testosterone therapy improves survival in 587 men with type 2 diabetes (mean follow-up: 5.8 years) Muraleedaran et al. [21].

confounders for analysis. Symptoms were not considered, yet these are key to the diagnosis of hypogonadism. Men were likely to be treated with TRT on the basis of symptoms if they suffered from erectile dysfunction, and the presence of ED has been shown to be an independent risk factor, particularly in hypogonadal men, increasing the risk of cardiac events by over 50% [16, 58].

Therapies used were mainly short acting injection and patches, both with high discontinuation rates. 16% filled only one prescription but were included in the “treatment” group. Only 60% had any record of a follow-up testosterone level and in those the mean treatment level was 10.2 nmol/L, suggesting suboptimal therapy.

Despite these issues, the paper was given an editorial and a separate paper warning patients about the risks of testosterone was included in the same journal [59]. The level of criticism of this paper led to an immediate revision of the conclusions shortly after publication. A recent online publication on ischaemic heart disease mortality in men concluded optimal androgen levels are a biomarker for survival [17]. A recent systematic and meta-analysis of placebo-controlled trials of T therapy lasting more than 12 weeks concluded that testosterone therapy may increase the risk of cardiovascular-related events [60] but most studies involved small cohorts with a small number of events but once again the nonrandomised studies failed to consider the impact of symptoms as an indication for TRT prescribing.

A meta-analysis of 1000 patient years [61] versus placebo suggests a slight reduction in myocardial infarction and CVA but a reduction in coronary interventions. There was a 6% incidence of raised haematocrit (>50%) without significant

consequences and no deaths in the active treatment group versus 5 in the placebo cohort.

#### 4. Long-Term Safety of Testosterone Therapy on the Prostate

At least 7 observational studies have reported no association of LUTS with serum testosterone level and 5 have shown an inverse relationship [62]. No studies to date show an increase in LUTS/BPH symptoms with higher serum testosterone levels [62]. A recent long-term registry of 5 years TRT shows sustained reduction in IPSS, postresidual volume, and bladder wall thickness, despite minor increase in prostate volume [63]. Another 5-year study involving a smaller cohort showed no impact on LUTS/BPH parameters [64]. As TRT has been shown to upregulate PDE5 [65] and enhance the effect of PDE5Is (now an accepted therapy for both ED and LUTS), it no longer seems logical to advice avoidance of TRT in men with mild to moderate BPH.

Calof et al. [61] also found that patients on testosterone were 12 times more likely to get a prostate biopsy but no more likely to have a positive finding. Several meta-analyses have failed to show a link between TRT and development of prostate cancer [66] but some studies have shown a tendency for more aggressive prostate cancer in men with low testosterone. One recent study of 279 consecutive patients referred for biopsy on the basis of abnormal DRE or raised PSA found that *low* bioavailable testosterone and high SHBG were associated with a 4.9- and 3.2-fold risk of positive biopsy [67].



Current EAU, ISSAM, and BSSM guidance [1, 2] is that there is “no evidence TRT is associated with increased risk of prostate cancer or activation of subclinical cancer.”

Despite these conclusions, many patients are deprived of clinical and metabolic benefit because of minor physiological increases in PSA and concerns that no long-term study has conclusively proved absolute safety.

## 5. Effects of Androgen Ablation Therapy

Men with prostate cancer, treated with androgen deprivation, develop an increase of fat mass with an altered lipid profile. Total cholesterol by 9, 7, 11, and 26.5%, respectively. These patients also appear to develop insulin resistance, hyperinsulinemia, and hyperglycaemia. The risks of diabetes mellitus increase by 44% and mortality of cardiovascular diseases by 16% during a follow-up of up to 10 years [68]. The authors concluded that before commencing ADT, the overall health, comorbidities, and life expectancy of the patient need to be fully assessed.

## 6. Testosterone and Erectile Dysfunction

Several studies have clearly shown that TRT can be effective as monotherapy for ED [26, 28], in men without other multiple comorbidities. A recent double blind placebo controlled study in men with diabetes showed prompt improvement in IIEF in men with severe hypogonadism and a secondary improvement with 12 to 18 months of therapy, dependent on obtaining prolonged sustained levels in the normal range [69]. Results from a 5-year registry showed 12.3-point improvements in IIEF in 260 men treated with long acting TU [64]. A systematic review and meta-analysis of placebo-controlled studies published in the past 30 years aimed to study effects of testosterone on the different domains of sexual life. This latter study concluded that T treatment might be useful for improving vasculogenic ED in selected subjects with low or low-normal T levels [70].

Erectile dysfunction is an established marker for future cardiovascular risk and the major presenting symptom leading to a diagnosis of low testosterone [58]. Current guidelines suggest that *all* patients presenting with ED, irrespective of age, should be screened for low testosterone, as it is a *potentially curable cause of ED*, especially in men without other comorbidities [1, 2]. NICE guidance [71] suggests that all men with type 2 diabetes be assessed for ED *annually* and the GP contract now includes routine assessment for ED, and increased demand for testosterone supplementation will be a natural consequence of this correction of previous underdiagnosis and undertreatment [72].

## 7. Conclusions

Men with low testosterone usually present with bothersome symptoms, particularly ED, and require treatment to address those problems, not simply for cardiovascular prevention purposes. The benefits of conventional cardiovascular risk

reduction with exercise and weight reduction are fundamental to management but are frequently unsuccessful. There is a considerable body of evidence that low testosterone is associated with increased cardiovascular and cancer mortality. A policy of taking little or no action for these men based on concerns of increased cardiovascular and cancer risk associated with physiological replacement would seem illogical. There is considerable evidence of modest cardiac and metabolic benefits that are shown to reduce cardiovascular risk plus sexual, mood, and quality of life changes associated with restoring testosterone levels. These may add up to substantial benefit to many patients. These benefits may potentially be denied to patients by fears over prostate and cardiac risk that is not currently supported by evidence. Ideally, we need large long-term studies to resolve these issues with certainty but such studies are unlikely to be done for logistic and financial reasons. Until then patients require advice and treatment based on the current best evidence.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

## References

- [1] C. Wang, E. Nieschlag, R. S. Swerdloff et al., “Investigation, treatment, and monitoring of late-onset hypogonadism in Males, ISA, ISSAM, EAU, EAA, ASA recommendation,” *European Urology*, vol. 55, pp. 21–130, 2009.
- [2] K. Wylie, M. Rees, G. Hackett et al., “Androgens, health and sexuality in women and men,” *Maturitas*, vol. 67, no. 3, pp. 275–289, 2010.
- [3] F. C. W. Wu, A. Tajar, J. M. Beynon et al., “Identification of late-onset hypogonadism in middle-aged and elderly men,” *The New England Journal of Medicine*, vol. 363, no. 2, pp. 123–135, 2010.
- [4] S. Bhasin, G. R. Cunningham, F. J. Hayes et al., “Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline,” *Journal of Clinical Endocrinology & Metabolism*, vol. 91, no. 6, pp. 1995–2010, 2006.
- [5] K.-T. Khaw, M. Dowsett, E. Folkard et al., “Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) prospective population study,” *Circulation*, vol. 116, no. 23, pp. 2694–2701, 2007.
- [6] J.-Y. Oh, E. Barrett-Connor, N. M. Wedick, and D. L. Wingard, “Endogenous sex hormones and the development of type 2 diabetes in older men and women: the Rancho Bernardo study,” *Diabetes Care*, vol. 25, no. 1, pp. 55–60, 2002.
- [7] M. M. Shores, A. M. Matsumoto, K. L. Sloan, and D. R. Kivlahan, “Low serum testosterone and mortality in male veterans,” *Archives of Internal Medicine*, vol. 166, no. 15, pp. 1660–1665, 2006.
- [8] Å. Tivesten, L. Vandenput, F. Labrie et al., “Low serum testosterone and estradiol predict mortality in elderly men,” *Journal of Clinical Endocrinology & Metabolism*, vol. 94, no. 7, pp. 2482–2488, 2009.
- [9] T. Vikan, H. Schirmer, I. Njølstad, and J. Svartberg, “Endogenous sex hormones and the prospective association with cardiovascular disease and mortality in men: the Tromsø study,”

- European Journal of Endocrinology*, vol. 161, no. 3, pp. 435–442, 2009.
- [10] G. Corona, M. Monami, V. Boddi et al., “Low testosterone is associated with an increased risk of MACE lethality in subjects with erectile dysfunction,” *Journal of Sexual Medicine*, vol. 7, no. 4, pp. 1557–1564, 2010.
  - [11] M. Maggio, F. Lauretani, G. P. Ceda et al., “Relationship between low levels of anabolic hormones and 6-year mortality in older men: the aging in the chianti area (InCHIANTI) study,” *Archives of Internal Medicine*, vol. 167, no. 20, pp. 2249–2254, 2007.
  - [12] Z. Hyde, P. E. Norman, L. Flicker et al., “Low free testosterone predicts mortality from cardiovascular disease but not other causes: the health in men study,” *Journal of Clinical Endocrinology & Metabolism*, vol. 97, no. 1, pp. 179–189, 2012.
  - [13] B. B. Yeap, Z. Hyde, O. P. Almeida et al., “Lower testosterone levels predict incident stroke and transient ischemic attack in older men,” *Journal of Clinical Endocrinology & Metabolism*, vol. 94, no. 7, pp. 2353–2359, 2009.
  - [14] A. B. Araujo, J. M. Dixon, E. A. Suarez, M. H. Murad, L. T. Guey, and G. A. Wittert, “Endogenous testosterone and mortality in men: a systematic review and meta-analysis,” *Journal of Clinical Endocrinology & Metabolism*, vol. 96, no. 10, pp. 3007–3019, 2011.
  - [15] R. Haring, H. V. Völzke, A. Steveling et al., “Association of low testosterone levels with all-cause mortality by different cut-offs from recent studies,” *European Heart Journal*, vol. 31, pp. 1494–1501, 2010.
  - [16] S. R. Pye, I. T. Huhtaniemi, J. D. Finn et al., “Late-onset hypogonadism and mortality in aging men,” *The Journal of Clinical Endocrinology & Metabolism*, 2013.
  - [17] B. B. Yeap, H. Alfonso, S. A. P. Chubb et al., “In older men an optimal plasma testosterone is associated with reduced all-cause mortality and higher dihydrotestosterone with reduced ischemic heart disease mortality, while estradiol levels do not predict mortality,” *Journal of Clinical Endocrinology & Metabolism*, vol. 99, no. 1, 2014.
  - [18] M. Peyman, M. D. Oskui, W. J. French et al., “Testosterone and the cardiovascular system. A comprehensive review of the literature,” *The American Heart Association Contemporary Reviews*, vol. 2, Article ID e000272, 2013.
  - [19] L. Li, C. Y. Guo, E. Z. Jia et al., “Testosterone is negatively associated with the severity of coronary artery disease in men,” *Asian Journal of Andrology*, vol. 14, pp. 875–878, 2012.
  - [20] C. J. Malkin, P. J. Pugh, P. D. Morris, S. Asif, T. H. Jones, and K. S. Channer, “Low serum testosterone and increased mortality in men with coronary heart disease,” *Heart*, vol. 96, no. 22, pp. 1821–1825, 2010.
  - [21] V. Muraleedaran, H. Marsh, D. Kapoor, K. S. Channer, and T. H. Jones, “Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes,” *European Journal of Endocrinology*, vol. 169, no. 6, pp. 725–733, 2013.
  - [22] D. Kapoor, H. Aldred, S. Clark, K. S. Channer, and T. H. Jones, “Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity,” *Diabetes Care*, vol. 30, no. 4, pp. 911–917, 2007.
  - [23] G. I. Hackett, N. S. Cole, A. A. Deshpande, M. D. Popple, D. Kennedy, and P. Wilkinson, “Biochemical hypogonadism in men with type 2 diabetes in primary care practice,” *British Journal of Diabetes and Vascular Disease*, vol. 9, no. 5, pp. 226–231, 2009.
  - [24] F. Saad, A. Aversa, A. M. Isidori, L. Zafalon, M. Zitzmann, and L. Gooren, “Onset of effects of testosterone treatment and time span until maximum effects are achieved,” *European Journal of Endocrinology*, vol. 165, no. 5, pp. 675–685, 2011.
  - [25] S. M. Haffner, J. Shaten, M. P. Stern, G. D. Smith, and L. Kuller, “Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. MRFIT Research Group. Multiple Risk Factor Intervention Trial,” *The American Journal of Epidemiology*, vol. 143, no. 9, pp. 889–897, 1996.
  - [26] A. M. Traish, A. Haider, G. Doros, and F. Saad, “Long-term testosterone therapy in hypogonadal men ameliorates elements of the metabolic syndrome: an observational, long-term registry study,” *International Journal of Clinical Practice*, vol. 68, no. 3, pp. 314–329, 2014.
  - [27] S. Y. Kalinchenko, Y. A. Tishova, G. J. Mskhalaya, L. J. G. Gooren, E. J. Giltay, and F. Saad, “Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study,” *Clinical Endocrinology*, vol. 73, no. 5, pp. 602–612, 2010.
  - [28] A. E. Heufelder, F. Saad, M. C. Bunck, and L. Gooren, “Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone,” *Journal of Andrology*, vol. 30, no. 6, pp. 726–733, 2009.
  - [29] K. M. English, O. Mandour, R. P. Steeds, M. J. Diver, T. H. Jones, and K. S. Channer, “Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms,” *European Heart Journal*, vol. 21, no. 11, pp. 890–894, 2000.
  - [30] G. Caminiti, M. Volterrani, F. Iellamo et al., “Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure. A double-blind, placebo-controlled, randomized study,” *Journal of the American College of Cardiology*, vol. 54, no. 10, pp. 919–927, 2009.
  - [31] J. Svartberg, D. von Mühlen, E. Mathiesen, O. Joakimsen, K. H. Bønaa, and E. Stensland-Bugge, “Low testosterone levels are associated with carotid atherosclerosis in men,” *Journal of Internal Medicine*, vol. 259, no. 6, pp. 576–582, 2006.
  - [32] S. Basaria, A. D. Coviello, T. G. Travison et al., “Adverse events associated with testosterone administration,” *The New England Journal of Medicine*, vol. 363, no. 2, pp. 109–122, 2010.
  - [33] D. Kapoor, H. Aldred, S. Clark, K. S. Channer, and T. H. Jones, “Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity,” *Diabetes Care*, vol. 30, no. 4, pp. 911–917, 2007.
  - [34] S. Dobrzycki, W. Serwatka, S. Nadlewski et al., “An assessment of correlations between endogenous sex hormone levels and the extensiveness of coronary heart disease and the ejection fraction of the left ventricle in males,” *The Journal of Medical Investigation*, vol. 50, pp. 162–169, 2003.
  - [35] G. Rosano, I. Sheiban, R. Massaro et al., “Low testosterone levels are associated with coronary artery disease in male patients with angina,” *International Journal of Impotence Research*, vol. 19, pp. 176–182, 2007.

- [36] L. Li, C. Y. Guo, E. Z. Jia et al., "Testosterone is negatively associated with the severity of coronary atherosclerosis in men," *Asian Journal of Andrology*, vol. 14, pp. 875–878, 2012.
- [37] G. B. Phillips, B. H. Pinkernell, and T. Y. Jing, "The association of hypotestosteronemia with coronary artery disease in men," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 14, pp. 701–706, 1994.
- [38] G. Hackett, N. Cole, M. Bhartia et al., "The response to testosterone undecanoate in men with type 2 diabetes is dependent on achieving threshold serum levels (the BLAST study)," *International Journal of Clinical Practice*, vol. 68, no. 2, pp. 203–215, 2014.
- [39] A. Mathur, C. Malkin, B. Saleem, R. Muthusamy, C. H. Jones, and K. Channer, "The long term benefits of testosterone on angina threshold and atheroma in men," *European Journal of Endocrinology*, vol. 161, no. 3, pp. 443–449, 2009.
- [40] K. M. English, R. P. Steeds, T. H. Jones, M. J. Diver, and K. S. Channer, "Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a randomized, double-blind, placebo-controlled study," *Circulation*, vol. 102, no. 16, pp. 1906–1911, 2000.
- [41] C.-X. Bai, J. Kurokawa, M. Tamagawa, H. Nakaya, and T. Furukawa, "Nontranscriptional regulation of cardiac repolarization currents by testosterone," *Circulation*, vol. 112, no. 12, pp. 1701–1710, 2005.
- [42] E. Selvin, M. Feinleib, L. Zhang et al., "Androgens and diabetes in men: results from the third National Health and Nutrition Survey (NHANES-III)," *Diabetes Care*, vol. 30, pp. 234–238, 2007.
- [43] R. K. Stellato, H. A. Feldman, O. Hamdy, E. S. Horton, and J. B. McKinlay, "Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts male aging study," *Diabetes Care*, vol. 23, no. 4, pp. 490–494, 2000.
- [44] M. Maggio, S. Basaria, A. Ble et al., "Correlation between testosterone and the inflammatory marker soluble interleukin-6 receptor in older men," *Journal of Clinical Endocrinology & Metabolism*, vol. 91, no. 1, pp. 345–347, 2006.
- [45] S. Migliaccio, D. Francomano, R. Bruzziches et al., "Trunk fat negatively influences skeletal and testicular functions in obese men: clinical implications for the aging male," *International Journal of Endocrinology*, vol. 2013, Article ID 182753, 6 pages, 2013.
- [46] J. Macleod, G. Davey Smith, C. Metcalfe, and C. Hart, "INTER-HEART," *The Lancet*, vol. 365, no. 9454, pp. 118–119, 2005.
- [47] C. Wang, R. S. Swerdloff, R. Iranmanesh et al., "Testosterone gel improves sexual function, mood, muscle strength and body composition in hypogonadal men," *The Journal of Clinical Endocrinology & Metabolism*, vol. 85, no. 8, pp. 2839–2853, 2000.
- [48] <https://www.diabetes.org.uk/Documents/Reports/State-of-the-Nation-2012.pdf>.
- [49] T. H. Jones, "A placebo controlled study on the effects of transdermal testosterone gel in hypogonadal men with type ii diabetes or metabolic syndrome in diabetic control and insulin sensitivity: the TIMES 2 study," *Diabetes Care*, vol. 34, pp. 828–837, 2011.
- [50] D. Kapoor, E. Goodwin, K. S. Channer, and T. H. Jones, "Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes," *European Journal of Endocrinology*, vol. 154, no. 6, pp. 899–906, 2006.
- [51] M. I. Naharci, M. Pinar, E. Bolu, and A. Olgun, "Effect of testosterone on insulin sensitivity in men with idiopathic hypogonadotropic hypogonadism," *Endocrine Practice*, vol. 13, no. 6, pp. 629–635, 2007.
- [52] M. A. Boyanov, Z. Boneva, and V. G. Christov, "Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency," *Aging Male*, vol. 6, no. 1, pp. 1–7, 2003.
- [53] G. Hackett, N. Cole, M. Bhartia et al., "The response to testosterone undecanoate in men with type 2 diabetes is dependent on achieving threshold serum levels (the BLAST study)," *International Journal of Clinical Practice*, vol. 68, no. 2, pp. 203–215, 2014.
- [54] G. Hackett, N. Cole, M. Bhartia, P. Wilkinson, J. Raju, and P. Wilkinson, "Testosterone replacement therapy improves metabolic parameters in hypogonadal men with type 2 diabetes but not in men with coexisting depression: the BLAST study," *The Journal of Sexual Medicine*, 2013.
- [55] M. Shores, N. L. Smith, C. W. Forsberg, and B. D. Anawalt, "Marsumoto AM Testosterone treatment and mortality in men with low testosterone," *The Journal of Clinical Endocrinology & Metabolism*, vol. 97, no. 6, 2012.
- [56] L. Morganuv, I. Denisola, T. Rohzkova et al., "Androgen deficit and its treatment in stroke male patients with type II diabetes," *Zhurnal Nevrologii i Psikhiiatrii Imeni S.S. Korsakova*, vol. 111, no. 8, part 2, pp. 21–24, 2011.
- [57] R. Vigen, C. I. O'Donnell, A. E. Baron et al., "Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels," *The Journal of the American Medical Association*, vol. 310, no. 17, pp. 1829–1836, 2013.
- [58] A. Nehra, G. Jackson, M. Miner et al., "The Princeton III consensus recommendations for the management of erectile dysfunction and cardiovascular disease," *Mayo Clinic Proceedings*, vol. 8, pp. 766–778, 2013.
- [59] A. R. Cappola, "Testosterone therapy and risk of cardiovascular disease in men," *The Journal of the American Medical Association*, vol. 310, no. 17, pp. 1805–1806, 2013.
- [60] L. Xu, G. Freeman, B. J. Cowling, and C. M. Schooling, "Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials," *BMC Medicine*, vol. 11, article 108, 2013.
- [61] O. M. Calof, A. B. Singh, M. L. Lee et al., "Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials," *Journals of Gerontology A*, vol. 60, no. 11, pp. 1451–1457, 2005.
- [62] J. K. Parsons, "Benign prostatic hyperplasia and male lower urinary tract symptoms: epidemiology and risk factors," *Current Bladder Dysfunction Reports*, vol. 5, pp. 212–218, 2010.
- [63] D. J. Yassin, Y. El Douaihy, A. A. Yassin, J. Kashanian, R. Shabsigh, and J. Hammerer, "Lower urinary tract symptoms improve with testosterone replacement therapy in men with late-onset hypogonadism: 5-year prospective, observational and longitudinal registry study," *World Journal of Urology*, 2013.
- [64] D. Francomano, A. Ilacqua, R. Bruzziches, A. Lenzi, and A. Aversa, "Effects of 5-year treatment with testosterone undecanoate on lower urinary tract symptoms in obese men with hypogonadism and metabolic syndrome," *Urology*, vol. 83, no. 1, pp. 167–174, 2014.

- [65] I. Eardley, "Optimisation of PDE5 inhibitor therapy in men with erectile dysfunction: converting "non-responders" into 'responders,'" *European Urology*, vol. 50, no. 1, pp. 31–33, 2006.
- [66] L. S. Marks, N. A. Mazer, E. Mostaghel et al., "Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial," *Journal of the American Medical Association*, vol. 296, no. 19, pp. 2351–2361, 2006.
- [67] E. García-Cruz, M. Piqueras, M. J. Ribal et al., "Low testosterone level predicts prostate cancer in re-biopsy in patients with high grade prostatic intraepithelial neoplasia," *BJU International*, vol. 110, no. 6, part B, pp. E199–E202, 2012.
- [68] N. L. Keating, A. J. O'Malley, S. J. Freedland, and M. R. Smith, "Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer," *Journal of the National Cancer Institute*, vol. 102, no. 1, pp. 39–46, 2010.
- [69] G. Hackett, N. Cole, M. Bhartia, D. Kennedy, J. Raju, and P. Wilkinson, "Testosterone replacement therapy with long-acting testosterone undecanoate improves sexual function and quality-of-life parameters vs. placebo in a population of men with type 2 diabetes," *The Journal of Sexual Medicine*, vol. 10, no. 6, pp. 1612–1617, 2013.
- [70] A. M. Isidori, E. Giannetta, D. Gianfrilli et al., "Effects of testosterone on sexual function in men: results of a meta-analysis," *Clinical Endocrinology*, vol. 63, no. 4, pp. 381–394, 2005.
- [71] P. Home, J. Mant, J. Diaz, and C. Turner, "Management of type 2 diabetes: updated NICE guidance," *British Medical Journal*, vol. 336, no. 7656, pp. 1306–1308, 2008.
- [72] G. Hackett, G. Jackson, M. Kirby, and K. Wylie, "Evidence based medicine inevitably increase testosterone prescribing," *British Medical Journal*, vol. 345, Article ID e6167, 2012.



## Review Article

# Erectile Dysfunction in the Elderly: An Old Widespread Issue with Novel Treatment Perspectives

**Pietro Gareri,<sup>1</sup> Alberto Castagna,<sup>2</sup> Davide Francomano,<sup>3</sup>  
Gregorio Cermignani,<sup>4,5</sup> and Pasquale De Fazio<sup>4,5</sup>**

<sup>1</sup> Elderly Health Care, ASP Catanzaro, Via Spasari, 3, 88100 Catanzaro, Italy

<sup>2</sup> Geriatrician AUSL Modena, 41120 Modena, Italy

<sup>3</sup> Department of Medical Pathophysiology, "Sapienza" University of Rome, 00198 Rome, Italy

<sup>4</sup> Department of Science of Health, School of Medicine, University "Magna Græcia" of Catanzaro, 88100 Catanzaro, Italy

<sup>5</sup> Psychiatry Unit, "Mater Domini" University Hospital, 88100 Catanzaro, Italy

Correspondence should be addressed to Pietro Gareri; [pietro.gareri@alice.it](mailto:pietro.gareri@alice.it) and Alberto Castagna; [albertocastagna@tiscali.it](mailto:albertocastagna@tiscali.it)

Received 17 November 2013; Revised 6 January 2014; Accepted 7 January 2014; Published 17 March 2014

Academic Editor: Antonio Aversa

Copyright © 2014 Pietro Gareri et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Erectile dysfunction (ED) is one of the most common chronic diseases affecting men and its prevalence increases with aging. It is also the most frequently diagnosed sexual dysfunction in the older male population. A number of different diseases potentially worsening sexual function may occur in elderly people, together with polypharmacy. Related causes of ED are variable and can include arterial, neurogenic, hormonal, cavernosal, iatrogenic, and psychogenic causes. The aim of the present review was to examine the main aspects of erectile dysfunction going through epidemiology and pathophysiology and revise most of ED in elderly disabled men and in those affected with psychiatric disorders. Lastly we tried to focus on the main aspects of nonpharmacological and pharmacological treatments of ED and the recreational use in the elderly. Phosphodiesterase-5 inhibitors (PDE5-I) are commonly used for on-demand or chronic treatment of ED. It is widely known that PDE5-I have lower response rates in older men than in younger patients, but they have the advantages of ease of use and excellent safety profile, also in the elderly. The old and new PDE5-I as well as the alternative treatments for ED are extensively discussed.

## 1. Introduction

Erectile dysfunction (ED) is one of the most common chronic diseases affecting men and its prevalence increases with aging. It is also the most frequently diagnosed sexual dysfunction in the older male population [1]. ED is defined as the inability of a man to attain and maintain an adequate erection for satisfactory sexual intercourse. It has become an issue only in the late years, because before the 20th century individuals often did not live beyond the reproductive years. Furthermore, elderly men are often affected with several diseases, leading to polypharmacy; many drugs potentially worsen sexual function [2]. This also means that a careful assessment of potential drug-drug interactions is requested [2]. Related causes of ED are variable and can include arterial, neurogenic, hormonal, cavernosal, iatrogenic, and psychogenic causes [3].

It is now widely accepted that ED is predominantly due to underlying vascular causes, particularly atherosclerosis [4].

The aim of the present review was to examine the main aspects of erectile dysfunction going through epidemiology and pathophysiology and revise most of ED in elderly disabled men and in those affected with psychiatric disorders. Lastly we tried to focus the main aspects of treatment of ED and the recreational use in the elderly. In fact an active sexual life is perfectly in agreement with the geriatrics motto that doctors should help patients to add the life in their years and not the years in their life. An extensive Medline search was made using the keywords: elderly, comorbidities, erectile dysfunction, epidemiology, pathophysiology, endothelial dysfunction, phosphodiesterase-5 inhibitors, and polypharmacy. Due to the great amount of studies on this field, we chose only the most recent articles.

## 2. Epidemiology

In a large US study, the proportion of sexually active males declined from 83.7% in the age group 57–64 years to 38.5% in the age group 75–85 years [5]. All epidemiologic studies clearly show an increasing age-related prevalence and severity of ED. Data from the Massachusetts Male Aging Study documented a tripling of the overall probability of complete ED from 5% in men aged 40 years to 15% in men aged 70 years [6]. In the European Male Aging Study (EMAS), performed in eight European centers for the investigation of ED in men aged 40–79 years old, the prevalence of ED was higher in the old age groups, peaking in men 70 years old and older [7]. Some studies have pointed out that normal erectile function is not a prerequisite to remain sexually active [7–9]. Notwithstanding sexual problems are frequent among older adults, they are infrequently discussed with physicians [9]. Asking about sexual health remains difficult or embarrassing for many primary care physicians and at the same time many patients find that raising sexual issues with their doctor is difficult.

However, after the age of 60 years, the ED rate increases independently of comorbidities such as coronary artery disease, diabetes, and hypertension [10]. Furthermore, elderly men are often affected with several diseases and take a lot of drugs, many of which are potentially worsening sexual function. On the other hand, preserving a good sexuality in both old men and women is remarkable for trying to improve their quality of life.

ED is frequently found in the elderly because it is associated with the same underlying risk factors as vascular disease and includes hypertension, diabetes mellitus (DM), hyperlipidemia, smoking, and obesity which are common during aging. Some evidence shows that ED can be greatly improved not only by some drugs such as phosphodiesterase-inhibitors (PDE5-I), but also by treating the risk factors directly [11]. These include cessation of smoking, correction of hyperlipidemia, and amelioration of obesity through weight loss. In fact, all of them result in amelioration of endothelial health [11]. There is a close relationship between ED, aging, and endothelial dysfunction (EDys). Minor risk factors such as inflammation, hypoxia, oxidative stress, and hyperhomocysteinemia are also related to ED and EDys. ED problems due to organic causes comprise up to 80% of cases, while vascular disease is the most common pathophysiology of ED [12]. Data suggest that ED may be an early manifestation of endothelial dysfunction (EDys) in the presence or absence of cardiovascular risk factors (CRF) [13]. Therefore, men with ED may be at increased risk for cardiovascular adverse events and ED may be considered as a sentinel symptom in patients with occult cardiovascular disease (CVD) [14].

## 3. Pathophysiology

ED in aging males is the result of various factors which exert negative effects on multiple levels in erectile biology [15].

First, in the aging male, the vascular supply to the penis is compromised. In humans, postmortem studies have revealed

that aging is often associated with increasing degrees of atherosclerotic vascular alterations in the arterial bed of the penis [16].

Second, the relative proportion of  $\alpha_1$ -adrenergic receptor subtypes is modulated by aging in arteries. This means that a lot of age-related changes are found in the human prostatic, bladder, and erectile tissue [17]. Importantly, phenylephrine appears to be less effective in inducing contractions of vascular smooth muscle strips *in vitro* and this is significantly greater for those isolated from the corpus cavernosum of older (>60 years) men with ED than for those isolated from younger (<60 years) men with ED [18]. Another remarkable factor closely contributing to impaired vasodilation in the corpus cavernosum and the penile arterial supply of the older man is endothelial dysfunction. In fact, erectile function is dependent on nitric oxide (NO) production by penile endothelium and thus ED is associated with reduced plasma NO levels [11]. Deficiency of endothelial-derived NO is also believed to be the primary defect that links insulin resistance and EDys [11]. Clinical and biochemical markers of EDys include (1) reduced expression and activity of endothelial nitric oxide synthase (eNOS), reduced synthesis of NO, and increased production of the asymmetric dimethylarginine (ADMA), a competitive, endogenous inhibitor of eNOS; (2) increased production of free radicals of inflammatory cytokines such as interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and increased endothelial apoptosis [11, 19]. In fact, endothelial dysfunction in aging has been attributed to the presence of NO scavengers in the corpus cavernosum, the most obvious candidates being superoxide anions, whose production is augmented in aging endothelial cells [20]. This causative link is further strengthened by the fact that use of inhibitors of cyclooxygenase and vitamin C, which are both powerful antioxidants, can prevent age-related endothelium-dependent vasodilation decrease in humans [20].

Furthermore, the presence of reactive oxygen species (ROS) is able to cause an inflammatory state of the endothelium resulting in predisposition to atherosclerosis, thereby further reducing blood flow to the erectile tissue. In the aged endothelium, this further results in the inactivation of endothelium NO synthase (eNOS) through a decrease in phosphorylation of its positive regulatory site and an increase in phosphorylation of its negative regulatory site [21]. Animal models represented by aged rats have clearly shown that a decreased activity of eNOS is also responsible for the increase in apoptosis of the endothelium. Therefore, in summary, dysfunctional penile endothelium = reduction in NO release = increased vascular and sinusoidal smooth muscle tone [15].

Third, the percentage of smooth muscle steadily decreases with aging [11, 22]. In fact, corpora cavernosa of aged men present excessive deposition of collagen fibers which results in corporal fibrosis. These changes are similar to those ones observed in the media of the penile arteries [23]. It has been postulated that these histologic changes in the aged corpora, as well as endothelial dysfunction, are caused by increased oxidative stress and/or other profibrotic factors that stimulate smooth muscle apoptosis and collagen deposition [15, 16].

These alterations result in an impaired expandability of the erectile tissue, and therefore the mechanism by which the expanding sinusoids compress the emissary veins against the tunica albuginea becomes defective. This leads to corporeal venous leakage which typically presents as the inability to maintain an erection as it is frequently seen in the aged male.

Finally, another factor contributing to the above described changes in smooth muscle and collagen content of the corpus cavernosum is androgen deficiency. In fact, this can lead to a marked increase in connective tissue deposition. Moreover, venoocclusive dysfunction might be due to an increase in fat containing cells in the subtunical region of penile tissue sections, as shown from orchiectomized animals [24]. Overall, the presence of androgens regulates the normal morphology and function of the cavernous nerves and keeps the endothelium in a healthy condition. A low testosterone (T) level is positively associated with the presence and severity of atherosclerosis and a reduction in plasma T might contribute to increased arterial stiffness, which in turn has been associated with increased cardiovascular risk and mortality [25]. The Rotterdam study, a population-based cohort study, showed that low levels of endogenous androgens are associated with increased likelihood of atherosclerosis in elderly men [26]. Low T was linked to cardiovascular mortality, morbidity in men of varying age, and cardiovascular risk factors (CRF) [27]. Men have a higher rate of CVD than women [11]. The possible culprits appear to be T, dihydrotestosterone (DHT), dehydroepiandrosterone (DHEAS), and their metabolites [11]. However, randomized controlled trials (RCT) have clearly documented that DHEAS is not useful for ED elderly subjects [28]. The role of androgens in determining vasodilation has been recently investigated. T may activate the endothelium and stimulate the NO-cyclic guanosine monophosphate and/or the hyperpolarization-mediated vascular relaxation pathway and may thus add potential beneficial effects on coronary artery atherosclerosis. Additional endothelium-independent effects of T may involve inhibition of the signaling mechanism of vascular smooth muscle contraction, such as intracellular concentration  $[Ca^{2+}]$  and protein kinase C [11, 29]. However, the final role of T has still to be recognized, since three different meta-analyses have documented an association between low T and CV mortality but not with CV events [30–32]. In particular, low T has been linked to increased blood pressure, dyslipidemia, atherosclerosis, arrhythmias, thrombosis, endothelial dysfunction, and impaired left ventricular function. On the other hand, treatments with T to restore “normal concentrations” have so far neither been proven to be beneficial with respect to cardiovascular disease nor have definitely shown specific adverse cardiovascular effects [30]. Recently, Isidori et al. [33] reported that molecular and clinical evidence supports the use of testosterone replacement therapy (TRT) in hypogonadal patients with ED, although the benefit-risk ratio is uncertain in advanced age. The development of a pathophysiology-oriented algorithm designed to avoid inappropriate treatments and support whether to start with TRT, PDE5-I only, or both is requested, in order to improve diagnosis and individualize a correct management

[33]. On the same line, it has been shown that, in late-onset hypogonadism (LOH), TRT is able to improve central obesity in patients affected with metabolic syndrome (MetS) and glycometabolic control in patients with MetS and type-2 diabetes mellitus as well as to increase lean body mass, along with insulin resistance and peripheral oxygenation [34, 35]. Importantly, the increased waist circumference is the major determinant of MetS-associated hypogonadism, whereas androgen deprivation increases abdominal adiposity. Moreover, in cross-sectional studies longitudinal evidence has shown that low T is associated with a higher risk of subsequent development of MetS, although the reverse condition is also possible [34, 35]. In summary, subjects with MetS have lower levels of total T (TT) (about 3 nmol/L), and hypogonadism is more evident in subjects with, than in those without, ED. It has not yet been clarified which are the possible factors in MetS responsible for the low T [34]. However, it should be recognized that the number of studies on benefits of T supplementation is too limited to draw final conclusions [35]. The confusion still continues, due to the recent results of a retrospective national cohort study of men with low testosterone levels ( $<300$  ng/dL) who underwent coronary angiography in the Veterans Affairs system between 2005 and 2011. The aim was to assess the association between testosterone therapy and all-cause mortality, myocardial infarction, or stroke. Of the 8709 men with a total testosterone level lower than 300 ng/dL, 1223 patients started testosterone therapy after a median of 531 days following coronary angiography. The absolute rate of events was 19.9% in the no testosterone therapy group versus 25.7% in the testosterone therapy group, with an absolute risk difference of 5.8% (95% CI,  $-1.4\%$  to  $13.1\%$ ) at 3 years after coronary angiography. Therefore, the use of testosterone therapy was associated with increased risk of adverse outcomes. No significant difference in the effect size of testosterone therapy among those with and without coronary artery disease (test for interaction,  $P = 0.41$ ) was reported [36].

#### 4. ED in Elderly Disabled Men

A number of related heart conditions are common causes of ED, including hypertension, dyslipidemia, atherosclerosis, heart disease and, among metabolic diseases, diabetes. Stroke, Parkinson's disease, and multiple sclerosis are other potential causes of ED. Some types of physical trauma and injuries, especially those affecting the pelvic area or spinal cord, may cause nerve damage leading to erectile dysfunction. Orthopedic surgery, fistula surgery, and surgeries on prostate, colon, or rectal cancer can also significantly contribute to the decrease of sexual function. All of these conditions are very frequent in elderly patients; comorbidities and polytreatment are a hard challenge in elderly people health management. Furthermore, in the elderly, we have to distinguish the effects of a number of different diseases and/or their treatments on erectile function and the effects which the same diseases can have on functional independence. In fact, sexual function requires abilities in movements which can be hampered. In

the following section we will try to examine in detail some different diseases potentially able to interfere with sexual function in the elderly.

**4.1. Diabetes.** Data collected from 1,195 randomly selected, community-dwelling men as part of the Florey Adelaide Male Ageing Study showed that with increasing age diabetes appears to be independently associated with moderate-to-severe ED [37]. In particular, several studies have shown that lower levels of glycated hemoglobin and therefore a good glycemic control are able to reduce the prevalence of ED and its severity [38–40]. In any case, phosphodiesterase-5 inhibitors (PDE5-I) improve ED in diabetic men [40, 41].

**4.2. Hypertension.** The prevalence of ED varies between 15 and 25% in people affected with hypertension [42]; hypertension is very common in the elderly and is a well-known risk factor for cardiovascular events. ED is reported more than twice as often in men with systolic blood pressure (SBP) > 140 mmHg than in men with SBP < 140 mmHg. Importantly, pulse pressure, that is, the difference between systolic and diastolic blood pressure, an index of arterial stiffness, was suggested to predict incident major cardiovascular events in patients affected with ED [43, 44]. In a consecutive series of 1,093 (mean age  $52.1 \pm 13.0$  years) male patients with ED and without a previous history of hypertension or not taking any antihypertensive drugs it was shown that elevated PP is associated with arteriogenic ED and male hypogonadism [44]. Furthermore, the prevalence of overt hypogonadism (calculated free testosterone < 180 pmol/L or free testosterone < 37 pmol/L) increased as a function of PP quartiles (17.1% versus 39.7%, and 30.8% versus 58.6% for the first versus fourth quartile, respectively, for calculated free testosterone and free testosterone; all  $P < 0.0001$  for trend) [44].

**4.3. Cardiovascular Diseases.** ED may predict the onset of cardiovascular events from 2 to 5 years earlier; both conditions share the same pathogenetic mechanism, which is endothelial dysfunction [43]. Congestive heart failure (CHF) is another frequent disease in elderly patients potentially leading to ED. A sufficient control of symptoms is able to improve sexual dysfunction; if this approach does not work, PDE5-I are the first-line therapy [45]. They can also indirectly improve depressive symptoms and quality of life and can be used in CHF patients classified as New York Heart Association (NYHA) II and III. Of course, sexual activity is contraindicated in patients classified as NYHA IV.

ED ranges from 42% to 75% in patients affected with coronary artery disease and PDE5-I can also be safe and effective in these men [46].

**4.4. Spinal Cord Injuries.** Spinal cord injuries can be present in elderly men as a result of juvenile or recent trauma; PDE5-I are also safe and effective options for these men.

**4.5. Stroke.** The sexual desire, erectile, and ejaculatory functions are impaired after stroke. A lack of sexual desire is the major cause of an absence of sexual intercourse. The

specific locations of the stroke lesions, such as the left basal ganglia and right cerebellum, might be associated with sexual desire and ejaculation disorder, respectively [47]. In a survey on 109 stroke patients (mean age  $64.93 \pm 8.81$  years) the lack of sexual desire was the largest cause (59.4%) of an absence of sexual intercourse [47]. Of course, the complete or partial disabilities in moving are a further obstacle other than sexual dysfunction *per se*, when elderly patients are affected with spinal cord injuries or stroke. This on turn can lead to depression, feelings of inutility, and impairment of the ability to recover.

**4.6. Multiple Sclerosis.** Sexual dysfunction (SD) is also a frequent problem for multiple sclerosis patients and appears to be associated with gender. In fact women report more SD than men. Overall, this is another disease where the emotional dimension of SD is related to disability in the aged men [48].

**4.7. Parkinson's Disease.** SD is common and often underrecognized in patients with Parkinson's disease (PD), playing a major role in the deterioration of quality of life of patients and their partners. Loss of desire and dissatisfaction with their sexual life are encountered in both genders and worsen concomitantly to the progression of Parkinsonian symptoms. Hypersexuality, erectile dysfunction, and problems with ejaculation are found in male patients.

Bladder dysfunction (urinary urgency/frequency), bowel dysfunction (constipation), and sexual dysfunction (erectile dysfunction) (also called "pelvic organ" dysfunctions) are common nonmotor disorders in PD [49]. Hypothalamic dysfunction is mostly responsible for the sexual dysfunction (decrease in libido and erection) in PD, via altered dopamine-oxytocin pathways, which normally promote libido and erection. The pathophysiology of the pelvic organ dysfunction in PD differs from that in multiple system atrophy [49]. A relationship among ED, perception of patients' sexual life, and depression is often found in elderly patients affected with PD [50]. Optimal dopaminergic treatment should facilitate sexual encounters of the couple and appropriate counselling diminishes some of the problems (i.e., reluctance to engage in sex and problems with ejaculation) [51].

**4.8. Dementia.** At present ED is often underrecognized and undertreated in dementia and few data are available. Loss of desire can be present in different forms of dementia, whereas hypersexuality can be found in the early-to-moderate stages of frontal dementia. In particular, hypersexual behavior may be a particular feature of behavioral variant frontotemporal dementia (bvFTD), which affects ventromedial frontal and adjacent anterior temporal regions specialized in interpersonal behavior. A recent study reviewed 47 patients with bvFTD compared to 58 patients with Alzheimer's disease for the presence of heightened sexual activity to the point of distress to caregivers and others. Hypersexual behavior occurred in 6 (13%) bvFTD patients compared to none of the AD patients [52]. One patient, with early and predominant right anterior temporal involvement,



was easily aroused by slight stimuli, such as touching her palms [52].

## 5. ED in Elderly Men Affected with Psychiatric Disorders

ED is often the cause of depressive disorders in elderly people [28]. Andropause, ED, and psychiatric disorders often share specific physical and psychological symptoms which complicate the clinical management of elderly men. In particular, anxiety disorders and depression are more frequently linked to sexual dysfunction.

**5.1. Mood Disorders.** Mood disorders may enhance the risk of ED in elderly people. Depressive symptoms are related to sexual dysfunction more frequently than anxiety symptoms. However, according to some authors, ED in elderly psychiatric patients seems to be the expression of androgenic deficit rather than psychiatric symptoms *per se* [53].

ED, the perception of the quality of patient's sexual intercourse and his subjective satisfaction, becomes worse with increasing depressive symptoms. Moreover, in elderly psychiatric patients, symptoms related to hypogonadism have a relationship with ED and both of them can influence sexual performance [54].

Recently some biopsychosocial risk factors have been considered to be responsible for ED. Erectile function worsens with increasing age and fat abdominal mass. Furthermore, the lack of a regular partner, alcohol abuse, and last but not least the presence of depressive and anxiety symptoms worsens its severity [37]. A sample of 203 subjects aged between 45 and 74 years old was assessed through the administration of International Index of Erectile Function 5 (IIEF-5) and Geriatric Depression Scale (GDS), in order to define the presence of a relationship between depressive symptoms and ED severity. ED was shown to be closely linked to depressive symptoms, together with some factors such as life style, smoking, and alcohol [55].

Hypogonadism, ED, and premature ejaculation show significant correlations with physical and mental health in men and in particular with quality of life, metabolic syndrome, cardiovascular diseases, and depressive symptoms [56].

Definitely concomitant ED and depression are really very high; the temporal relationship between these disorders may also be inverted. In other words, ED may be the cause or the consequence of depressive disorder. Men with severe depression have a twofold probability for ED compared to nondepressed subjects [57]. Depression as the consequence of ED was assessed in a recent Canadian study together with the effect of sildenafil citrate, PDE5-I, in patients with untreated depressive symptoms [58].

On the other hand, pharmacological treatment of depressive disorder, in particular with selective serotonin reuptake inhibitors (SSRI), may represent another cause of ED and negatively influence patient's quality of life, his self-esteem, and the relationship with his partner [59].

**5.2. Bipolar Disorder.** ED in elderly psychiatric patients is not only found in depressive and anxiety disorders, but also can represent the complication of antipsychotic treatment in long lasting treatment of bipolar disorder.

ED was found in 42% out of patients affected with bipolar disorder remitted or clinically stabilized by the use of antipsychotics. First generation of antipsychotics is more frequently involved in sexual performance worsening, compared to second-generation drugs [60].

Lastly, ED may represent a frequent symptom in somatization disorders, especially in men of over 45 years old [61].

## 6. Treatment Strategies in ED and Novel Perspectives

Treatment strategies include nonpharmacological and pharmacological procedures. Nonpharmacological treatment includes counseling, life style changes, and medication changes, because a lot of drugs taken by old people can result in negative interference on sexual function.

**6.1. Counseling.** An open communication with the patient and his partner is the first step to set realistic outcome goals. Patient and his partner need to be educated about the anatomy and physiology of sexual function and the right understanding of the pathophysiology of ED. Current oral pharmacological treatments for ED do not "cure" ED but can generally improve erectile function in patients without important comorbidities or underlying disorders such as diabetes or after radical prostatectomy. Furthermore, due to comorbidities and multiple pathophysiologic changes in the old patient's penis, vasculature, and nervous system, a fully rigid erection will be hard to be accomplished with the use of the oral pharmacotherapy alone [15]. Therefore, it is remarkable to provide full information to the couple about the possible pharmacological and mechanical treatment options. The choice of treatment should be made by the patient and his partner supported by the physician, who ideally does not assume an authoritative role in this decision process [62]. In order to preserve mental health and referral to a sexologist or relationship therapist for more extensive counseling, alternative forms of intimacy that do not rely on penetrative sexual intercourse but are as well satisfactory might be helpful [63]. Furthermore, in some patients with psychogenic or mixed psychogenic-organic ED, specialized psychosexual therapy may help relieve anxiety and remove unrealistic expectations associated with medical or surgical therapy [62].

**6.2. Life Style Changes.** Obesity, sedentary life and smoke are related to a higher incidence of ED. First of all, at any age, patients should be educated about the beneficial effects of weight loss, increasing exercise, and quitting smoking on erectile function. In particular, a meta-analysis of 24 studies showed that weight loss is associated with an increase in both bound and unbound testosterone levels. Overall, both a low-calorie diet and bariatric surgery are associated with a significant ( $P < 0.0001$ ) increase in plasma

sex hormone-binding globulin-bound and -unbound testosterone levels (total testosterone, TT), with bariatric surgery being more effective in comparison with the low-calorie diet (TT increase: 8.73 (6.51–10.95) versus 2.87 (1.68–4.07) for bariatric surgery and the low-calorie diet, respectively; both  $P < 0.0001$  versus baseline) [64]. The normalization of sex hormones induced by body weight loss might be a mechanism contributing to the beneficial effects of surgery in morbid obesity. Moreover, androgen rise seems to be greater in those patients who lose more weight as well as in younger, nondiabetic subjects with a greater degree of obesity [64].

Another systematic review and meta-analysis of randomized controlled trials with a follow-up of at least six weeks evaluated the effect of lifestyle interventions and pharmacotherapy for cardiovascular risk factors on the severity of ED [65]. Lifestyle modifications and pharmacotherapy for CV risk factors were associated with statistically significant improvement in sexual function (IIEF-5 score).

Furthermore, the addition of a statin to men suffering from ED and hypercholesterolemia has shown beneficial effects on erectile function [66].

**6.3. Medication Changes.** A number of different medications can contribute to the cause or worsening of ED such as diuretics, particularly thiazides, and central antihypertensives such as  $\alpha$ -adrenergic antagonists and nonspecific  $\alpha$ -antagonists. Tricyclic antidepressants have been linked to both loss of libido up to 70% and ED in 1.7–6.4% [67, 68]. Furthermore, they increase ejaculatory latency time and are currently even prescribed for the treatment of premature ejaculation.

In a study on 344 patients treated with selective serotonin reuptake inhibitors [68], paroxetine provoked more delay of orgasm or ejaculation and more impotence than fluvoxamine, fluoxetine, and sertraline (chi square,  $P < 0.05$ ). Only 24.5% of the patients had a good tolerance of their sexual dysfunction [68]. Twelve male patients who suffered from premature ejaculation before the treatment reported delayed ejaculation, but their sexual satisfaction clearly improved. A positive correlation was shown with dosage and treatment interruption.

Androgen blockers used for treatment of prostate cancer can worsen erectile function and libido. Antihistamines, nonsteroidal anti-inflammatory drugs, antiarrhythmics, and drugs for the treatment of Parkinson's disease have been linked to ED.

Importantly, we underline the role of geriatrician in changing drugs potentially causing sexual dysfunction or at least changing its dosage. Another crucial factor is to know the drug interactions potentially able to increase the effects of drugs influencing erectile function [2]. Geriatrician ought to interrupt patient's nonessential drugs with negative impact on erectile function and possibly replace essential drugs by their counterparts or with drugs from another family with less impact on erectile function.

As a matter of fact, treatment of hypertension with calcium channel blockers and angiotensin converting enzyme inhibitors may reverse ED in some patients; switching to an  $\alpha_1$ -specific agonist, such as doxazosin, preserves erectile

function [15]. Angiotensin receptor blockers such as candesartan, losartan, and valsartan seem to have beneficial effects on erectile function [15].

Alcohol and other abused drugs such as amphetamines, cocaine, marijuana, and opiates have been linked to ED, and the patient should be counseled about these facts [15, 62]. A list of the drugs potentially causing or worsening sexual function are shown as follows:

- (i) abused drugs (amphetamines, opiates, cocaine, marijuana, nicotine, and heroin);
- (ii) alcohol;
- (iii) antiarrhythmics;
- (iv) antidepressants (tricyclics, SSRI, and MAO-inhibitors);
- (v) antihistamines (dimenhydrinate, diphenhydramine, and promethazine);
- (vi) antipsychotics: butyrophenones (haloperidol) and phenothiazines (promazine);
- (vii) barbiturates;
- (viii) benzodiazepines;
- (ix)  $\beta$ -blockers (dose-dependent; propranolol, atenolol, and carvedilol in decreasing order; nebivolol seems to have beneficial effects);
- (x) central antihypertensives;
- (xi) 5 $\alpha$ -reductase inhibitors;
- (xii) digoxin;
- (xiii) diuretics (thiazide diuretics);
- (xiv) drugs for Parkinson's disease;
- (xv) fibrates (clofibrate, gemfibrozil);
- (xvi) H<sub>2</sub>-blockers (cimetidine, ranitidine);
- (xvii) Lithium;
- (xviii) Muscle relaxers;
- (xix) Nonsteroidal anti-inflammatory drugs.

**6.4. Pharmacological Treatment.** Pharmacological treatment of ED includes a number of drugs; phosphodiesterase-5 inhibitors (PDE5-I), yohimbine, an  $\alpha_2$ -antagonist, PGE1, and papaverine. Intraurethral PGE1 (MUSE), vacuum constriction device, and surgery (penile prosthesis) are other possible therapeutic opportunities.

**6.4.1. Use of Phosphodiesterase-5 Inhibitors (PDE5-I) in Elderly Men.** The advent of safe and effective oral treatment of ED by PDE5-I has brought a great attention to the disease. In fact, in the elderly, PDE5-I are commonly used for on-demand or chronic treatment of ED and are one of the first-line treatments for patients complaining of ED [69]. As above mentioned, owing to the great number of drugs often taken by geriatric population, a careful assessment of potential interactions between PDE5-I and other drugs is requested. At present, four PDE5-I (sildenafil, vardenafil,

tadalafil, and avanafil) are approved worldwide, and two agents (udenafil and mirodenafil) are approved only in Korea [2].

It is widely known that PDE5-I have lower response rates in older men than in younger patients [70], but they have the advantages of ease of use and excellent safety profile, also in the elderly [15, 71]. They are nonhydrolysable analogs of cGMP acting as intracellular signal amplifiers. They work by slowing the degradation of cGMP by PDE5, leading to subsequent penile smooth muscle relaxation. The endogenous nitric oxide (NO), the release of which is evoked by sexual stimulation and is a neurologically mediated event, is decreased during aging. It is further diminished by comorbidities such as hypogonadism, diabetes, and atherosclerosis [70].

All PDE5-I appear to be roughly equivalent in efficacy, with some substantial differences in absorption after oral administration and duration of effect. Vardenafil orodispersible preparation is reported to have the fastest onset of action, that is, as fast as 15 minutes, while tadalafil is reported to have the longer duration of action, that is, as long as 36 hours (more details are reported below) [2]. Sildenafil and vardenafil (film-coated tablets) have only a limited oral bioactivity (about 40% and 15%, resp.) because of extensive presystemic metabolism in the gut wall and liver via CYP3A4 and/or CYP3A5 pathways [40]. This aspect should be carefully considered when planning an ED treatment because it can influence the window of opportunity available for sexual activity [40]. Moreover, a high-fat meal (about 910 Kcal, 57% of which from fat) has no significant effect on the rate and extent of absorption of tadalafil but decreases the rate of absorption for sildenafil and vardenafil, possibly affecting the onset of effectiveness [71, 72].

Recently avanafil, a new PDE5-I, was approved for marketing in Europe; this drug has shown to have advantageous properties, that is, a fast effect, about 35 min following its administration, and low side effects related to the combined treatment with nitrates and potential opportunities in elderly patients too (such as in patients who underwent a radical prostatectomy or affected with hyperglycemia or heart diseases). Avanafil has higher selectivity (120-fold) against PDE6 than sildenafil (16-fold) and vardenafil (21-fold) and high selectivity (>10,000-fold) against PDE1 compared with sildenafil (380-fold) and vardenafil (1000-fold); it does not inhibit PDE11 [73].

These drugs sometimes are not efficacious with the first dose, but results are generally improved with repeated dosing. On-demand treatment regimens have shown efficacy rates of 60–70% [74]. Furthermore, as above mentioned, 30–50% out of the patients that initially do not respond to PDE5-I may be converted to responders by counseling the patient and his partner [15]. Usual starting dose is 50 mg for sildenafil and 10 mg for vardenafil and tadalafil; doses may be increased up to 100 mg for sildenafil and 20 mg for vardenafil and tadalafil. Avanafil is available in 50, 100, or 200 mg tablets [73].

The year 2013 marked the 15th anniversary of the introduction of the first commercially available highly selective PDE5-I for ED; it also represents the year in which sildenafil's patent will start to expire throughout the world [2]. Sildenafil

orodispersible tablets (50 mg) will be available in the next days.

Some patients who do not benefit from PDE5-I on-demand treatment may benefit from a daily low-dose administration [74–76]. This can be especially applied to elderly patients, where chronic administration can also work for other conditions frequently reported such as low urinary tract symptoms (LUTS). On the other hand, chronic administration of PDE5-I may improve erectile and endothelial responsiveness of men previously nonresponsive to on-demand regimens [11]. At this purpose, sildenafil may be used in a daily dose of 25 mg [77, 78], tadalafil is available in a daily dose of 2.5 and 5 mg, and vardenafil is available in a daily dose of 2.5 mg in some countries [15]. In a study performed for analyzing the efficacy and safety of sildenafil citrate in the geriatric population, these PDE5-I were found to be an effective agent in elderly men but with a lower efficacy rate especially in men aged >80 years old [79]. In this study 167 patients, mean age  $72 \pm 9$  years old, were divided into three groups: 60–69, 70–79, and  $\geq 80$  years. Overall 54% of men responded to sildenafil, with a mean increase in International Index of Erectile Function (IIEF) domain score of 5.7. The incidence of adverse events (AEs) was similar to that in the general population taking sildenafil; importantly, no difference in AEs was found in the three age groups [79]. Furthermore, in those men affected with ED and late-onset hypogonadism, supplementation with testosterone may enhance the efficacy of PDE5-I [15]. This occurs for two main reasons: first, testosterone keeps the erectile tissue and the supplying nerves in a healthy condition and second it is widely known that testosterone increases the efficacy of PDE5-I by increasing the bioavailable NO in the cavernous smooth muscle [80, 81]. Furthermore, testosterone has been shown to be one of the main modulators of the expression of penile phosphodiesterase type 5 isoenzyme [11].

The main differences in the PDE5-I are in duration of action; tadalafil is able to potentiate sexual spontaneity by its longer half-life. In fact, its half-life is 17–21 h, whereas sildenafil and vardenafil half-lives are 4.6 h and 5 h, respectively. Avanafil presents a mean half-life of 5–10 hours [73].

Recently an orodispersible tablet (ODT) formulation of vardenafil has been developed, which dissolves in the subject's mouth (supralingual formulation) [82]. Vardenafil ODT is very advantageous because it has a 1.21-to-1.44-fold higher bioavailability than the film-coated tablet formulation (as measured by the area under the plasma concentration versus time curve (AUC)), and maximum concentrations in plasma after a single dose ( $C_{max}$ ) are comparable between the two formulations [82]. Therefore, the pharmacokinetics of ODT vardenafil is not equivalent to that of the film-coated tablets, because the ODT formulation provides greater vardenafil systemic exposure [83]. The primary objective of POTENT I (pivotal phase III trial to investigate the efficacy and safety of an orodispersible tablet vardenafil versus placebo in the treatment of men with erectile dysfunction: a fixed-dose, double-blind, randomized, multicenter trial) was to compare the efficacy and safety of on-demand 10 mg vardenafil ODT with placebo after 12 weeks of treatment or last observation carried forward (LOCF) in a general population of men



with ED [82]. Importantly, the POTENT I study included a very large number of subjects aged  $\geq 65$  years (54.8%). 40 centers in Belgium, France, Germany, the Netherlands, Spain, and South Africa were involved in the study. This study demonstrated that 10 mg vardenafil ODT, taken on demand, improved erectile function and was well tolerated in a broad population of men with ED, irrespective of age. Vardenafil ODT definitely offers a more convenient therapeutic option for the treatment of ED, compared with the film-coated tablet formulation.

The POTENT II randomized trial was a double-blind, multicentre, randomized, parallel-group, placebo-controlled study conducted at 35 centres in Australia, Canada, Mexico, and USA. Subjects with ED for at least 6 months were randomized to receive 12 weeks of on-demand treatment with either 10 mg vardenafil ODT or placebo. Importantly, approximately half of the subjects were aged  $\geq 65$  years [84]. Of the 473 men enrolled in the study (51.4% aged  $\geq 65$  years), 331 were included in the intent-to-treat population (vardenafil ODT,  $n = 169$ ; placebo,  $n = 162$ ). Vardenafil ODT therapy was statistically significantly superior to placebo for all primary and secondary efficacy variables ( $P < 0.0001$ ) [84]. Primary variables were International Index of Erectile Function (IIEF-EF) and Sexual Encounter Profile questions 2 (SEP2) and 3 (SEP3). Treatment with 10 mg vardenafil ODT, taken on demand, significantly improved erectile function and was effective and well tolerated. What these studies have added is that, compared with existing film-coated formulations, a more convenient method of taking vardenafil, in particular without the need for water or other liquids, may be absolutely preferable [83].

PDE5-I are also used in ED following nerve-sparing radical prostatectomy and in lower urinary tract symptoms (LUTS).

In a recent study acceptance and discontinuation data were analyzed in 100 consecutive, age-comparable, and preoperatively self-reported potent patients who underwent bilateral nerve-sparing radical prostatectomy (BNSRP) and at the hospital discharge received a PDE5-I treatment [85]. Medical and sexual history was collected on hospital admission and the IIEF was administered every 6 months post-operatively up to the 18-month follow-up. 49 patients freely decided not to start any treatment; 36 patients opted for an as-needed PDE5-I treatment, whereas 15 patients decided to use a daily PDE5-I. At the end of the study roughly 73% of patients who started therapy eventually discontinued it and a treatment effect below expectations was the main reason for stopping it [85].

The Multinational Survey of the Aging Male (MSAM-7) showed that roughly 50% out of the patients affected with moderate-to-severe LUTS present a concurrent ED, especially in those aged over 70 years old [86]. For those high numbers of patients PDE5-I might be a remarkable tool for treating both diseases; among the available drugs, tadalafil seems to be preferred for its well-known long half-life. The mechanism of action of these drugs in LUTS is not quite clear; however, PDE5 is found in prostate, bladder, urethra, and their respective blood vessels. A crucial role

is also played by NO, which is able to mediate urinary function through a number of pathways. However, PDE5-I can potentially improve LUTS by increasing cGMP, which is the final mediator in the NO pathway [87, 88].

Furthermore, the safety profile of the currently available PDE5-I is excellent in the elderly too. No increased rate in myocardial infarction was found in elderly patients receiving these agents compared to expected rate in age-matched populations [70]. Of course, as well as in younger patients, PDE5-I are contraindicated in patients with unstable angina pectoris, recent myocardial infarction, some arrhythmias, and poorly controlled hypertension [15]. Headache, facial and ocular hyperaemia, nasal congestion, and back pain are commonly reported following PDE5-I treatment. Cross reactivity with PDE6 in the retina causes visual blurring [15]. Flushing and dyspepsia are sometimes reported in elderly patients treated with sildenafil and tadalafil [88, 89]. Furthermore, vision loss due to nonarteritic ischemic optic neuropathy was associated with the use of PDE5-I [2]; people of 50 years old or older, affected with hypertension and/or heart disease, diabetes, hypercholesterolemia, and smokers are more usually involved.

Drug-disease interactions and pharmacodynamic interactions are potentially dangerous; therefore, patients who are treated with nitrates or nitrate donors should not take PDE5-I, except for avanafil, which seems to be safer even when used with these drugs concurrently [73]. Past use of nitrates, usually  $>2$  weeks, is not a contraindication but a period superior to 24 hours for short acting PDE5-I (sildenafil and vardenafil) and superior to 48 hours for long-acting tadalafil is strictly recommended before taking nitrates [40]. Short acting PDE5-I such as sildenafil, vardenafil, and avanafil should also be preferred in patients affected with cardiovascular disease [43]. Concurrent treatment of PDE5-I and  $\alpha$ -blockers might result in postural hypotension and needs to be carefully assessed. Precaution is suggested in the use of labetalol and carvedilol, which present mixed  $\alpha$ - and  $\beta$ -blocker activity [66].

However, when doses of 100, 150, and 200 mg of sildenafil (doses in excess of the recommended range) were administered in a group of healthy but young volunteers, the mean maximum decrease in standing systolic blood pressure was  $-10/-7$  mmHg, with the maximum change occurring 3 hours after dosing [90]. None of the PDE5-Is are dangerously associated with QTc prolongation, although vardenafil has a warning for patients at risk for QTc prolongation [90]. However, it has been shown that a large range of vardenafil doses/concentrations (up to 80 mg/day) may produce a small QTc prolongation that is not associated with absolute QT prolongation [91]. This prolongation is similar to that observed with sildenafil and is unlikely to be clinically relevant [92]. On the contrary, vardenafil is not recommended in patients taking type 1A antiarrhythmics (such as quinidine or procainamide) or type 3 antiarrhythmics (amiodarone or sotalol) [91, 93].

Elderly people often take several drugs; when taking PDE5-I, one should be careful to potential pharmacokinetic interactions via cytochromes (CYP) [94]. Sildenafil

TABLE 1: Some examples on potential interactions among PDE5I and other drugs via CYP450.

| Cytochrome | Substrates  | Inhibitors  | Inductors  |
|------------|---|---|--|
| CYP1A2     | <i>PDE5I</i> : sildenafil<br>Antidepressants: tricyclics, fluvoxamine, mirtazapine<br>Antipsychotics: haloperidol, olanzapine, clozapine<br>Methylxantines: caffeine, theophylline<br>Other drugs: R-warfarin, tacrine, paracetamol   | Ciprofloxacin<br>Fluvoxamine  | Barbiturates<br>Carbamazepine<br>Phenytoin<br>Rifampicin<br>Tobacco  |
|            | <i>PDE5I</i> : sildenafil, tadalafil, vardenafil<br>Antidepressants: tricyclics, venlafaxine, citalopram, mirtazapine<br>Benzodiazepines: diazepam, bromazepam<br>Nonbenzodiazepine anxiolytics: buspirone<br>Antipsychotics: haloperidol, clozapine, risperidone, ziprasidone, sertindole, quetiapine, aripiprazole<br>Anticonvulsants: carbamazepine, felbamate, tiagabine<br>Calcium-antagonists: nifedipine, diltiazem, verapamil<br>Other drugs: amiodarone, quinidine, terfenadine, astemizole, macrolides (erythromycin, clarithromycin), tamoxifen, cyclosporine, | Antiarrhythmics: quinidine, amiodarone<br>Antifungal drugs (fluconazole, itraconazole, ketoconazole)<br>Antidepressants: fluvoxamine, fluoxetine, nefazodone<br>Antihistamines: loratadine<br>Antiviral drugs: indinavir, ritonavir<br>Grapefruit juice (at least 250 mL)<br><br>Macrolides: clarithromycin<br>Erythromycin<br>Calcium channel blockers: diltiazem, verapamil<br>Proton pump inhibitors: omeprazole, testosterone | Barbiturates<br>Carbamazepine<br>Felbamate*<br>Hypericum<br>Oxcarbazepine*<br>Phenytoin<br>Rifampicin<br>Topiramate* |

\* refers to the activity of felbamate, oxcarbazepine and topiramate as weak enzymatic inductors.

is mainly metabolized through CYP3A4 and secondarily via CYP2C9. This means that drugs inhibiting or inducing these enzymes may lead to, respectively, an increase or a reduction in plasma concentrations of sildenafil (Table 1) [94]. Concurrent administration of sildenafil and warfarin may potentially lead to an increased risk of bleeding. In fact, *in vitro* studies have also shown that sildenafil is a weak inhibitor of CYPs 1A2, 2C19, 2D6, 2E1, and 3A4. Tadalafil and vardenafil are mainly metabolized by CYP3A4; all the inhibitors of CYP3A4 (ketoconazole, fluconazole, ritonavir, indinavir, amiodarone, erythromycin, fluoxetine, fluvoxamine, omeprazole, and grapefruit juice) increase the area under the concentration curve (AUC) of tadalafil and vardenafil (Table 1). Drugs prolonging QTc interval should be cautiously administered together with vardenafil for the potential risk of further increase in QTc (Table 1) [91, 93].

**6.4.2. Other Pharmacological Treatments for ED.** In the late years a number of herbal and nutritional supplements have been used in the treatment of ED, even if they lack strong evidence, for example, yohimbine, icariin, and ginseng [15]. Yohimbine is a peripherally and central  $\alpha_2$ -blocking agent derived from the bark of an evergreen tree; it is also a mild monoamine oxidase inhibitor (MAOI). It blocks the pre- and postsynaptic  $\alpha_2$  receptors, but in particular the blockade of  $\alpha_2$  receptors facilitates the release of several neurotransmitters in both the central and peripheral nervous system and the corpus cavernosum, such as nitric oxide and norepinephrine [15, 95]. It can be used at dosages of 15 mg/day (5 mg three times a day) or 15 mg 1-2 hours before sexual

activity together with 6 g arginine glutamate (50% arginine, 50% glutamic acid) [96]. It is not used in elderly people because of the possible side effects, such as hypertension, tachycardia, anxiety, insomnia, hallucinations, and dizziness.

Icariin is a flavonol glycoside derived from horny goat weed or *Herba Epimedii*, used for centuries in China for enhancing sexual performances; it can have an inhibitory effect of both PDE4 and PDE5, thus enhancing the production of bioactive nitric oxide and mimicking the effects of testosterone [97–99].

Ginseng is another widely known aphrodisiac which can increase erectile function, even if data are preliminary and need further trials [15].

The vacuum constriction device is a manually operated device that creates negative pressure around the penis, thus resulting in passive engorgement of the sinusoidal spaces and erection; the maintenance of the erection is facilitated by a rubber cuff applied around the penile base [15]. It is used in men who do not wish medical treatment or penile implantation surgery or do not respond to medical treatment. It is effective up to 90% of patients, even if the turgidity occurs distal to the constriction band; the use of the constriction band is possible for 30 min in order to avoid skin necrosis [100] and it has to be used cautiously in patients taking anticoagulants or presenting with bleeding disorders [101].

The intracavernous and intraurethral administration of vasoactive substances is the recommended second-line treatment in patients that fails to respond to PDE5-I for ED; it is safe, effective (up to 80% out of the cases), and with a rapid

TABLE 2: Summarizing the possible treatment options for ED in elderly patients.

| Drug                       | Dose                    | $t_{1/2}$ (h) | Frequency          | Advantages   | Side effects   |
|----------------------------|-------------------------|---------------|--------------------|--|--|
| Sildenafil                 | 25, 50*, 100 mg         | 4.6           | On demand or daily | Safe; available on demand as well as continuous low dose (sildenafil 2.5 mg, tadalafil 2.5 mg) | Headache, myalgia, back pain, blurred vision, facial flushing, nasal congestion, dizziness |
| Tadalafil                  | 2.5, 5, 10, 20 mg       | 17–21         |                    |  |  |
| Vardenafil                 | 2.5, 5, 10*, 20 mg      | 4–5           |                    |  |  |
| Avanafil                   | 50, 100, 200 mg         | 5–10          |                    |  |  |
| Yohimbine                  | 5–15 mg                 | 0.25–2.5      | Three times daily  | Natural product  | Hypertension, tachycardia, anxiety   |
| Vacuum constriction device | /                       | /             | On demand          | Effective in 90% of patients; not expensive  | Skin necrosis, priapism, cold penis, unnatural erection                                    |
| Papaverine                 | 30–110 mg               | 1.5–2.5       | On demand          | Broad efficacy, safety, and efficacy in neurogenic ED  | Priapism, pain, penile fibrosis, injection training requested                              |
| PGE1                       | 5–40 µg                 | 0.30          |                    |  |  |
| Phentolamine               | 1.25–2 mg               | 0.19          |                    |  |  |
| MUSE                       | 125, 250, 500, 1,000 µg | 0.30          | On demand          | No injections needed   | Hypotension, pain, urethral burning, syncope, vaginal irritation in the partner            |
| Penile prosthesis          | /                       | /             | On demand          | High satisfaction rates  | Irreversible, infection, erectile length loss, autoinflation                               |

$t_{1/2}$ : plasma half-life; h: hours; \* also available in orodispersible formulation (supralingual).

onset of action [15]. The most common vasoactive substances are prostaglandin E1 (alprostadil or PGE1), papaverine, and phentolamine. PGE1 and papaverine increase the intracellular concentration of the second messenger cGMP and cyclic adenosine monophosphate, thus resulting in cavernous smooth muscle relaxation, whereas phentolamine is an  $\alpha$ -adrenergic antagonist [15].

Alprostadil (PGE1) is also available as an intraurethral administrated pellet (medicated urethral suppository for erection (MUSE)). The medicine is a small pellet contained inside a thin tube that is inserted into the urethra. The pellet can be released by pressing a button on the applicator and an erection develops in about 10 minutes and lasts at least 30 minutes, but usually less than 60 minutes, depending on the dosage [15].

Side effects of MUSE are usually minor and may include pain in the penis or urethra, mild injury to the urethra, such as a small scrape that produces a drop of blood at the tip of the urethra, and priapism. If an erection lasts longer than 3 hours and it is not relieved, it may damage tissues inside the penis.

The MUSE system does not cause bruising or scar tissue, like injections may. Partners of men who have vision problems or who may have difficulty inserting the pellet can be taught how to use these products. The medicine may cause irritation for partner after ejaculating [15, 101, 102].

**6.4.3. Surgical Procedures.** Surgical treatment is indicated in elderly patients in which conservative treatments for ED have failed or those declining pharmacotherapy; it usually consists of penile prosthesis. There are three types of penile prosthesis, but the three-piece inflatable prosthesis is the preferred device. It consists of two implantable rods, connected to a

pump device placed in the scrotum and a reservoir which is placed in the preperitoneal space in the lower abdomen [15]. It has a 90–98% satisfaction rate [100]. Possible adverse events are infections, occurring in 1–2% of the patients, autoinflation, and erectile length loss, especially in patients with Peyronie's disease and after radical prostatectomy. Table 2 summarizes the possible treatment options for ED in elderly patients.

## 7. Recreational Use of ED Medications in the Elderly

Use of ED medication could result in men experiencing “ideal” erections that are both firmer and more durable. This even occurs in the elderly, especially in healthy young elderly, where keeping a normal sexual life may be a marker of healthy and successful aging.

Sometimes the use of ED medications as an exclusive therapy can reveal or reinforce other sexual problems, such as a lack of sexual desire and premature ejaculation. In most cases, recreational use concerns young people: in fact, in a previous study by Harte and Meston, 1,944 men, recruited from 497 undergraduate institutions across the USA, were asked about recreational PDE5-I and illicit drug use. Surprisingly, 4% of the study participants had recreationally used PDE5-I at some point in their lives and one-third of them reported current use. Most of them (44%) reported mixing PDE5-I with alcohol or illicit drugs, particularly while engaging in risky sexual behaviour. Illicit drugs taken concomitantly with PDE5-I included marijuana (61%), 3,4-methylenedioxymethylamphetamine (MDMA; 42%), methamphetamines (36%), cocaine (30%), alkyl nitrites, and ketamine [103, 104]. On the other hand, approximately 6 million men in Europe might currently bypass the healthcare

system to obtain PDE5-I [105]. In addition to the possible risks associated with the use of PDE5-I from uncontrolled sources, because most of these men have ED, they also miss the opportunity of important health information or medical follow-up.

However, use of recreational PDE5-I is independently associated with increased age, drug abuse, lifetime number of sexual partners, and lifetime number of “one night stands,” as well as with homosexual or bisexual orientation [106].

As above mentioned even elderly men can use ED medications only for improving sexual performances, especially PDE5-I; moreover, PDE5-I can at the same time improve LUTS. Young-old people, that is, people aged between 65 and 74 years old, can be mostly concerned in the recreational use of PDE5-I.

## 8. Future Perspectives

A man's ability to get and sustain an erection is often equated with virility and masculinity and is able to greatly affect men's self-esteem.

The availability of PDE5-I has significantly altered the way in which ED is treated. Furthermore, it has been shown the possible role of these drugs in synaptic function and in memory in an Alzheimer's disease mouse model of amyloid deposition [107]. In fact, sildenafil is able to enhance phosphorylation of cAMP response element binding protein (CREB), a molecule involved in memory, through elevation of cGMP levels [107].

Sildenafil can be also used in medical conditions different from ED, such as pulmonary arterial hypertension [108]. It has also been shown to be effective in treating severe Raynaud's phenomenon associated with systemic sclerosis and digital ulceration. Investigative studies have suggested that sildenafil has also promise in the treatment of respiratory disorders with ventilation/perfusion mismatch, congestive cardiac failure, hypertension, and even stroke [108].

Currently available oral pharmacotherapy has limited efficacy in older patients due to the lack of endogenous supply; some new compounds are currently in development, such as guanylate cyclase activators, Rho-kinase inhibitors, and maxi-K channel openers [15].

The use of stem cells for the treatment of ED represents an exciting new field, which still requires extensive basic research and human trials in diverse ED patient populations in order to define its role in the treatment of ED [109]. Pre-clinical studies have shown that these cells may reverse pathophysiological changes leading to ED, for example, following cavernous nerve injury and in Peyronie's disease, diabetes, aging, and hyperlipidemia. Overall, these studies have shown beneficial effects, while evidence on the mechanisms of action of stem cell therapy still varies between studies [109].

## 9. Concluding Remarks

In conclusion, increasing comorbidities and pathological changes in the erectile tissue and the supplying vessels result in a high prevalence of ED in the geriatric population.

ED is a multifactorial condition and, as such, prevention and treatment demand a multidisciplinary approach. Of course, it is always important for the physician to avoid the use of any medication to improve sexual activity if the underlying cardiac condition of the patient does not permit activity appropriate for sexual activity. At the same time, before starting a treatment for ED, physicians should always review all drugs potentially worsening erectile function; an accurate counseling should always be carried out. Various nonpharmacological, pharmacological, and surgical options are safe and effective in the elderly. PDE5-I are safe and usually effective drugs also in the elderly. Data acquired during a routine diagnostic workup for ED should be taken into account when choosing the best PDE5-I for the individual patient. An individualized treatment plan is recommended and going beyond “experience-based” subjective opinion and unfounded ideas and prejudice regarding currently available drugs may be appropriate [40]. Vardenafil orodispersible preparation is reported to have the fastest onset of action, while tadalafil is reported to have the longer duration of action. PDE5-I can also be used for indications other than ED (sildenafil in pulmonary hypertension and tadalafil in LUTS) and chronic administration seems to work better in elderly patients. New hopes might derive from the use of avanafil. Novel compounds are currently in development and are expected to have better efficacy in nonresponders. Future research will be soon available for improving the sexual health of older men.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

## References

- [1] L. J. Smith, J. P. Mulhall, S. Deveci, N. Monaghan, and M. C. Reid, “Sex after seventy: a pilot study of sexual function in older persons,” *The Journal of Sexual Medicine*, vol. 4, no. 5, pp. 1247–1253, 2007.
- [2] R. Bruzziches, D. Francomano, P. Gareri, A. Lenzi, and A. Aversa, “An update on pharmacological treatment of erectile dysfunction with phosphodiesterase type-5 inhibitors,” *Expert Opinion on Pharmacotherapy*, vol. 14, no. 10, pp. 1333–1344, 2013.
- [3] T. F. Lue, “Erectile dysfunction,” *The New England Journal of Medicine*, vol. 342, no. 24, pp. 1802–1813, 2000.
- [4] H. Solomon, J. W. Man, and G. Jackson, “Erectile dysfunction and the cardiovascular patient: endothelial dysfunction is the common denominator,” *Heart*, vol. 89, no. 3, pp. 251–254, 2003.
- [5] S. T. Lindau, L. P. Schumm, E. O. Laumann, W. Levinson, C. A. O'Muircheartaigh, and L. J. Waite, “A study of sexuality and health among older adults in the United States,” *England Journal of Medicine*, vol. 357, no. 8, pp. 762–774, 2007.
- [6] H. A. Feldman, I. Goldstein, D. G. Hatzichristou, R. J. Krane, and J. B. McKinlay, “Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study,” *The Journal of Urology*, vol. 151, no. 1, pp. 54–61, 1994.
- [7] G. Corona, D. M. Lee, G. Forti et al., “Age-related changes in general and sexual health in middle-aged and older men: results



- from the European Male Ageing Study (EMAS)," *The Journal of Sexual Medicine*, vol. 7, no. 4, pp. 1362–1380, 2010.
- [8] C. A. Holden, R. I. McLachlan, M. Pitts et al., "Men in Australia Telephone Survey (MATeS): a national survey of the reproductive health and concerns of middle-aged and older Australian men," *The Lancet*, vol. 366, no. 9481, pp. 218–224, 2005.
  - [9] S. T. Lindau, E. Abramo, K. Gosch et al., "Patterns and loss of sexual activity in the year following hospitalization for acute myocardial infarction (A U.S. National, Multi-Site Observational Study)," *The American Journal of Cardiology*, vol. 109, no. 10, pp. 1439–1444, 2012.
  - [10] R. Shiri, J. Koskimäki, J. Häkkinen et al., "Effects of age, comorbidity and lifestyle factors on erectile function: Tampere Ageing Male Urological Study (TAMUS)," *European Urology*, vol. 45, no. 5, pp. 628–633, 2004.
  - [11] A. Aversa, R. Bruziches, D. Francomano, M. Natali, P. Gareri, and G. Spera, "Endothelial dysfunction and erectile dysfunction in the aging man," *International Journal of Urology*, vol. 17, no. 1, pp. 38–47, 2010.
  - [12] E. Chiurlia, R. D'Amico, C. Ratti, A. R. Granata, R. Romagnoli, and M. G. Modena, "Subclinical coronary artery atherosclerosis in patients with erectile dysfunction," *Journal of the American College of Cardiology*, vol. 46, no. 8, pp. 1503–1506, 2005.
  - [13] C. Gazzaruso, S. B. Solerte, A. Pujia et al., "Erectile dysfunction as a predictor of cardiovascular events and death in diabetic patients with angiographically proven asymptomatic coronary artery disease: a potential protective role for statins and 5-phosphodiesterase inhibitors," *Journal of the American College of Cardiology*, vol. 51, no. 21, pp. 2040–2044, 2008.
  - [14] I. M. Thompson, C. M. Tangen, P. J. Goodman, J. L. Probstfield, C. M. Moinpour, and C. A. Coltman, "Erectile dysfunction and subsequent cardiovascular disease," *Journal of the American Medical Association*, vol. 294, no. 23, pp. 2996–3002, 2005.
  - [15] M. Albersen, H. Orabi, and T. F. Lue, "Evaluation and treatment of erectile dysfunction in the aging male: a mini-review," *Gerontology*, vol. 58, no. 1, pp. 3–14, 2012.
  - [16] A. I. El-Sakka and A. A. Yassin, "Review: amelioration of penile fibrosis: myth or reality," *Journal of Andrology*, vol. 31, no. 4, pp. 324–335, 2010.
  - [17] X. L. Rudner, D. E. Berkowitz, J. V. Booth et al., "Subtype specific regulation of human vascular  $\alpha$ 1-adrenergic receptors by vessel bed and age," *Circulation*, vol. 100, no. 23, pp. 2336–2343, 1999.
  - [18] G. J. Christ, B. Stone, and A. Melman, "Age-dependent alterations in the efficacy of phenylephrine-induced contractions in vascular smooth muscle isolated from the corpus cavernosum of impotent men," *Canadian Journal of Physiology and Pharmacology*, vol. 69, no. 7, pp. 909–913, 1991.
  - [19] D. Browne, D. Meeking, K. Shaw, and M. Cummings, "Endothelial dysfunction and pre-symptomatic atherosclerosis in type 1 diabetes—pathogenesis and identification," *British Journal of Diabetes and Vascular Disease*, vol. 3, no. 1, pp. 27–34, 2003.
  - [20] P. M. Vanhoutte, "Ageing and endothelial dysfunction," *European Heart Journal Supplements*, vol. 4, pp. A8–A17, 2002.
  - [21] B. Musicki, M. F. Kramer, R. E. Becker, A. L. Burnett, and I. S. de Tejada, "Age-related changes in phosphorylation of endothelial nitric oxide synthase in the rat penis," *The Journal of Sexual Medicine*, vol. 2, no. 3, pp. 347–357, 2005.
  - [22] E. Wespes, "The ageing penis," *World Journal of Urology*, vol. 20, no. 1, pp. 36–39, 2002.
  - [23] M. G. Ferrini, H. H. Davila, E. G. A. Valente, N. F. Gonzalez-Cadavid, and J. Rajfer, "Aging-related induction of inducible nitric oxide synthase is vasculo-protective to the arterial media," *Cardiovascular Research*, vol. 61, no. 4, pp. 796–805, 2004.
  - [24] A. Traish and N. Kim, "The physiological role of androgens in penile erection: regulation of corpus cavernosum structure and function," *The Journal of Sexual Medicine*, vol. 2, no. 6, pp. 759–770, 2005.
  - [25] H. Hougaku, J. L. Fleg, S. S. Najjar et al., "Relationship between androgenic hormones and arterial stiffness, based on longitudinal hormone measurements," *American Journal of Physiology—Endocrinology and Metabolism*, vol. 290, no. 2, pp. E234–E242, 2006.
  - [26] A. E. Hak, J. C. M. Witteman, F. H. de Jong, M. I. Geerlings, A. Hofman, and H. A. P. Pols, "Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study," *The Journal of Clinical Endocrinology and Metabolism*, vol. 87, no. 8, pp. 3632–3639, 2002.
  - [27] G. A. Laughlin, E. Barrett-Connor, and J. Bergstrom, "Low serum testosterone and mortality in older men," *The Journal of Clinical Endocrinology and Metabolism*, vol. 93, no. 1, pp. 68–75, 2008.
  - [28] G. Corona, G. Rastrelli, E. Maseroli, G. Forti, and M. Maggi, "Sexual function of the ageing male," *Best Practice & Research: Clinical Endocrinology & Metabolism*, vol. 27, no. 4, pp. 581–601, 2013.
  - [29] J. K. Crews and R. A. Khalil, "Antagonistic effects of 17 $\beta$ -estradiol, progesterone, and testosterone on Ca<sup>2+</sup> entry mechanisms of coronary vasoconstriction," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 19, no. 4, pp. 1034–1040, 1999.
  - [30] J. B. Ruige, D. M. Ouwens, and J. M. Kaufman, "Beneficial and adverse effects of testosterone on the cardiovascular system in men," *The Journal of Clinical Endocrinology & Metabolism*, vol. 98, no. 11, pp. 4300–4310, 2013.
  - [31] G. Corona, M. Gacci, E. Baldi, R. Mancina, G. Forti, and M. Maggi, "Androgen deprivation therapy in prostate cancer: focusing on sexual side effects," *The Journal of Sexual Medicine*, vol. 9, no. 3, pp. 887–902, 2012.
  - [32] A. B. Araujo, J. M. Dixon, E. A. Suarez, M. H. Murad, L. T. Guey, and G. A. Wittert, "Endogenous testosterone and mortality in men: a systematic review and meta-analysis," *The Journal of Clinical Endocrinology and Metabolism*, vol. 96, no. 10, pp. 3007–3019, 2011.
  - [33] A. M. Isidori, J. Buvat, G. Corona et al., "A critical analysis of the role of testosterone in erectile function: from pathophysiology to treatment—a systematic review," *European Urology*, vol. 65, no. 1, pp. 99–112, 2014.
  - [34] G. Corona, G. Rastrelli, A. Morelli, L. Vignozzi, E. Mannucci, and M. Maggi, "Hypogonadism and metabolic syndrome," *Journal of Endocrinological Investigation*, vol. 34, no. 7, pp. 557–567, 2011.
  - [35] G. Corona, G. Rastrelli, and M. Maggi, "Diagnosis and treatment of late-onset hypogonadism: systematic review and meta-analysis of TRT outcomes," *Best Practice & Research: Clinical Endocrinology & Metabolism*, vol. 27, no. 4, pp. 557–579, 2013.
  - [36] R. Vigen, C. I. O'Donnell, A. E. Barón et al., "Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels," *The Journal of the American Medical Association*, vol. 310, no. 17, pp. 1829–1836, 2013.
  - [37] S. Martin, E. Atlantis, D. Wilson et al., "Clinical and biopsychosocial determinants of sexual dysfunction in middle-aged



- and older Australian men," *The Journal of Sexual Medicine*, vol. 9, no. 8, pp. 2093–2103, 2013.
- [38] C. Foresta, N. Caretta, G. Corona et al., "Clinical and metabolic evaluation of subjects with erectile dysfunction: a review with a proposal flowchart," *International Journal of Andrology*, vol. 32, no. 3, pp. 198–211, 2009.
- [39] B. D. Sachs, "The false organic-psychogenic distinction and related problems in the classification of erectile dysfunction," *International Journal of Impotence Research*, vol. 15, no. 1, pp. 72–78, 2003.
- [40] G. Corona, N. Mondaini, A. Ungar, E. Razzoli, A. Rossi, and F. Fusco, "Phosphodiesterase type 5 (PDE5) inhibitors in erectile dysfunction: the proper drug for the proper patient," *The Journal of Sexual Medicine*, vol. 8, no. 12, pp. 3418–3432, 2011.
- [41] M. Vardi and A. Nini, "Phosphodiesterase inhibitors for erectile dysfunction in patients with diabetes mellitus," *Cochrane Database of Systematic Reviews*, no. 1, Article ID CD002187, 2007.
- [42] G. Corona, D. M. Lee, G. Forti et al., "Age-related changes in general and sexual health in middle-aged and older men: results from the European Male Ageing Study (EMAS)," *The Journal of Sexual Medicine*, vol. 7, no. 4, pp. 1362–1380, 2010.
- [43] G. Corona, M. Monami, V. Boddi et al., "Male sexuality and cardiovascular risk. A cohort study in patients with erectile dysfunction," *The Journal of Sexual Medicine*, vol. 7, no. 5, pp. 1918–1927, 2010.
- [44] G. Corona, E. Mannucci, F. Lotti et al., "Pulse pressure, an index of arterial stiffness, is associated with androgen deficiency and impaired penile blood flow in men with ED," *The Journal of Sexual Medicine*, vol. 6, no. 1, pp. 285–293, 2009.
- [45] G. Jackson, R. C. Rosen, R. A. Kloner, and J. B. Kostis, "The second Princeton consensus on sexual dysfunction and cardiac risk: new guidelines for sexual medicine," *The Journal of Sexual Medicine*, vol. 3, no. 1, pp. 28–36, 2006.
- [46] I. Eardley, C. Donatucci, J. Corbin et al., "Pharmacotherapy for erectile dysfunction," *The Journal of Sexual Medicine*, vol. 7, no. 1, pp. 524–540, 2010.
- [47] J.-H. Jung, S.-C. Kam, S.-M. Choi, S.-U. Jae, S.-H. Lee, and J.-S. Hyun, "Sexual dysfunction in male stroke patients: correlation between brain lesions and sexual function," *Urology*, vol. 71, no. 1, pp. 99–103, 2008.
- [48] D. B. Celik, E. C. Poyraz, A. Bingöl, E. Idiman, S. Ozakbaş, and D. Kaya, "Sexual dysfunction in multiple sclerosis: gender differences," *Journal of the Neurological Sciences*, vol. 324, no. 1–2, pp. 17–20, 2013.
- [49] R. Sakakibara, M. Kishi, E. Ogawa et al., "Bladder, bowel, and sexual dysfunction in Parkinson's disease," *Parkinson's Disease*, vol. 2011, Article ID 924605, 21 pages, 2011.
- [50] P. Kotková and P. Weiss, "Psychiatric factors related to sexual functioning in patients with Parkinson's disease," *Clinical Neurology and Neurosurgery*, vol. 115, no. 4, pp. 419–424, 2013.
- [51] G. Bronner and D. B. Vodusek, "Management of sexual dysfunction in Parkinson's disease," *Therapeutic Advances in Neurological Disorders*, vol. 4, no. 6, pp. 375–383, 2011.
- [52] M. F. Mendez and J. S. Shapira, "Hypersexual behavior in frontotemporal dementia: a comparison with early-onset Alzheimer's disease," *Archives of Sexual Behavior*, vol. 42, no. 3, pp. 501–519, 2013.
- [53] C. Y. Chen, C. P. Lee, Y. Chen, J. R. Jiang, C. L. Chu, and C. L. Chen, "The correlation between emotional distress and aging males' symptoms at a psychiatric outpatient clinic: sexual dysfunction as a distinguishing characteristic between andropause and anxiety/depression in aging men," *Clinical Interventions in Aging*, vol. 8, pp. 635–640, 2013.
- [54] A. W. Pastuszak, N. Badhiwala, L. I. Lipshultz, and M. Khera, "Depression is correlated with the psychological and physical aspects of sexual dysfunction in men," *International Journal of Impotence Research*, vol. 25, no. 5, pp. 194–199, 2013.
- [55] J.-Y. Jeong, S. K. Lee, Y.-W. Kang, S.-N. Jang, Y. J. Choi, and D.-H. Kim, "Relationship between ED and depression among middle-aged and elderly men in Korea: Hallym aging study," *International Journal of Impotence Research*, vol. 23, no. 5, pp. 227–234, 2011.
- [56] H. M. Tan, S. F. Tong, and C. C. K. Ho, "Men's health: sexual dysfunction, physical, and psychological health—is there a link?" *The Journal of Sexual Medicine*, vol. 9, no. 3, pp. 663–671, 2012.
- [57] M. A. Perelman, "Erectile dysfunction and depression: screening and treatment," *Urologic Clinics of North America*, vol. 38, no. 2, pp. 125–139, 2011.
- [58] S. H. Kennedy, H. Dugré, and I. Defoy, "A multicenter, double-blind, placebo-controlled study of sildenafil citrate in Canadian men with erectile dysfunction and untreated symptoms of depression, in the absence of major depressive disorder," *International Clinical Psychopharmacology*, vol. 26, no. 3, pp. 151–158, 2011.
- [59] J. F. Kinzl, "Major depressive disorder, antidepressants and sexual dysfunction," *Neuropsychiatrie*, vol. 23, no. 2, pp. 134–138, 2009.
- [60] A. K. Nagaraj, H. S. Nizamie, S. Akhtar, B. N. Sinha, and N. Goyal, "A comparative study of sexual dysfunction due to typical and atypical antipsychotics in remitted bipolar-I disorder," *Indian Journal of Psychiatry*, vol. 46, no. 3, pp. 261–266, 2004.
- [61] W. Hiller, W. Rief, and E. Brähler, "Somatization in the population: from mild bodily misperceptions to disabling symptoms," *Social Psychiatry and Psychiatric Epidemiology*, vol. 41, no. 9, pp. 704–712, 2006.
- [62] T. F. Lue and G. A. Broderick, "Evaluation and nonsurgical management of erectile dysfunction and premature ejaculation," in *Campbell-Walsh Urology*, Elsevier, Amsterdam, The Netherlands, 9th edition, 2007.
- [63] I. J. Korfage, S. Pluijm, M. Roobol, G. R. Dohle, F. H. Schröder, and M.-L. Essink-Bot, "Erectile dysfunction and mental health in a general population of older men," *The Journal of Sexual Medicine*, vol. 6, no. 2, pp. 505–512, 2009.
- [64] G. Corona, G. Rastrelli, M. Monami et al., "Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis," *European Journal of Endocrinology*, vol. 168, no. 6, pp. 829–843, 2013.
- [65] B. P. Gupta, M. H. Murad, M. M. Clifton, L. Prokop, A. Nehra, and S. L. Kopecky, "The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis," *Archives of Internal Medicine*, vol. 171, no. 20, pp. 1797–1803, 2011.
- [66] E. A. Saltzman, A. T. Guay, and J. Jacobson, "Improvement in erectile function in men with organic erectile dysfunction by correction of elevated cholesterol levels: a clinical observation," *The Journal of Urology*, vol. 172, no. 1, pp. 255–258, 2004.
- [67] A. L. Montejó-González, G. Llorca, J. A. Izquierdo et al., "SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients," *Journal of Sex and Marital Therapy*, vol. 23, no. 3, pp. 176–194, 1997.

- [68] R. C. Rosen, R. M. Lane, and M. Menza, "Effects of SSRIs on sexual function: a critical review," *Journal of Clinical Psychopharmacology*, vol. 19, no. 1, pp. 67–85, 1999.
- [69] E. Wespes, E. Amar, D. Hatzichristou et al., "EAU guidelines on erectile dysfunction: an update," *European Urology*, vol. 49, no. 5, pp. 806–815, 2006.
- [70] M. Albersen, A. W. Shindel, K. B. Mwamukonda, and T. F. Lue, "The future is today: emerging drugs for the treatment of erectile dysfunction," *Expert Opinion on Emerging Drugs*, vol. 15, no. 3, pp. 467–480, 2010.
- [71] S. P. C. Sildenafil, "Sildenafil Summary of Product Characteristics," [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000202/WC500-049830.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000202/WC500-049830.pdf).
- [72] S. P. C. Vardenafil, "Vardenafil Summary of Product Characteristics," [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000475/WC50-0039992.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000475/WC50-0039992.pdf).
- [73] J. Jung, S. Choi, S. H. Cho et al., "Tolerability and pharmacokinetics of avanafil, a phosphodiesterase type 5 inhibitor: a single- and multiple-dose, double-blind, randomized, placebo-controlled, dose-escalation study in healthy Korean male volunteers," *Clinical Therapeutics*, vol. 32, no. 6, pp. 1178–1187, 2010.
- [74] M. Fujisawa and K. Sawada, "Clinical efficacy and safety of sildenafil in elderly patients with erectile dysfunction," *Archives of Andrology*, vol. 50, no. 4, pp. 255–260, 2004.
- [75] K. Hatzimouratidis and D. G. Hatzichristou, "A comparative review of the options for treatment of erectile dysfunction: which treatment for which patient?" *Drugs*, vol. 65, no. 12, pp. 1621–1650, 2005.
- [76] A. J. Bella, L. X. Deyoung, M. Al-Numi, and G. B. Brock, "Daily administration of phosphodiesterase type 5 inhibitors for urological and nonurological indications," *European Urology*, vol. 52, no. 4, pp. 990–1005, 2007.
- [77] A. W. Shindel, "2009 update on phosphodiesterase type 5 inhibitor therapy part 1: recent studies on routine dosing for penile rehabilitation, lower urinary tract symptoms, and other indications (CME)," *The Journal of Sexual Medicine*, vol. 6, no. 7, pp. 1794–1808, 2009.
- [78] A. Konstantinopoulos, K. Giannitsas, A. Athanasopoulos, D. Spathas, and P. Perimenis, "The impact of daily sildenafil on levels of soluble molecular markers of endothelial function in plasma in patients with erectile dysfunction," *Expert Opinion on Pharmacotherapy*, vol. 10, no. 2, pp. 155–160, 2009.
- [79] A. Müller, L. Smith, M. Parker, and J. P. Mulhall, "Analysis of the efficacy and safety of sildenafil citrate in the geriatric population," *BJU International*, vol. 100, no. 1, pp. 117–121, 2007.
- [80] R. Shabsigh, J. M. Kaufman, C. Steidle, and H. Padma-Nathan, "Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone," *The Journal of Urology*, vol. 172, no. 2, pp. 658–663, 2004.
- [81] A. Aversa, A. M. Isidori, G. Spera, A. Lenzi, and A. Fabbrì, "Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction," *Clinical Endocrinology*, vol. 58, no. 5, pp. 632–638, 2003.
- [82] H. Sperling, F. Debruyne, A. Boermans, M. Beneke, E. Ulbrich, and S. Ewald, "The POTENT I randomized trial: efficacy and safety of an orodispersible vardenafil formulation for the treatment of erectile dysfunction," *The Journal of Sexual Medicine*, vol. 7, no. 4, pp. 1497–1507, 2010.
- [83] M. Sanford, "Vardenafil orodispersible tablet," *Drugs*, vol. 72, no. 1, pp. 87–98, 2012.
- [84] M. Gittelman, C. G. McMahon, J. A. Rodríguez-Rivera, M. Beneke, E. Ulbrich, and S. Ewald, "The POTENT II randomised trial: efficacy and safety of an orodispersible vardenafil formulation for the treatment of erectile dysfunction," *International Journal of Clinical Practice*, vol. 64, no. 5, pp. 594–603, 2010.
- [85] A. Salonia, A. Gallina, G. Zanni et al., "Acceptance of and discontinuation rate from erectile dysfunction oral treatment in patients following bilateral nerve-sparing radical prostatectomy," *European Urology*, vol. 53, no. 3, pp. 564–570, 2008.
- [86] R. Rosen, J. Altwein, P. Boyle et al., "Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7)," *European Urology*, vol. 44, no. 6, pp. 637–649, 2003.
- [87] C. G. Roehrborn, "Lower urinary tract symptoms, benign prostatic hyperplasia, erectile dysfunction, and phosphodiesterase-5 inhibitors," *Reviews in Urology*, vol. 6, no. 3, pp. 121–127, 2004.
- [88] K.-E. Andersson, W. C. de Groat, K. T. McVary et al., "Tadalafil for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia: pathophysiology and mechanism(s) of action," *Neurourology and Urodynamics*, vol. 30, no. 3, pp. 292–301, 2011.
- [89] M. Fujisawa and K. Sawada, "Clinical efficacy and safety of sildenafil in elderly patients with erectile dysfunction," *Archives of Andrology*, vol. 50, no. 4, pp. 255–260, 2004.
- [90] C. C. Carson III, "Cardiac safety in clinical trials of phosphodiesterase 5 inhibitors," *American Journal of Cardiology*, vol. 96, no. 12, pp. 37M–41M, 2005.
- [91] F. Giuliano, C. Donatucci, F. Montorsi et al., "Vardenafil is effective and well-tolerated for treating erectile dysfunction in a broad population of men, irrespective of age," *BJU International*, vol. 95, no. 1, pp. 110–116, 2005.
- [92] J. Borer and P. Armstrong, "Proceedings of the 99th meeting of the Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee. May 29th and 30th, 2003," *Circulation*, vol. 107, no. 23, article e9052, 2003.
- [93] G. Corona, E. Razzoli, G. Forti, and M. Maggi, "The use of phosphodiesterase 5 inhibitors with concomitant medications," *Journal of Endocrinological Investigation*, vol. 31, no. 9, pp. 799–808, 2008.
- [94] P. Gareri and G. de Sarro, "Principi di farmacologia geriatrica," in *Geriatrics nel territorio. Un metodo per i vecchi, per i medici e per il futuro*, S. Putignano, A. Cester, and P. Gareri, Eds., pp. 361–404, Critical Medicine Publishing s.r.l., Roma, Italy, 2012.
- [95] T. Hedner, B. Edgar, L. Edvinsson, J. Hedner, B. Persson, and A. Pettersson, "Yohimbine pharmacokinetics and interaction with the sympathetic nervous system in normal volunteers," *European Journal of Clinical Pharmacology*, vol. 43, no. 6, pp. 651–656, 1992.
- [96] T. Lebre, J.-M. Hervé, P. Gorny, M. Worcel, and H. Botto, "Efficacy and safety of a novel combination of L-arginine glutamate and yohimbine hydrochloride: a new oral therapy for erectile dysfunction," *European Urology*, vol. 41, no. 6, pp. 608–613, 2002.
- [97] H. Ning, Z.-C. Xin, G. Lin, L. Banie, T. F. Lue, and C.-S. Lin, "Effects of icariin on phosphodiesterase-5 activity in vitro and cyclic guanosine monophosphate level in cavernous smooth muscle cells," *Urology*, vol. 68, no. 6, pp. 1350–1354, 2006.
- [98] H.-B. Xu and Z.-Q. Huang, "Icariin enhances endothelial nitric-oxide synthase expression on human endothelial cells in vitro," *Vascular Pharmacology*, vol. 47, no. 1, pp. 18–24, 2007.

- [99] Z.-B. Zhang and Q.-T. Yang, "The testosterone mimetic properties of icariin," *Asian Journal of Andrology*, vol. 8, no. 5, pp. 601–605, 2006.
- [100] W. J. G. Hellstrom, D. K. Montague, I. Moncada et al., "Implants, mechanical devices, and vascular surgery for erectile dysfunction," *The Journal of Sexual Medicine*, vol. 7, no. 1, pp. 501–523, 2010.
- [101] K. Hatzimouratidis, E. Amar, I. Eardley et al., "Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation," *European Urology*, vol. 57, no. 5, pp. 804–814, 2010.
- [102] P. Tharyan and G. Gopalakrishnan, "Erectile dysfunction," *Clinical Evidence*, vol. 15, pp. 1227–1251, 2006.
- [103] C. B. Harte and C. M. Meston, "Recreational use of erectile dysfunction medications in undergraduate men in the United States: characteristics and associated risk factors," *Archives of Sexual Behavior*, vol. 40, no. 3, pp. 597–606, 2011.
- [104] F. Korkes, A. Costa-matos, R. Gasperini, P. V. Reginato, and M. D. C. Perez, "Recreational use of PDE5 inhibitors by young healthy men: recognizing this issue among medical students," *The Journal of Sexual Medicine*, vol. 5, no. 10, pp. 2414–2418, 2008.
- [105] G. Schnetzler, I. Banks, M. Kirby, K. H. Zou, and T. Symonds, "Characteristics, behaviors, and attitudes of men bypassing the healthcare system when obtaining phosphodiesterase type 5 inhibitors," *The Journal of Sexual Medicine*, vol. 7, no. 3, pp. 1237–1246, 2010.
- [106] T. Melnik, "The psychological effects of recreational PDE5 inhibitor use," *Nature Reviews Urology*, vol. 9, pp. 479–480, 2012.
- [107] D. Puzzo, A. Staniszewski, S. XianDeng et al., "Phosphodiesterase 5 inhibition improves synaptic function, memory, and amyloid- $\beta$  load in an Alzheimer's disease mouse model," *Journal of Neuroscience*, vol. 29, no. 25, pp. 8075–8086, 2009.
- [108] H. A. Ghofrani, I. H. Osterloh, and F. Grimminger, "Sildenafil: from angina to erectile dysfunction to pulmonary hypertension and beyond," *Nature Reviews Drug Discovery*, vol. 5, no. 8, pp. 689–702, 2006.
- [109] M. Albersen, E. Weyne, and T. J. Bivalacqua, "Stem cell therapy for erectile dysfunction: progress and future directions," *Sexual Medicine Reviews*, vol. 1, no. 1, pp. 50–64, 2013.

## Review Article

# Quality of Life and Sexual Health in the Aging of PCa Survivors

**Mauro Gacci,<sup>1</sup> Elisabetta Baldi,<sup>2</sup> Lara Tamburrino,<sup>2</sup> Beatrice Detti,<sup>3</sup> Lorenzo Livi,<sup>3</sup> Cosimo De Nunzio,<sup>4</sup> Andrea Tubaro,<sup>4</sup> Stavros Gravas,<sup>5</sup> Marco Carini,<sup>1</sup> and Sergio Serni<sup>1</sup>**

<sup>1</sup> Department of Urology, University of Florence, Careggi Hospital, Viale Gramsci 7, 50121 Florence, Italy

<sup>2</sup> Department of Experimental and Clinical Biomedical Sciences, Section of Clinical Pathophysiology, University of Florence, Italy

<sup>3</sup> Radiotherapy, University Hospital Careggi, University of Florence, Italy

<sup>4</sup> Department of Urology, Sant'Andrea Hospital, University "La Sapienza", Rome, Italy

<sup>5</sup> Department of Urology, University Hospital of Larissa, Larissa, Greece

Correspondence should be addressed to Mauro Gacci; [maurogacci@yahoo.it](mailto:maurogacci@yahoo.it)

Received 27 October 2013; Accepted 2 February 2014; Published 17 March 2014

Academic Editor: Lorenzo Maria Donini

Copyright © 2014 Mauro Gacci et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Prostate cancer (PCa) is the most common malignancy in elderly men. The progressive ageing of the world male population will further increase the need for tailored assessment and treatment of PCa patients. The determinant role of androgens and sexual hormones for PCa growth and progression has been established. However, several trials on androgens and PCa are recently focused on urinary continence, quality of life, and sexual function, suggesting a new point of view on the whole endocrinological aspect of PCa. During aging, metabolic syndrome, including diabetes, hypertension, dyslipidemia, and central obesity, can be associated with a chronic, low-grade inflammation of the prostate and with changes in the sex steroid pathways. These factors may affect both the carcinogenesis processes and treatment outcomes of PCa. Any treatment for PCa can have a long-lasting negative impact on quality of life and sexual health, which should be assessed by validated self-reported questionnaires. In particular, sexual health, urinary continence, and bowel function can be worsened after prostatectomy, radiotherapy, or hormone treatment, mostly in the elderly population. In the present review we summarized the current knowledge on the role of hormones, metabolic features, and primary treatments for PCa on the quality of life and sexual health of elderly Pca survivors.

## 1. Introduction

Prostate cancer (PCa) is the most common malignancy in elderly men. Age is a relevant risk factor, with a proven histological PCa being found in 60% of men by the age of 70 years and 80% by the age of 80 [1]. In fact, PCa is considered a chronic disease, needing a long period for initiation, development, and progression, through the development of early and later precancerous modifications, such as high-grade prostate intraepithelial neoplasia (HG-PIN), leading to the development of a clinically relevant cancer [2, 3]. Therefore, PCa is frequent in old men, likely becoming the prevalent cancer because of the ageing of population [4].

Although androgen receptor (AR) pathway is crucial for prostate cancer growth and progression, evidence supporting a favorable risk-benefit ratio of androgen deprivation therapy (ADT) is currently limited to high-risk PCa or metastatic

disease [5, 6]. Furthermore, hypogonadism is common in elderly men and men who have PCa: the symptoms of hypogonadism, such as depression, erectile dysfunction (ED), and lower urinary tract symptoms, can impair a man's quality of life (QoL) [7]. Therefore, androgens and AR play a critical role in management of elderly men with PCa.

The current literature suggests an association between metabolic syndrome (MetS) and PCa, although the evidence for a causal relationship remains unknown [8]. In particular, a recent review pointed out that men with MetS seem to have more likely high-grade and advanced PCa: moreover, they resulted in greater risk of progression and cancer specific death, even if the overall analyses did not reveal any association between MetS and the risk to develop the disease [8]. Therefore, MetS should be assessed as a new domain in basic and clinical research in elderly men with PCa.



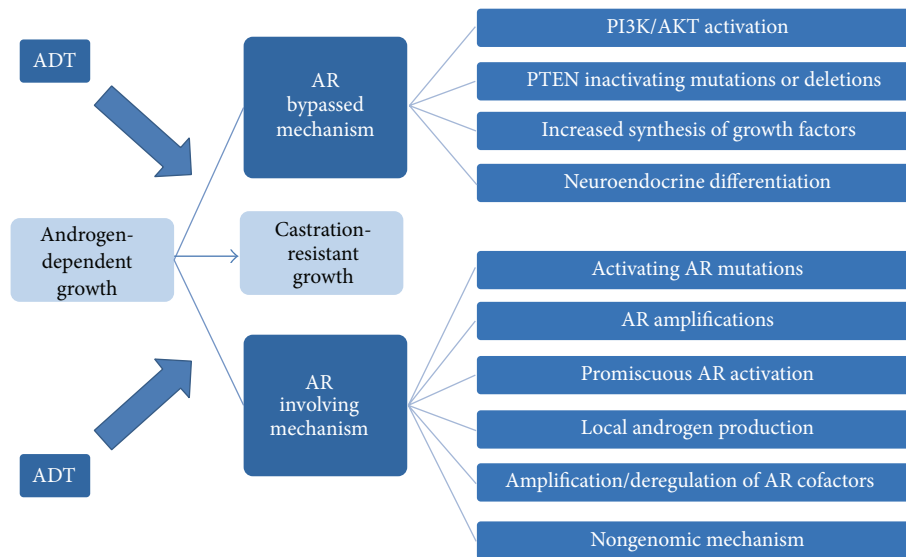


FIGURE 1: Schematic representation of the main pathways involved in development of castration-resistant prostate cancer (CRPC). ADT: androgen-deprivation therapy, AR: androgen receptor. Modified from 43.

The primary goal of any definitive treatment of PCa is the improvement of survival and QoL: although surgery, radiotherapy, and hormone therapy can lead to long-term survival, these treatments can cause lasting side effects [9]. Therefore, patients survival has to be considered in treatment decision making, but patients' quality of life must also be considered before and after any treatment [10]. Moreover, an accurate assessment of QoL in PCa patients must be performed with validated, self-reported, and disease specific instruments [11]. Therefore, there is a need for a tailored approach in the management of PCa in the elderly men, to avoid unnecessary intervention with permanent adverse event [12].

The aim of present review is to summarize the current knowledge on the role of androgens pathways, metabolic factors, and primary treatments on the overall QoL and sexual health of elderly PCa survivors.

## 2. Endocrinological Aspects of Prostate Cancer

**2.1. The Role of Androgens and of Androgen Receptor (AR) in Carcinogenesis and Progression of Prostate Cancer.** Prostate volume and function are age- and androgen-dependent [13] and in hypogonadal subjects therapy with testosterone restores the volume of the prostate to that of eugonadal men [14]. Androgens and AR play a fundamental role in the development of PCa which is androgen-dependent for its growth, as demonstrated in the pioneering work of Huggins and Hodges [15] who showed that castration causes complete regression of the disease.

How actions of AR become tumorigenic and lead to uncontrolled growth remains poorly understood. In a high percentage of PCa, fusions between the androgen-dependent gene *TMPRSS2* and *ETS* transcription factors (such as *ERG*) occur through chromosomal translocations [16], leading

to elevated expression of these oncogenic factors under androgen control. However, whether *TMPRSS2:ETS* fusions are sufficient to promote PCa is discussed [17, 18] and the initial enthusiasm about such chromosomal aberrations has been dampened by the controversial results of clinical studies investigating their role in PCa progression [19].

Androgen deprivation therapy (ADT) represents a valuable treatment of metastatic PCa. However, ADT provides palliation but not cure and most PCa regrow as castration-resistant PCa (CRPCa) able to survive and grow in a milieu virtually deprived of androgens. The detailed mechanisms of why ADT ultimately fails and a more aggressive cancer recurs remain unclear (Figure 1). In the past decade, based on in vitro or in vivo evidence, several hypotheses involving the AR have been generated to explain development of CRPCa, such as AR mutations (found in about 20% of metastatic specimens) or amplifications that confer the ability to bind other steroids and even antiandrogens (acting as agonists), changes in AR-coregulators interactions, and activation of AR by growth factors or other signal pathways (reviewed in [20]). In addition, recent work has highlighted the role of intraprostatic androgen synthesis as the driving force of recurrent disease (see below for further details).

Interestingly, low expression of mutated AR may drive in vitro growth of CRPCa cell lines also by nongenomic (rapid signalling) mechanisms [21]. However, more studies are needed in order to better understand the role, if any, of nongenomic AR signalling in PCa growth and progression. These AR-involving hypotheses do not completely explain why patients receiving ADT tend to have an earlier development of more aggressive cancer. Alternative pathways of growth and invasion may develop in PCa cells (Figure 1) bypassing the necessity of androgens: among these, PTEN inactivating mutation has been found in a high proportion of PCa [22] leading to suppression of apoptotic pathways

and consequent uncontrolled growth. Neuroendocrine differentiation also plays an important role in development of CRPCa [23]. In summary, development of CRPCa is a very complex event, potentially involving both androgen-regulated and androgen-alternative pathways (Figure 1). Such a complexity makes the development of therapeutic strategies very difficult, and, as today, CRPCa is basically incurable.

Currently, research is mainly directed to understand the role of these multiple pathways and their interregulation with the aim of identifying potential therapeutical targets. One hot topic of research is aimed at understating the role of AR. In a recent survey of the literature concerning the relationship between AR expression in PCa specimen and disease prognosis, we have highlighted the conflicting results reported so far [24]. These studies evidenced both the highly variable expression of AR among different cancers and a different relation with prognosis. Most studies did not find any association between AR expression and prognosis, including a large one by Minner et al. [25], whereas some studies found an association between high AR expression and better or worse prognosis. Although such contrasting findings may depend on several factors [24], one possible explanation may be related to a different role of AR depending on its location (stroma or epithelium) in the tumor. Recently, a mouse cancer model lacking the AR only in the prostatic epithelium and/or stroma has been generated (ARKO-TRAMP) [26, 27]. These mice paradoxically develop poorly differentiated PCa and, most importantly, restoration of AR function in epithelial basal cells leads to tumor suppression. Conversely, restoration of AR in stromal cells stimulates cancer progression, supporting a differential role of AR in PCa depending on its location. Studies in mice models suggest that stromal AR may promote prostate tumorigenesis via induction of proinflammatory cytokines/chemokines expression [28].

These results substantiate *in vitro* studies showing that enforced expression of AR in AR-negative PCa cells decreases the metastatic/invasive potential of the cells [26, 29–35]. In a recent paper evaluating the role of androgen signalling in epithelial-mesenchymal transition, Zhu and Kyprianou [36] demonstrated that overexpression of AR in PCa cell lines suppresses androgen-induced epithelial-mesenchymal transition, suggesting that downregulation of AR occurring in androgen-deprived condition [37] may facilitate mesenchymal transition and promote metastasis [36]. There is also evidence that inducing AR expression in PCa cells by targeting methylation of promoter increases differentiation of carcinoma cells and suppresses self-renewal/proliferation of stem cells and tumorigenesis [38].

Clinical data supporting a differentiating role of AR in PCa and, as such, limiting invasiveness have been also published. Following androgen ablation metastatic PCa is promoted *in vitro* [39] and there is clinical evidence that intermittent ADT benefits patients in PCa progression [40]. In addition, patients with CRPCa displaying amplification of AR gene survive longer than patients without amplification [41]. Results of long-term survival in the PCa prevention trial with the 5  $\alpha$ -reductase inhibitor finasteride demonstrated that, although the risk of developing PC is decreased, the Gleason score of developing cancers is significantly higher

in the finasteride group and, overall, no difference in life expectancy between the treated and placebo group was observed [42]. Finally, there is evidence in the literature that, in some instances, CRPCa may benefit from androgen-replacement therapies [43–45]. Overall, these studies suggest that AR may have both negative and positive roles in PCa progression by regulating cell growth and invasion ability [46, 47].

In such a complex scenario, it is clear that more studies are needed to define the role of AR in the different PCa compartments. In addition, investigations should be aimed at evaluating the different AR variants present in the tumors. Indeed a recent study [48], performed in a small series of CRPCa bone metastases ( $n = 30$ ), demonstrated that expression of AR variants lacking the ligand binding domain was associated with poor prognosis and shorter survival rates. If these results will be confirmed in a larger series of subjects, they can open new therapeutic perspectives to target other portions of AR. Of interest, an AR antagonist, EPI-001, able to bind the N-terminal domain of AR, has been recently developed [49, 50]. This antagonist has been found to reduce the growth of CRPCa xenografts [51].

**2.2. Prostate Cancer in Hypogonadal Men.** Although a causative role for circulating androgens on PCa has been envisaged since the Huggins and Hodges studies, data clearly showed that such a link is at best unproved. In a meta-analysis of 18 prospective studies, including almost 4000 men with incident PCa and 6500 control subjects, no associations were found between the risk of PCa and serum concentrations of Testosterone (T), calculated FT, DHT, and other androgens [52]. Furthermore, some authors have documented that low serum T is associated with more aggressive, ADT-resistant tumors suggesting that low levels of androgens create a selective pressure for PCa cells leading to androgen-independence ([53, 54]; for review see [55, 56]).

In line with these data, the pooled odds ratio for Testosterone Replacement Therapy (TRT) derived from 19 randomized clinical trials was 1.09 (0.48–2.49, 95% CI) for PC and 1.19 (0.67–2.09, 95% CI) for PSA > 4 ng/dL or 1.5% increase during study (for review see [55, 56]). Based on critical analysis of clinical trials and on the aforementioned experimental data on PCa cell lines, so far 11 investigators evaluated the effect of TRT even in PCa patients, with the aim of inducing differentiation in the tumor [55, 56]. Overall these studies included 279 subjects previously treated with radical prostatectomy or radiotherapy. In the vast majority of patients no association with progression or clinical recurrence was reported. Despite this evidence, it should be recognized that the number of reported cases is still small and heterogeneous. In the absence of randomized controlled trials (RCT), the concept of using TRT for PCa survivors is debatable. Accordingly, current recommendations suggest limiting TRT to symptomatic hypogonadal men successfully treated for PCa, after a prudent interval, although the length of that interval is not specified [57].

**2.3. Intraprostatic Synthesis of Steroids: Role in PCa Progression.** As mentioned above, intraprostatic androgen synthesis

may support PCa cell growth even in the virtual absence of androgens contributing to development of CRPCa [13]. There is evidence that androgen levels may remain elevated in the prostate during ADT [58, 59]. Moreover, androgens have been found in locally recurrent CRPCa [60] and in distant metastasis [61]. These studies suggest that the PCa may acquire the capability to synthesize androgens although a direct proof can be only obtained by demonstrating the occurrence of steroidogenic machinery in the cells. Results of the latter experiments are contrasting [62, 63]. In particular, in a recent study [62], expression of the steroidogenic enzymes CYP17A1 and HSD3B1, essential for androgen synthesis, has been detected at low levels only in 19 of the 88 tumor samples leading to the conclusion that intratumoral steroid biosynthesis has a limited contribution. However, the elevated expression of 5  $\alpha$ -reductase found in CRPCa samples [63] suggests that *de novo* steroidogenesis may occur bypassing the requirement of T by 5  $\alpha$ -reduction of adrenal precursor steroids [13]. Targeting androgen synthesis in CRPC with abiraterone acetate, a potent inhibitor of CYP17, resulted to be safe and well tolerated, leading to a reduction of the risk of death and increased median survival of some months compared to placebo [64]. At present ongoing investigations are evaluating the efficiency of abiraterone acetate (in combination with other treatments) in the early stages of PC. Efforts are currently directed to understand the mechanisms of resistance to abiraterone acetate and how to prevent it.

**2.4. Modifications of Sex Hormone after Radical Treatment for Prostate Cancer.** Several studies have analyzed the modifications in the levels of T and gonadotropins following radical treatment, producing controversial results [65–68]. In particular, in 55 males treated with radical prostatectomy (RP), a remarkable increase in T, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) has been reported 1 year after RP [69]. These data were confirmed by Olsson et al. [66]. In a group of 49 men, LH and FSH were increased by 71 and 63%, respectively, 12 months after RP without any evident changes in T, suggesting that the hypothalamic pituitary axis was inhibited in patients with PCa and that this inhibition has been removed following RP [69].

Recently, we enrolled 100 men affected by PCa in a single center prospective study, with the aim to evaluate the changes in the serum levels of T, LH, and FSH within the first 3 months after RP for clinically localized PCa and to analyze the correlation between LH and T at various follow-up times [67]. As expected, we found a remarkable positive correlation between T and LH before surgery ( $r = 0.370$ ;  $P < 0.0001$ ), but not 1 month after RP ( $r = 0.109$ ;  $P = 0.303$ ). Three months after prostatectomy, the correlation between T and LH was restored ( $r = 0.273$ ;  $P = 0.054$ ). Therefore, our data demonstrated that RP can induce an early significant decline in the T levels and a compensatory increase in LH and FSH levels. These data have a critical relevance, suggesting that hormone modifications could have an important role in the loss and the subsequent recovery of both urinary continence and potency [70]. Three months after RP, the full recovery of T levels, with persistent high levels of gonadotropins, seems

to delineate the features of compensated hypergonadotropic hypogonadism.

To confirm these data and to analyze the influence of T on sexual activity and urinary continence in men with PCa, we consecutively enrolled 257 patients treated with RP in our center [71]. As expected both age and BMI have a negative impact on preoperative T levels. Moreover, in men with normal T, urinary continence was significantly correlated with sexual function and sexual bother ( $r = 0.2544$ ;  $P = 0.01$  and  $r = 0.2512$ ;  $P = 0.01$ ), whereas this correlation was lost in hypogonadal men.

### 3. Metabolic Syndrome and Prostate Cancer in Elderly Men

Metabolic syndrome describes the combination or clustering of several metabolic abnormalities including central obesity, dyslipidemia, hypertension, insulin resistance with compensatory hyperinsulinemia, and glucose intolerance [72–74]. Recently, epidemiological, histopathological, molecular pathological, and clinical studies have provided emerging evidence of a possible role of MetS and its components in PCa development and progression [74, 75].

Although the only well-established risk factors associated with PCa are age, race, and family history, the large geographical variations in PCa risk suggest that lifestyle and environmental factors may also contribute to its etiology. The possibility to prevent and treat MetS and its components led to novel therapeutic approaches that have been proposed as a new frontier in the prevention and treatment of PCa [74, 76, 77].

**3.1. Definition, Epidemiology, and Pathophysiology.** MetS is a constellation of physiological and biochemical abnormalities characterized by diabetes or high fasting glucose, central obesity, abnormal cholesterol and triglyceride levels, and hypertension [78]. Currently, the two most widely used definitions are those proposed by the National Cholesterol Educational Program Adult Treatment Panel III (NCEP:ATP III) and by the International Diabetes Federation (IDF) focusing on abdominal obesity measured by waist circumference. In contrast, the World Health Organization (WHO) and the European Group for the study on Insulin Resistance (EGIR) definitions are principally focused on IR [73, 74].

Prevalence of MetS increases linearly from the age of 20 until age of 50, when it plateaus and affects more than 40% of the population in the United States and nearly 30% in Europe [79, 80]. Similar to western countries, the prevalence of MetS is rapidly increasing in developing countries, ranging from 9.8% in males from urban north India, to 16.3% in Morocco, to 25.4% in urban Brazil, to 33.5% in South Africa, and to 33.7% in Iran [74, 78, 79]. People with MetS are estimated to have twice the risk of developing cardiovascular disease compared to healthy individuals and a fivefold increased risk of type-2 diabetes. MetS has been recently linked to a number of urological diseases including PCa [72, 75]. Although IR and obesity are considered at the core of the pathophysiology

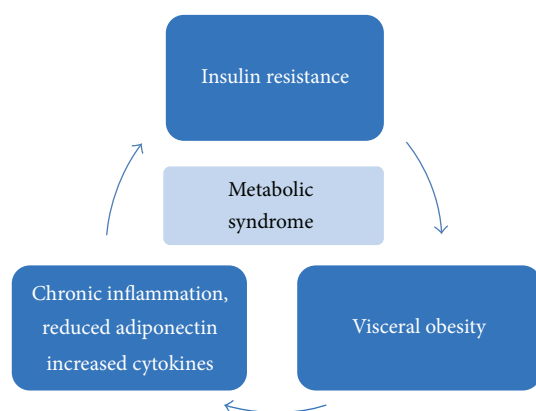


FIGURE 2: The pathophysiological loop of metabolic syndrome.

of MetS, a number of other factors can also be involved in its pathogenesis and potential interactions [73, 74].

In most cases MetS develops as a result of poor eating habits and/or sedentary lifestyles which are associated with IR and obesity. IR occurs when there is a decrease in the responsiveness of peripheral tissues (skeletal muscle, fat, and liver) to the effect of insulin with a concomitant hyperinsulinemia [80]. Hyperinsulinemia is also responsible for stimulating Insulin Growth Factor-1 (IGF) production in the liver. IGF-1 is a potent mitogenic factor and apoptosis inhibitor which has been linked with PCa risk [81].

Central obesity is also considered an early step in the development and progression of MetS. Visceral adipose tissue secretes various bioactive substances known as adipocytokines which can induce IR and have proinflammatory and proatherogenic effects (Figure 2). Cytokines including resistin, leptin, tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-6 (IL-6), C-reactive protein (PCR), fibrinogen, and plasminogen activator inhibitor (PAI-1) are normally increased in obese patients and in patients with DMT2. On the contrary, adiponectin, is lower in individuals with visceral fat accumulation. Adiponectin stimulates glucose metabolism and fatty acid oxidation in the muscle, enhances insulin sensitivity in the liver, increases free fatty acid oxidation, reduces hepatic glucose output, and inhibits monocyte adhesion and macrophage transformation to foam cells within the vascular wall [80, 82]. Visceral adiposity may also contribute to hypogonadism, frequently associated with MetS in men, through increased aromatase activity. Its increased activity in obese patients raises estradiol levels, which results in feedback inhibition at the level of the hypothalamus/pituitary to lower T leading to hypogonadotropic hypogonadism. Elevated estrogen levels lead to a further increase in visceral adipose deposition creating a self-sustained loop [74, 80, 82].

MetS has also been associated with a state of chronic, low-grade inflammation. Several studies showed that patients with MetS were more likely than those without to have elevated levels of a marker of inflammation such as C-reactive protein (CRP) as well as proinflammatory cytokines such as TNF- $\alpha$ , IL-8, IL-6, and IL-1 $\beta$  [83, 84].

**3.2. Relationship between MetS and PCa.** MetS has frequently been associated in human and animal models with carcinogenesis (see Table 1) [85]. It has recently been suggested that evaluating MetS as a single condition may be an inappropriate approach to investigating PCa risk. Specifically, combining all the multiple components of the syndrome into a single variable may confound or obscure the independent effects and interactions of these metabolic components on PCa risk [86]. Each of the primary components of the MetS have been individually observed to be directly associated with PCa risk. DMT2 has been associated with a reduction in PCa risk, probably in relation to the changing action of insulin over the course of diabetes progression [86, 87]. The presence of hypertension may increase PCa risk, in part through increased sympathetic nervous system activity, which can result in androgen-mediated stimulation of PCa cell growth [86]. Men with lower plasma cholesterol were less likely to develop high-grade PCa than men with higher concentrations; this effect might be mediated by several pathways including androgen metabolism and intracellular cholesterol-mediated signaling [88, 89]. Most recent large studies suggest that obesity is associated with a decreased risk of low-grade disease, but an increased risk of high-grade and advanced PCa [74].

Moreover, obesity was associated with an increased risk of intraoperative and perioperative complications and with a worse functional outcome, in men treated with RP [90]. In particular, obese men are at threefold greater risk of intraoperative complications and blood transfusions than not-obese men (adjusted odds ratio (OR) = 3.116,  $P < 0.001$ , and OR = 2.763,  $P < 0.050$ , resp.). Furthermore, the risk of needing at least two pads per day is two and a half times greater in men with a waist circumference of at least 102 cm than in those with a WC below 102 cm (adjusted OR = 2.435,  $P = 0.007$ ).

In conclusion, further basic and clinical studies are needed to evaluate this association by investigating all these metabolic conditions as a whole and to better evaluate the role the MetS and its mediators with the development and progression of PCa.

## 4. Measurement of Quality of Life and Sexual Health in Men with Prostate Cancer

Any treatment of PCa can affect urinary and sexual activity, psychosocial function, and overall wellbeing. Several validated questionnaires have been used to assess QoL after RP. An effective evaluation should consider at least 3 categories of QoL: (1) the organ specific function (urinary and sexual); (2) the physical status and the mental health in the patients with any type of cancer; (3) the general health status. The following validated questionnaires are the most accurate to assess the overall health and quality of life for men with PCa.

**4.1. UCLA-PCI.** The University of California-Los Angeles Prostate Cancer Index (UCLA-PCI) is very accurate to evaluate all aspects related to QoL before and after any treatment for PCA. This questionnaire investigates urinary, bowel and



TABLE 1: Relevant clinical studies of the relationship between MetS and prostate cancer.

| Authors, year                     | Study design                 | Country | Population   | Time      | Age years<br>(range or mean<br>± SD) | Cohort size                                      | Exposure assessment:<br>MetS criteria  | Number<br>of cases | Results (outcome: PCa)   | Level of<br>evidence |
|-----------------------------------|------------------------------|---------|--|-----------|--------------------------------------|--|--|--------------------|--|----------------------|
| Laukkanen et al.,<br>2004 [91]    | Longitudinal<br>cohort study | Finland | Kuopio<br>communities                                  | 1984–2001 | 42–62                                | 1880 (White)                                     | WHO  | 56                 | Risk increase (RR: 1.94,<br>95% CI: 1.06–3.53)   | 2b                   |
| Håheim et al., 2006<br>[92]       | Longitudinal<br>cohort study | Norway  | Oslo study   | 1972–1998 | 40–49                                | 15 933 (White)                                   | Upper quartile levels<br>ATP III criteria  | 507                | Risk increase (RR: 1.56;<br>95 %CI: 1.21–2)  | 2b                   |
| Martin et al., 2009<br>[93]       | Longitudinal<br>cohort study | Norway  | Nord-<br>Trøndelag<br>Health study<br>(HUNT 2)         | 1996–2005 | 48 ± 16.4                            | 29 364 (White)                                   | NCEP: ATP III  | 687                | No association (HR:<br>0.91, 95% CI, 0.877–1.09)   | 2b                   |
| Beebe-Dimmer et al.,<br>2009 [94] | Case-control<br>study        | USA     | Environment<br>and Prostate<br>Cancer study<br>(GECAP) | 2001–2004 | 62 ± 10.4                            | 881 (56%<br>White; 44%<br>African-<br>American)  | NCEP: ATP III  | 637                | Risk increase in<br>African-American<br>population (OR: 1.71,<br>95% CI: 0.97–3.01)  | 3                    |
| Tande et al., 2006 [95]           | Longitudinal<br>cohort study | USA     | Atherosclerosis<br>Risk in<br>Communities<br>(ARIC);   | 1987–2000 | 45–64                                | 6429 (49%<br>White; 61%<br>African-<br>American) | NCEP: ATP III  | 385                | Risk reduction (RR: 0.77;<br>95% CI, 0.51–1.05)  | 2b                   |
| Kheterpal et al., 2012<br>[96]    | Longitudinal<br>cohort study | USA     | Robotic radical<br>prostatectomy                       | 2005–2008 | 45–65                                | 2756   | BMI ≥30 and ≥2 of<br>the following:<br>hypertension,<br>diabetes or elevated<br>blood glucose, and<br>dyslipidemia | 357                | Greater pathology<br>Gleason grade (≥7: 78%<br>versus 64%, $P < 0.001$ )<br>and pathologic stage<br>(≥T3 disease: 43% versus<br>32%, $P < 0.001$ ) | 3                    |
| C. De Nunzio et al.,<br>2011 [78] | Cohort study                 | Italy   | Prostate biopsy<br>cohort study                        | 2009–2010 | 47–83                                | 195 (White)                                      | NCEP: ATP III  | 102                | No association (OR:<br>0.97, 95% CI: 0.48–1.95);<br>Increased risk for<br>Gleason score ≥7 in pts<br>with PCA (OR: 3.82,<br>95% CI: 1.33–10.9)     | 3                    |

sexual function (UF, BF, and SF), and bowel and sexual bother (UB, BB, and SB) and has been designed either for urologists or radiotherapists [97, 98]. The majority of questions were assigned a score from 0 to 100 (0 = worse health; 100 = better health).

**4.2. European Organisation for Research and Treatment of Cancer (Cancer Generic): EORTC QLQ-C-30.** This validated questionnaire, designed to evaluate the QoL in men affected by or treated for any cancer, is a 30-item questionnaire composed of multi-item scales and single items that reflect the multidimensionality of the quality-of-life construct [99]. It incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting), and a global health and QoL scale.

**4.3. Short Form-12 (SF-12).** The SF-12 is the short version of the SF-36 questionnaire [100]. Through 12 questions, it allows investigating, instead of the 8 original scales, only two indices: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The strengths of this form are the brevity and relative ease of use from both patients and physicians. For every question there are from 3 to 5 options.

**4.4. International Index of Erectile Function (IIEF).** The IIEF questionnaire is a validated multidimensional self-administered questionnaire used to assess the erectile function and the response to treatment in clinical trials. A score of 0–5 is awarded to each question that evaluates 4 domains of sexual health: sexual desire, erectile function, orgasmic function, and intercourse satisfaction [101]. Recently, a short form (IIEF-5), based on 5 questions instead of the original 15 questions, has been used.

## 5. Impact of Primary Treatment for Pca on QoL and Sexual Health

Currently, more than half of all PCa are clinically localized at the diagnosis, with a 5-year biochemical disease-free survival above 85% [102]. Treatment options for clinically localized PCa include watchful waiting, radical prostatectomy, radical external beam radiation, and hormone treatment. Nevertheless, while active surveillance may have a minimal impact on either QoL or sexual health, more invasive therapies can lead to clinically significant and lasting side effects [103].

In particular, erectile dysfunction and urinary incontinence after RP, bowel, urinary, and sexual complications after radiotherapy or sexual and continence and mood bothersome after hormone treatment can have a negative impact on all the aspects of QoL, including vitality, social and physical, and emotional limitations.

**5.1. Primary Treatment in the Elderly Men.** The appropriate management of the older men can be a challenge: elderly men are more likely to be diagnosed with higher-grade cancer and the presence of comorbidity and functional decline can impact on treatment tolerance and side effects [104, 105]. Therefore, RT and/or ADT are more commonly used because

they are less invasive and do not carry the risk of surgery and anesthesia.

PC is often diagnosed as a result of routine screening in asymptomatic patients, so the development of late treatment sequelae may be particularly alarming [106], also considering the improvement of life expectancy in elderly population (over 17 years at 65 years old) [107].

QoL is a key criterion in the choice of treatment, particularly for early PC or elderly patients, but it is difficult to assess despite the availability of validated questionnaires [108–112]. Late QoL impact is well documented in the literature, but most of the longest QoL studies did not include pretreatment evaluation [113, 114] or collected it retrospectively [115–117].

Generally, recent cohort prospective studies of patients show a different pattern of late sequelae: an increased prevalence of urinary incontinence after prostatectomy, of urinary irritative obstructive symptoms after brachytherapy, of bowel side effects after EBRT, whereas sexual dysfunction as common late event after all these treatment including ADT [110, 111, 118–120].

In particular, erectile dysfunction (ED) is a critical point related to QoL in men treated for PCa and it is strongly associated with depression and significant distress [119, 121, 122]. ED in these patients is the result of several factors: anatomic changes after surgery or radiotherapy, not only hormonal therapy but also psychological and social factors and finally specific comorbidities that often occur in elderly men (metabolic syndrome, diabetes, obesity, osteoporosis, reduced muscle mass, and strength) [123–126].

**5.2. Radical Prostatectomy.** The major concerns for patients undergoing RP are postprostatectomy incontinence (PPI) and ED. Both QoL and sexual health after RP are strongly dependent on patient age, aging, tumor characteristics, and disease progression [112]. While slight urinary or sexual dysfunction can lead to important bother in younger men, remarkable symptoms can generate minimal bother in the elderly. QoL and sexual health can progressively change owing to anatomical modifications, treatment for PCa, or the natural aging [127]. Therefore, age at time of treatment and perspectives in both sexual and general health have the same clinical relevance of tumor features [128]. Finally, tumor progression or recurrence after RP can generate anxiety and fear that can further worsen QoL and sexual health [129]. In a retrospective, cross-sectional study, enrolling 595 men with PCa treated with radical treatment as primary therapy, we demonstrated that pretreatment tumor characteristics (clinical stage, bioptical Gleason score, and total PSA), treatment timing (age at time of treatment, follow-up duration after treatment, and age at time of follow-up), and posttreatment outcomes (biochemical recurrence and hormonal status) had a remarkable impact on QoL.

One of the leading determinants of QoL and sexual health after RP is the surgical approach: a more conservative procedure, sparing neurovascular bundles, bladder neck, and proximal urethra can strongly increase the chance of better functional outcomes [130, 131]. The decision for the surgical approach is usually a compromise between patient's desire to

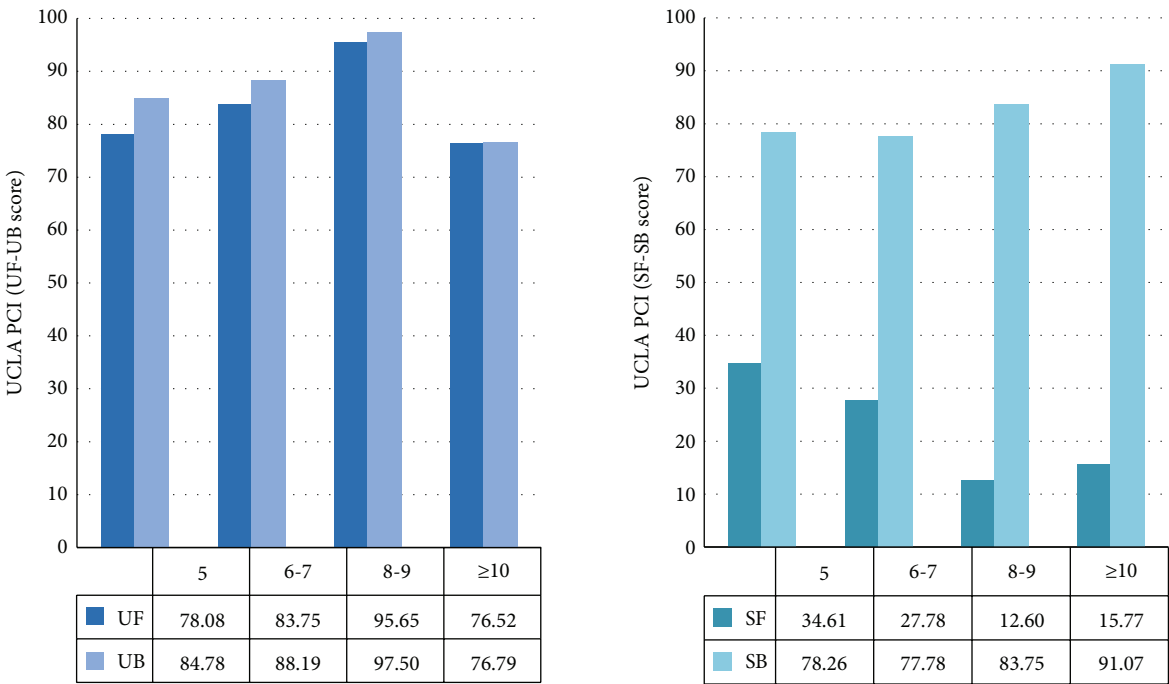


FIGURE 3: Comparison of function and bother in long-term disease-free survivors after nerve sparing RP without hormone treatment: UF: urinary function; UB: urinary bother; SF: sexual function; SB: sexual bother; RP: radical prostatectomy (adapted from [70]).

preserve sexual activity and the eligibility to a conservative surgery based on tumor characteristics (PSA, Clinical stage, bioptical Gleason Score). In a prospective survey on 2,408 PCa patients treated with RP, we demonstrated that at least 737 men (30.6%) were interested in preservation of sexual activity, but not eligible for a nerve-sparing procedure, based on their high-risk PCa features [132]. For 372 (50.5%) of these patients a nerve sparing approach (monolateral or bilateral) was chosen: in these highly selected cases, surgeons' strategy was performed in accordance with patients' desire, without compromising surgical margin status.

The complete recovery of urinary continence after RP is mandatory to preserve general health and to maximize the outcomes of sexual rehabilitation: after catheter removal, most patients reported some level of urinary incontinence [132]. In a multicenter prospective study, we enrolled 1972 men with full continence preoperatively and complete post-operative data: 1 month after RP, 644 (32.7%) were fully continent, 810 (41.1%) were using 0-1 pad/day, and 518 (26.3%) >1pad/day. Age and nerve sparing were not significant predictors of continence recovery after RP, while preoperative erectile function allowed predicting PPI: the integrity of pelvic vasculature and nerves prior to RP was determinant to avoid of early PPI.

ED and urinary continence can improve even beyond more than 1 year postoperatively, with an average time to sexual and urinary recovery of >6 months [133]. Moreover, Phosphodiesterase type 5 inhibitors (PDE5-I), either in nightly or on-demand dosing, are the gold standard to recover sexual function after nerve-sparing prostatectomy [134]. In a multicenter RCT we have randomized men treated

with nerve sparing prostatectomy for localized PCa into 3 groups: (1) PDE5-Is on demand; (2) PDE5-Is once a day; (3) placebo [135]. PDE5-IS improved continence recovery compared with placebo (Improvement of Urinary Function at 3, 6, and 9 months after PDE5-Is once a day versus placebo:  $P = 0.042$ ,  $P = 0.044$ , and  $P = 0.039$ , resp.): the positive effect of PDE5-I on continence recovery, even in the absence of the prostatic gland, suggested a direct activity of PD5-Is on lower urinary tract by a pathway not including prostate. Therefore, the long-term use of PDE5-Is after RP can strongly influence the general QoL, the urinary function, and the sexual health.

During the natural aging process in disease-free survivors after RP, both urinary and sexual symptoms and bother can be strongly modified, due to hormonal modification and both vascular and nerve impairment. Moreover, after long-term disease-free follow-up, several men reconsider their QoL status [136]. In two tertiary referral center for PCa we recruited 367 men treated with RP (for clinically localized PCa), without biochemical failure ( $PSA \leq 0.2$  ng/mL) at the follow-up  $\geq 5$  years, with the aim to evaluate long-term general QoL and sexual health in elderly PCa survivors [70]. Older men presented worse urinary continence regardless of age at time of surgery or follow-up duration. Moreover, after more than 8 years after nerve sparing RP without hormone treatment, patients reported substantial sexual dysfunction, but, interestingly, they were minimally sexually bothered (see Figure 3). Our data confirmed that slight urinary incontinence is poorly tolerated even after several years of complete cancer control, while sexual dysfunction is better tolerated, in the daily life of long-term disease-free survivors, perhaps because patients consider ED as a part of their natural aging.

**5.3. Radiotherapy.** Current indications for external-beam radiotherapy (EBRT) in PC include primary treatment (in localized intracapsular tumors or combined with ADT in locally advanced and high-risk PC), adjuvant treatment in patient with adverse pathologic features, (extracapsular extension, positive surgical margins), and salvage radiotherapy (after radical prostatectomy) [137].

However, over recent years, radiotherapy (RT) has seen major advances such as the introduction of intensity-modulated radiation therapy (IMRT) and image-guided RT (IGRT) [138, 139]. The higher radiation doses that can be delivered to the prostate by these new techniques, whilst sparing surrounding organs, have improved progression-free survival and reduced acute and late toxicities [140, 141]. Several studies investigated this aspect of QoL [119] with a short (1–3 years) or intermediate (4–5 years) follow-up, while longer-term outcomes remain largely unknown. Regarding age of patients, some studies have found equal rates of both acute and late side effects in all age groups [142, 143] while others have found older age to be associated with faster onset and more frequent side effects [71]. A prospective trial evaluating patients more than one year following EBRT treatments with final dose of 70–72 Gy found that older age and diabetes were predictive of both preexisting ED and post-EBRT acquired ED [144].

Sanda et al. concluded a substantial decline from baseline of sexual function at 2 years after surgery, but only a moderate decline after EBRT or brachytherapy. Recovery of sexual function was worse in patients treated with androgen suppression combined with radiotherapy, in older patients, obese patients, and patients with a larger prostate size and a high pretreatment PSA. The patient's QoL concerning sexual function was also significantly related to satisfaction in the partner [111].

Pardo et al., in a Spanish study, had similar results after a follow-up of 3 years in patients treated by surgery or EBRT or brachytherapy [145], as well as Rice et al. in a USA study: the authors concluded that EBRT had no significant impact on sexual function at 12 months and may be offered to older patients with minimal QoL impact [146]. As reported in the studies of Potosky et al. [115], the Prostate Cancer Outcomes Study (PCOS), and the one of Miller et al. [113], the patients treated by surgery had an improvement in their sexual function at 2 years after diagnosis, whereas the patients treated by EBRT had slight declines: a possible explanation of this result is the older age of the group of patients treated by radiotherapy. Instead in the Litwin's et al. report long-term sexual function scores were better among surgical patients, but return to baseline was more rapid in patients treated by EBRT [147].

In their report of a long-term follow-up, Resnick et al. [148] described that, although patients undergoing RP were more likely to have ED at 2–5 years, at 15 years the prevalence of ED is very common, affecting 87% of men treated by surgery and 93.9% of men treated by EBRT: it is matter of debate if this decline is due to late sequelae of oncologic treatments, to normal aging process, or to a combination of these factors. Van der Wielen et al. studied the correlation between ED and dose to penile bulb in patients treated with

doses of 68–78 Gy: but there was no relation found [149]. Mangar et al. demonstrated that a dose received by 90% of the penile bulb (D90) >50 Gy was significantly associated with ED ( $P = 0.006$ ) [150], results comparable to the outcomes of the study of Wernicke et al. [151].

The Radiation Therapy Oncology Group 9406 trial examined 158 men with a regular erectile function at baseline and found a greater risk of impotence with a penile mean dose >52.5 Gy ( $P = 0.039$ ) [152]. So these data are suggestive for a correlation between dose to penile bulb and ED, but more prospective studies are indispensable for predicting preservation of sexual function.

Regarding alternative fractionations, the low  $\alpha/\beta$  ratio of PC causes the high sensitivity of these cells to higher doses for fraction than other tumors [153, 154], even if it is well known that hypofractionated treatments can result in increased rate of late toxicity. In a Canadian prospective study, at 39 months of follow-up, moderate and severe distress related to urinary and bowel symptoms was minimal (3% and 5% of patients, resp.), and the rate of sexual dysfunction was in line with the studies with conventional fractionations [155].

Finally, the few studies available concerning QoL after dose-escalated radiotherapy (thanks to advances in radiotherapy techniques) suggest an increased radiation dose does not result in decline of QoL [156–159].

**5.4. Androgen Deprivation Therapy (ADT).** Approximately 50% of men with PCa receive ADT at some time after diagnosis, and most will take it for at least 2 to 3 years [160, 161]. Currently, luteinizing hormone-releasing hormone (LHRH) agonists are the most frequently used agents for ADT. However, other agents including high-dose estrogen, high-dose ketoconazole, abiraterone, and LHRH antagonists can also be used to achieve a castrate level of T. Single-agent antiandrogen therapy is also used as a form of ADT, but it is more likely to reach lower serum T levels [162].

ADT presents several symptoms of “castration syndrome” as side effects, based on low serum T concentration. The symptoms include loss of libido and sexual interest, erectile dysfunction, general fatigue, decreased intellectual ability, depression, loss of muscle strength, increased abdominal fat mass, and loss of vigor [163]. Several cross-sectional studies have described the effect of ADT on self-reported physical function; these studies consistently found that ADT treated men reported decreased physical function in comparison to nontreated [164, 165].

Regarding the side effects of hormonal therapy, in a Canadian retrospective study of Joly et al. [166, 167] patients treated with ADT for at least 3 months for localized PCa both as adjuvant therapy and as biochemical relapse were enrolled. Tests were administered to assess the: patients had significantly poorer scores than controls, especially for urinary disorders and sexuality ( $P < 0.01$ ). The urinary and sexual symptoms may be primarily due to the prior local treatment. ADT contributed to deterioration in sexual functions, but this study was not designed to address this question; of the patients, 90% reported sexual problem, in agreement with results of other studies [168]. However elderly



patients often report that urinary symptoms have a greater impact than sexual functions on global QoL [166, 169].

In an Australian longitudinal study the authors investigated the change to QoL and T level in men starting an intermittent maximal androgen blockade program. Two hundred and fifty men were recruited in this multicentre study: T suppression leads to a significant reduction in global QoL and deterioration in most function as sexual function. Complete loss of libido increased from 37.2% before treatment to 72.2% after hormonal deprivation. Complete sexual inactivity increased from 54.3% to 86.9%. Following treatment cessation, T recovery was gradual and median time to eugonadal levels of the hormone was 9.3 months with an improvement in emotional function, sexual function, fatigue, sleep, and hot flushes [170].

In the American study of Lubeck, QoL of 1178 newly diagnosed patients was examined (mean age at diagnosis was 73 years) which were enrolled in the Cancer of the Prostate Strategic Urologic Research Endeavor Database. General and disease specific QoL outcomes were measured with tests at study entry and quarterly thereafter. Patients were randomized in 3 groups: ADT, surveillance, radical prostatectomy, or EBRT. Men receiving ADT reported poorer urinary and sexual function and a higher rate of urinary and sexual symptoms than patients selecting surveillance. ADT and surveillance QoL scores remained low in the year after treatment, whereas men treated by RP showed improvement in these scales [167].

In the Australian phase 3 trial of Denham, all patients were given six months of leuporelin, and radiotherapy to the prostate and seminal vesicles after 5 months from randomisation. After leuporelin, patients were given either no further treatment or an additional 12 months of leuporelin. In addition to androgen suppression, men who were randomly allocated to the two bisphosphonate groups were given zoledronic acid for 18 months. In this study, 18 months of androgen suppression worsened the adverse changes in the "patients-reported-outcome" score caused by 6 months of androgen suppression and radiotherapy. However, these increases were restricted to only sexual activity, hormone treatment related symptoms, fatigue, and financial problems at 18 months after randomization. The increases were also restricted in time [171].

Mature survival data from men with previously untreated, locally-advanced disease reveal that bicalutamide monotherapy provides survival benefits that do not differ significantly from castration, while offering important advantages with respect to the maintenance of physical capacity and sexual interest [172]. Also the study of Stav confirms that sexual interest appears to be better preserved with bicalutamide than with castration [173].

In the two largest phase III studies comparing bicalutamide 150 mg/die monotherapy with castration (orchiectomy or the LH-RH agonist goserelin acetate) in 1453 patients, the combined analysis at 12 months showed that bicalutamide was associated with a significant advantage for sexual interest compared with castration ( $P = 0.029$ ), although a decrease was recorded in both groups [174].

## 6. Conclusions

In conclusion, the present review underlines the double role of androgens and the androgen receptor in the development and proliferation of PCa as well as in maintaining a correct functional state of the prostate of elderly men. Evidence in the literature suggests that maintaining a correct function of the androgen receptor may limit PCa progression by keeping a more differentiate state of the cells. Although more RCT are needed to better define the risk/benefit of androgen therapy in elderly men previously cured for PCa, current evidence indicates that treatment with androgens of hypogonadal men with previous PCa may be safe and may ameliorate both sexual health and QoL.

There are several lines of evidence regarding the emerging role of MetS and its components in PCa development and progression. Moreover, MetS can be associated with a state of chronic, low-grade inflammation, in particular in elderly men. We have summarized the evidence about the involvement of MetS in the pathogenesis of PCa, particularly of high-grade disease and we suggested that MetS should be assessed as a new domain in basic and clinical research in elderly men with PCa. In particular, all the components of MetS should be adequately assessed either before or after any treatment of PCa.

It is mandatory to use validated questionnaire to provide adequate details to patients not only regarding urinary and bowel symptoms, but also regarding their sexual function in order to avoid anxiety in patients and their families, to provide adequate medical and psychological counseling, and to analyze the progressive modifications during the follow-up of PCa survivors.

The adverse effects of surgery, radiotherapy, or androgen deprivation may be more pronounced in the elderly population, especially those with lower functional status and increased comorbidities, in particular regarding their sexual health. Therefore it is important to consider the specific benefits and risks for each treatment modality as they apply to the elderly because of the greater risk in both short- and long-term postoperative complications and mortality following any radical treatment.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

## References

- [1] W. A. Sakr, G. P. Haas, B. F. Cassin, J. E. Pontes, and J. D. Crissman, "The frequency of carcinoma and intraepithelial neoplasia of the prostate in young male patients," *Journal of Urology*, vol. 150, no. 2, pp. 379–385, 1993.
- [2] T. J. Guzzo, A. Kutikov, D. J. Canter et al., "The clinical and pathological history of prostate cancer progression in men with a prior history of high grade prostatic intraepithelial neoplasia," *The Canadian Journal of Urology*, vol. 15, no. 4, pp. 4174–4179, 2008.

- [3] A. Alva and M. Hussain, "The changing natural history of metastatic prostate cancer," *Cancer Journal*, vol. 19, no. 1, pp. 19–24, 2013.
- [4] P. Boyle, P. Maisonneuve, and P. Napalkov, "Incidence of prostate cancer will double by the year 2030: the argument for," *European Urology*, vol. 29, no. 2, pp. 3–9, 1996.
- [5] M. Grossmann, A. S. Cheung, and J. D. Zajac, "Androgens and prostate cancer, pathogenesis and deprivation therapy," *Best Practice and Research. Clinical Endocrinology and Metabolism*, vol. 27, no. 4, pp. 603–616, 2013.
- [6] W. J. G. Hellstrom, D. Paduch, and C. F. Donatucci, "Importance of hypogonadism and testosterone replacement therapy in current urologic practice: a review," *International Urology and Nephrology*, vol. 44, no. 1, pp. 61–70, 2012.
- [7] T. I. S. Hwang, H. C. Lo, T. F. Tsai, and H. Y. Chiou, "Association among hypogonadism, quality of life and erectile dysfunction in middle-aged and aged male in Taiwan," *International Journal of Impotence Research*, vol. 19, no. 1, pp. 69–75, 2007.
- [8] Y. Z. Xiang, H. Xiong, Z. L. Cui et al., "The association between metabolic syndrome and the risk of prostate cancer, high-grade prostate cancer, advanced prostate cancer, prostate cancer-specific mortality and biochemical recurrence," *Journal of Experimental and Clinical Cancer Research*, vol. 32, article 9, 2013.
- [9] S. A. Boorjian, J. A. Eastham, M. Graefen et al., "A critical analysis of the long-term impact of radical prostatectomy on cancer control and function outcomes," *European Urology*, vol. 61, no. 4, pp. 664–675, 2012.
- [10] A. E. Kyrдалen, A. A. Dahl, E. Hernes, M. C. Småstuen, and S. D. Fosså, "A national study of adverse effects and global quality of life among candidates for curative treatment for prostate cancer," *BJU International*, vol. 111, no. 2, pp. 221–232, 2013.
- [11] J. Bergman, C. S. Saigal, L. Kwan, and M. S. Litwin, "Responsiveness of the University of California-Los Angeles Prostate Cancer Index," *Urology*, vol. 75, no. 6, pp. 1418–1423, 2010.
- [12] H. Heinzer and T. Steuber, "Prostate cancer in the elderly," *Urologic Oncology*, vol. 27, no. 6, pp. 668–672, 2009.
- [13] A. A. Shafi, A. E. Yen, and N. L. Weigel, "Androgen receptors in hormone-dependent and castration-resistant prostate cancer," *Pharmacology and Therapeutics*, vol. 140, no. 3, pp. 223–238, 2013.
- [14] H. M. Behre, J. Bohmeyer, and E. Nieschlag, "Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls," *Clinical Endocrinology*, vol. 40, no. 3, pp. 341–349, 1994.
- [15] C. Huggins and C. V. Hodges, "Studies on prostatic cancer. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate," *Cancer Research*, vol. 1, pp. 293–297, 1941.
- [16] D. Hessels and J. A. Schalken, "Recurrent gene in prostate cancer: their clinical implications and uses," *Current Urology Reports*, vol. 14, pp. 214–222, 2013.
- [17] B. S. Carver, J. Tran, Z. Chen et al., "ETS rearrangements and prostate cancer initiation," *Nature*, vol. 457, no. 7231, p. E1, 2009.
- [18] Y. Zong, L. Xin, A. S. Goldstein, D. A. Lawson, M. A. Teitell, and O. N. Witte, "ETS family transcription factors collaborate with alternative signaling pathways to induce carcinoma from adult murine prostate cells," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 30, pp. 12465–12470, 2009.
- [19] A. Pettersson, R. E. Graff, S. R. Bauer et al., "The TMPRSS2:ERG rearrangement, ERG expression, and prostate cancer outcomes: a cohort study and meta-analysis," *Cancer Epidemiology, Biomarkers and Prevention*, vol. 21, no. 9, pp. 1497–1509, 2012.
- [20] M. J. McPhaul, "Mechanisms of prostate cancer progression to androgen independence," *Best Practice and Research. Clinical Endocrinology and Metabolism*, vol. 22, no. 2, pp. 373–388, 2008.
- [21] M. Jagla, M. Fève, P. Kessler et al., "A splicing variant of the androgen receptor detected in a metastatic prostate cancer exhibits exclusively cytoplasmic actions," *Endocrinology*, vol. 148, no. 9, pp. 4334–4343, 2007.
- [22] K. Choucair, J. Ejdelman, F. Brimo et al., "PTEN genomic deletion predicts prostate cancer recurrence and is associated with low AR expression and transcriptional activity," *BMC Cancer*, vol. 12, pp. 543–552, 2012.
- [23] L. Sagnak, H. Topaloglu, U. Ozok, and H. Ersoy, "Prognostic significance of neuroendocrine differentiation in prostate adenocarcinoma," *Clinical Genitourinary Cancer*, vol. 9, no. 2, pp. 73–80, 2011.
- [24] L. Tamburrino, F. Salvianti, S. Marchiani et al., "Androgen receptor (AR) expression in prostate cancer and progression of the tumor: lessons from cell lines, animal models and human specimens," *Steroids*, vol. 77, no. 10, pp. 996–1001, 2012.
- [25] S. Minner, M. Enodien, H. Sirma et al., "ERG status is unrelated to PSA recurrence in radically operated prostate cancer in the absence of antihormonal therapy," *Clinical Cancer Research*, vol. 17, no. 18, pp. 5878–5888, 2011.
- [26] Y. Niu, S. Altuwaijri, S. Yeh et al., "Targeting the stromal androgen receptor in primary prostate tumors at earlier stages," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 34, pp. 12188–12193, 2008.
- [27] Y. Niu, S. Altuwaijri, K. P. Lai et al., "Androgen receptor is a tumor suppressor and proliferator in prostate cancer," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 34, pp. 12182–12187, 2008.
- [28] M. Mimeault and S. K. Batra, "Development of animal models underlining mechanistic connections between prostate inflammation and cancer," *World Journal of Clinical Oncology*, vol. 4, no. 1, pp. 4–13, 2013.
- [29] L. Bonaccorsi, V. Carloni, M. Muratori et al., "Androgen receptor expression in prostate carcinoma cells suppresses  $\alpha\beta4$  integrin-mediated invasive phenotype," *Endocrinology*, vol. 141, no. 9, pp. 3172–3182, 2000.
- [30] L. Bonaccorsi, V. Carloni, M. Muratori et al., "EGF receptor (EGFR) signaling promoting invasion is disrupted in androgen-sensitive prostate cancer cells by an interaction between EGFR and androgen receptor (AR)," *International Journal of Cancer*, vol. 112, no. 1, pp. 78–86, 2004.
- [31] L. Bonaccorsi, D. Nosi, M. Muratori, L. Formigli, G. Forti, and E. Baldi, "Altered endocytosis of epidermal growth factor receptor in androgen receptor positive prostate cancer cell lines," *Journal of Molecular Endocrinology*, vol. 38, no. 1-2, pp. 51–66, 2007.
- [32] B. Cinar, K. S. Koeneman, M. Edlund, G. S. Prins, H. E. Zhau, and L. W. K. Chung, "Androgen receptor mediates the reduced tumor growth, enhanced androgen responsiveness, and selected target gene transactivation in a human prostate cancer cell line," *Cancer Research*, vol. 61, no. 19, pp. 7310–7317, 2001.
- [33] R. Davis, D. Jia, B. Cinar et al., "Functional androgen receptor confers sensitization of androgen-independent prostate cancer cells to anticancer therapy via caspase activation," *Biochemical and Biophysical Research Communications*, vol. 309, no. 4, pp. 937–945, 2003.

- [34] V. Guerini, D. Sau, E. Scaccianoce et al., "The androgen derivative 5 $\alpha$ -androstane-3 $\beta$ ,17 $\beta$ -diol inhibits prostate cancer cell migration through activation of the estrogen receptor  $\beta$  subtype," *Cancer Research*, vol. 65, no. 12, pp. 5445–5453, 2005.
- [35] Y. Niu, T. M. Chang, S. Yeh, W. L. Ma, Y. Z. Wang, and C. Chang, "Differential androgen receptor signals in different cells explain why androgen-deprivation therapy of prostate cancer fails," *Oncogene*, vol. 29, no. 25, pp. 3593–3604, 2010.
- [36] M.-L. Zhu and N. Kyprianou, "Role of androgens and the androgen receptor in epithelial-mesenchymal transition and invasion of prostate cancer cells," *The FASEB Journal*, vol. 24, no. 3, pp. 769–777, 2010.
- [37] S. Marchiani, L. Tamburrino, G. Nesi et al., "Androgen-responsive and -unresponsive prostate cancer cell lines respond differently to stimuli inducing neuroendocrine differentiation," *International Journal of Andrology*, vol. 33, no. 6, pp. 784–793, 2010.
- [38] J. Tian, S. O. Lee, L. Liang et al., "Targeting the unique methylation pattern of androgen receptor (AR) promoter in prostate stem/progenitor cells with 5-aza-2'-deoxycytidine (5-AZA) leads to suppressed prostate tumorigenesis," *Journal of Biological Chemistry*, vol. 287, no. 47, pp. 39954–39966, 2012.
- [39] W. Kleeberger, G. S. Bova, M. E. Nielsen et al., "Roles for the stem cell-associated intermediate filament nestin in prostate cancer migration and metastasis," *Cancer Research*, vol. 67, no. 19, pp. 9199–9206, 2007.
- [40] L. Boccon-Gibod, P. Hammerer, S. Madersbacher, N. Mottet, T. Prayer-Galetti, and U. Tunn, "The role of intermittent androgen deprivation in prostate cancer," *BJU International*, vol. 100, no. 4, pp. 738–743, 2007.
- [41] J. D. Debes and D. J. Tindall, "Mechanisms of androgen-refractory prostate cancer," *The New England Journal of Medicine*, vol. 351, no. 15, pp. 1488–1490, 2004.
- [42] I. M. Thompson Jr., P. J. Goodman, C. M. Tangen et al., "Long-term survival of participants in the prostate cancer prevention trial," *The New England Journal of Medicine*, vol. 369, no. 7, pp. 603–610, 2013.
- [43] P. Mathew, "Prolonged control of progressive castration-resistant metastatic prostate cancer with testosterone replacement therapy: the case for a prospective trial," *Annals of Oncology*, vol. 19, no. 2, pp. 395–396, 2008.
- [44] M. J. Morris, D. Huang, W. K. Kelly et al., "Phase 1 trial of high-dose exogenous testosterone in patients with castration-resistant metastatic prostate cancer," *European Urology*, vol. 56, no. 2, pp. 237–244, 2009.
- [45] C. P. Chu, J. M. Kokontis, R. A. Hiipakka et al., "Androgens as therapy for androgen receptor-positive castration-resistant prostate cancer," *Journal of Biomedical Science*, vol. 18, no. 1, article 63, 2011.
- [46] E. Baldi, L. Bonaccorsi, and G. Forti, "Androgen receptor: good guy or bad guy in prostate cancer invasion?" *Endocrinology*, vol. 144, no. 5, pp. 1653–1655, 2003.
- [47] S. Wen, Y. Niu, S. O. Lee, and C. Chang, "Androgen receptor (AR) positive vs negative roles in prostate cancer cell deaths including apoptosis, anoikis, entosis, necrosis and autophagic cell death," *Cancer Treatment Reviews*, vol. 40, no. 1, pp. 31–40, 2014.
- [48] E. Hörnberg, E. B. Ylitalo, S. Crnalic et al., "Expression of androgen receptor splice variants in prostate cancer bone metastases is associated with castration-resistance and short survival," *PLoS ONE*, vol. 6, no. 4, Article ID e19059, 2011.
- [49] R. J. Andersen, N. R. Mawji, J. Wang et al., "Regression of castrate-recurrent prostate cancer by a small-molecule inhibitor of the amino-terminus domain of the androgen receptor," *Cancer Cell*, vol. 17, no. 6, pp. 535–546, 2010.
- [50] M. D. Sadar, "Advances in small molecule inhibitors of androgen receptor for the treatment of advanced prostate cancer," *World Journal of Urology*, vol. 30, no. 3, pp. 311–318, 2012.
- [51] J. K. Myung, C. A. Banuelos, J. G. Fernandez et al., "An androgen receptor N-terminal domain antagonist for treating prostate cancer," *Journal of Clinical Investigation*, vol. 123, no. 7, pp. 2948–2960, 2013.
- [52] A. W. Roddam, N. E. Allen, P. Appleby, and T. J. Key, "Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies," *Journal of the National Cancer Institute*, vol. 100, no. 3, pp. 170–183, 2008.
- [53] G. Severi, H. A. Morris, R. J. MacInnis et al., "Circulating steroid hormones and the risk of prostate cancer," *Cancer Epidemiology Biomarkers and Prevention*, vol. 15, no. 1, pp. 86–91, 2006.
- [54] M. Sofikerim, S. Eskicorapci, Ö. Ozruç, and H. Özen, "Hormonal predictors of prostate cancer," *Urologia Internationalis*, vol. 79, no. 1, pp. 13–18, 2007.
- [55] G. Corona, E. Baldi, and M. Maggi, "Androgen regulation of prostate cancer: where are we now?" *Journal of Endocrinological Investigation*, vol. 34, no. 3, pp. 232–243, 2011.
- [56] G. Corona, M. Gacci, E. Baldi, R. Mancina, G. Forti, and M. Maggi, "Androgen deprivation therapy in prostate cancer: focusing on sexual side effects," *Journal of Sexual Medicine*, vol. 9, no. 3, pp. 887–902, 2012.
- [57] J. Buvat, M. Maggi, A. Guay, and L. O. Torres, "Testosterone deficiency in men: systematic review and standard operating procedures for diagnosis and treatment," *Journal of Sexual Medicine*, vol. 10, pp. 245–284, 2013.
- [58] T. Nishiyama, Y. Hashimoto, and K. Takahashi, "The influence of androgen deprivation therapy on dihydrotestosterone levels in the prostatic tissue of patients with prostate cancer," *Clinical Cancer Research*, vol. 10, no. 21, pp. 7121–7126, 2004.
- [59] S. T. Page, D. W. Lin, E. A. Mostaghel et al., "Persistent intraprostatic androgen concentrations after medical castration in healthy men," *Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 10, pp. 3850–3856, 2006.
- [60] M. A. Titus, M. J. Schell, F. B. Lih, K. B. Tomer, and J. L. Mohler, "Testosterone and dihydrotestosterone tissue levels in recurrent prostate cancer," *Clinical Cancer Research*, vol. 11, no. 13, pp. 4653–4657, 2005.
- [61] R. B. Montgomery, E. A. Mostaghel, R. Vessella et al., "Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth," *Cancer Research*, vol. 68, no. 11, pp. 4447–4454, 2008.
- [62] J. Hofland, W. M. van Weerden, N. F. J. Dits et al., "Evidence of limited contributions for intratumoral steroidogenesis in prostate cancer," *Cancer Research*, vol. 70, no. 3, pp. 1256–1264, 2010.
- [63] K. H. Chang, R. Li, M. Papari-Zareei et al., "Dihydrotestosterone synthesis bypasses testosterone to drive castration-resistant prostate cancer," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 33, pp. 13728–13733, 2011.
- [64] K. Fizazi, H. I. Scher, A. Molina et al., "Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study," *The Lancet Oncology*, vol. 13, no. 10, pp. 983–992, 2012.



- [65] L. R. Miller, A. W. Partin, D. W. Chan et al., "Influence of radical prostatectomy on serum hormone levels," *Journal of Urology*, vol. 160, no. 2, pp. 449–453, 1998.
- [66] S. Madersbacher, G. Schatzl, C. Bieglmayer et al., "Impact of radical prostatectomy and TURP on the hypothalamic-pituitary-gonadal hormone axis," *Urology*, vol. 60, no. 5, pp. 869–874, 2002.
- [67] J. E. Lackner, I. Maerk, A. Koller et al., "Serum inhibin not a cause of low testosterone levels in hypogonadal prostate cancer?" *Urology*, vol. 72, no. 5, pp. 1121–1124, 2008.
- [68] M. Olsson, L. Ekström, J. Schulze et al., "Radical prostatectomy: influence on serum and urinary androgen levels," *Prostate*, vol. 70, no. 2, pp. 200–205, 2010.
- [69] L. R. Miller, A. W. Partin, D. W. Chan et al., "Influence of radical prostatectomy on serum hormone levels," *Journal of Urology*, vol. 160, no. 2, pp. 449–453, 1998.
- [70] M. Gacci, A. Simonato, L. Masieri et al., "Urinary and sexual outcomes in long-term (5+ years) prostate cancer disease free survivors after radical prostatectomy," *Health and Quality of Life Outcomes*, vol. 7, article 94, 2009.
- [71] M. Gacci, G. Corona, A. Apolone et al., "Influence of serum testosterone on urinary continence and sexual activity in patients undergoing radical prostatectomy for clinically localized prostate cancer," *Prostate Cancer and Prostatic Diseases*, vol. 13, no. 2, pp. 168–172, 2010.
- [72] M. G. Kirby, A. Wagg, L. Cardozo et al., "Overactive bladder: is there a link to the metabolic syndrome in men?" *Neurourology and Urodynamics*, vol. 29, no. 8, pp. 1360–1364, 2010.
- [73] E. Kassi, P. Pervanidou, G. Kaltsas, and G. Chrousos, "Metabolic syndrome: definitions and controversies," *BMC Medicine*, vol. 9, article 48, 2011.
- [74] C. de Nunzio, W. Aronson, S. J. Freedland, E. Giovannucci, and J. K. Parsons, "The correlation between metabolic syndrome and prostatic diseases," *European Urology*, vol. 61, no. 3, pp. 560–570, 2012.
- [75] I. Gorbachinsky, H. Akpinar, and D. G. Assimos, "Metabolic syndrome and urologic diseases," *Reviews in Urology*, vol. 12, no. 4, pp. e157–e180, 2010.
- [76] A. W. Hsing, L. C. Sakoda, and S. Chua Jr., "Obesity, metabolic syndrome, and prostate cancer," *The American Journal of Clinical Nutrition*, vol. 86, no. 3, pp. s843–857, 2007.
- [77] W. C. Buschemeyer III and S. J. Freedland, "Obesity and prostate cancer: epidemiology and clinical implications," *European Urology*, vol. 52, no. 2, pp. 331–343, 2007.
- [78] C. De Nunzio, G. Kramer, M. Marberger et al., "The controversial relationship between benign prostatic hyperplasia and prostate cancer: the role of inflammation," *European Urology*, vol. 60, no. 1, pp. 106–117, 2011.
- [79] A. Gupta and V. Gupta, "Metabolic syndrome: what are the risks for humans?" *Bioscience Trends*, vol. 4, no. 5, pp. 204–212, 2010.
- [80] L. Duvnjak and M. Duvnjak, "The metabolic syndrome - an ongoing story," *Journal of Physiology and Pharmacology*, vol. 60, pp. 19–24, 2009.
- [81] T. H. Ngo, R. J. Barnard, P. S. Leung, P. Cohen, and W. J. Aronson, "Insulin-like growth factor I (IGF-I) and IGF binding protein-1 modulate prostate cancer cell growth and apoptosis: possible mediators for the effects of diet and exercise on cancer cell survival," *Endocrinology*, vol. 144, no. 6, pp. 2319–2324, 2003.
- [82] P. L. Huang, "A comprehensive definition for metabolic syndrome," *Disease Models and Mechanisms*, vol. 2, no. 5-6, pp. 231–237, 2009.
- [83] G. Penna, N. Mondaini, S. Amuchastegui et al., "Seminal plasma cytokines and chemokines in prostate inflammation: interleukin 8 as a predictive biomarker in chronic prostatitis/chronic pelvic pain syndrome and benign prostatic hyperplasia," *European Urology*, vol. 51, no. 2, pp. 524–533, 2007.
- [84] S. Devaraj, U. Singh, and I. Jialal, "Human C-reactive protein and the metabolic syndrome," *Current Opinion in Lipidology*, vol. 20, no. 3, pp. 182–189, 2009.
- [85] J. R. Jaggers, X. Sui, S. P. Hooker et al., "Metabolic syndrome and risk of cancer mortality in men," *European Journal of Cancer*, vol. 45, no. 10, pp. 1831–1838, 2009.
- [86] L. P. Wallner, H. Morgenstern, M. E. McGree et al., "The effects of metabolic conditions on prostate cancer incidence over 15 years of follow-up: results from the Olmsted County Study," *BJU International*, vol. 107, no. 6, pp. 929–935, 2011.
- [87] E. Giovannucci, E. B. Rimm, M. J. Stampfer, G. A. Colditz, and W. C. Willett, "Diabetes mellitus and risk of prostate cancer," *Cancer Causes and Control*, vol. 9, no. 1, pp. 3–9, 1998.
- [88] R. J. Hamilton and S. J. Freedland, "Review of recent evidence in support of a role for statins in the prevention of prostate cancer," *Current Opinion in Urology*, vol. 18, no. 3, pp. 333–339, 2008.
- [89] A. M. Mondul, S. L. Clipp, K. J. Helzlsouer, and E. A. Platz, "Association between plasma total cholesterol concentration and incident prostate cancer in the CLUE II cohort," *Cancer Causes and Control*, vol. 21, no. 1, pp. 61–68, 2010.
- [90] M. Gacci, A. Sebastianelli, M. Salvi et al., "Role of abdominal obesity for functional outcomes and complications in men treated with radical prostatectomy for prostate cancer: results of the Multicenter Italian Report on Radical Prostatectomy (MIRROR) study," *Scandinavian Journal of Urology*, 2013.
- [91] C. Laukkanen, A. J. Laukkanen, D. E. Laaksonen et al., "Metabolic syndrome and the risk of prostate cancer in Finnish men: a population-based study," *Cancer Epidemiology Biomarkers and Prevention*, vol. 13, no. 10, pp. 1646–1650, 2004.
- [92] L. L. Håheim, T. F. Wisløff, I. Holme, and P. Nafstad, "Metabolic syndrome predicts prostate cancer in a cohort of middle-aged Norwegian men followed for 27 years," *The American Journal of Epidemiology*, vol. 164, no. 8, pp. 769–774, 2006.
- [93] R. M. Martin, L. Vatten, D. Gunnell, P. Romundstad, and T. I. L. Nilsen, "Components of the metabolic syndrome and risk of prostate cancer: the HUNT 2 cohort, Norway," *Cancer Causes and Control*, vol. 20, no. 7, pp. 1181–1192, 2009.
- [94] J. L. Beebe-Dimmer, N. L. Nock, C. Neslund-Dudas et al., "Racial differences in risk of prostate cancer associated with metabolic syndrome," *Urology*, vol. 74, no. 1, pp. 185–190, 2009.
- [95] A. J. Tande, E. A. Platz, and A. R. Folsom, "The metabolic syndrome is associated with reduced risk of prostate cancer," *The American Journal of Epidemiology*, vol. 164, no. 11, pp. 1094–1102, 2006.
- [96] E. Kheterpal, J. D. Sammon, M. Diaz et al., "Effect of metabolic syndrome on pathologic features of prostate cancer," *Urologic Oncology*, vol. 31, no. 7, pp. 1054–1059.
- [97] M. S. Litwin, R. D. Hays, A. Fink, P. A. Ganz, B. Leake, and R. H. Brook, "The UCLA prostate cancer index: development, reliability, and validity of a health-related quality of life measure," *Medical Care*, vol. 36, no. 7, pp. 1002–1012, 1998.
- [98] M. Gacci, L. Livi, F. Paia et al., "Quality of life after radical treatment of prostate cancer: validation of the Italian version of the University of California-Los Angeles Prostate Cancer Index," *Urology*, vol. 66, no. 2, pp. 338–343, 2005.



- [99] M. J. Hjermsstad, S. D. Fossa, K. Bjordal, and S. Kaasa, "Test/retest study of the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire," *Journal of Clinical Oncology*, vol. 13, no. 5, pp. 1249–1254, 1995.
- [100] J. E. Ware Jr., M. Kosinski, and S. D. Keller, "A 12-Item short-form health survey: construction of scales and preliminary tests of reliability and validity," *Medical Care*, vol. 34, no. 3, pp. 220–233, 1996.
- [101] R. C. Rosen, A. Riley, G. Wagner, I. H. Osterloh, J. Kirkpatrick, and A. Mishra, "The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction," *Urology*, vol. 49, no. 6, pp. 822–830, 1997.
- [102] R. E. Mitchell, J. B. Shah, C. A. Olsson, M. C. Benson, and J. M. McKiernan, "Does year of radical prostatectomy independently predict outcome in prostate cancer?" *Urology*, vol. 67, no. 2, pp. 368–372, 2006.
- [103] J. J. Daubenmier, G. Weidner, R. Marlin et al., "Lifestyle and health-related quality of life of men with prostate cancer managed with active surveillance," *Urology*, vol. 67, no. 1, pp. 125–130, 2006.
- [104] K. E. Hoffman, "Management of older men with clinically localized prostate cancer: the significance of advanced age and comorbidity," *Seminars in Radiation Oncology*, vol. 22, no. 4, pp. 284–294, 2012.
- [105] S. X. Bian and K. E. Hoffman, "Management of prostate cancer in elderly men," *Seminars in Radiation Oncology*, vol. 23, no. 3, pp. 198–205, 2013.
- [106] S. Cameron, C. Springer, S. Fox-Wasylyshyn, and M. M. El-Masri, "A descriptive study of functions, symptoms, and perceived health state after radiotherapy for prostate cancer," *European Journal of Oncology Nursing*, vol. 16, no. 3, pp. 310–314, 2012.
- [107] National Center for Health Statistics, *Health, United States, 2010: with Special Feature on Death and Dying*, National Center for Health Statistics, Hyattsville, Md, USA, 2011.
- [108] A. Goineau, V. Marchand, J. Rigaud et al., "Prospective evaluation of quality of life 54 months after high-dose intensity-modulated radiotherapy for localized prostate cancer," *Radiation Oncology*, vol. 8, article 53, 2013.
- [109] H. E. Niezgodna and J. L. Pater, "A validation study of the domains of the core EORTC quality of life questionnaire," *Quality of Life Research*, vol. 2, no. 5, pp. 319–325, 1993.
- [110] M. Ferrer, J. F. Suárez, F. Guedea et al., "Health-related quality of life 2 years after treatment with radical prostatectomy, prostate brachytherapy, or external beam radiotherapy in patients with clinically localized prostate cancer," *International Journal of Radiation Oncology Biology Physics*, vol. 72, no. 2, pp. 421–432, 2008.
- [111] M. G. Sanda, R. L. Dunn, J. Michalski et al., "Quality of life and satisfaction with outcome among prostate-cancer survivors," *The New England Journal of Medicine*, vol. 358, no. 12, pp. 1250–1261, 2008.
- [112] J. T. Wei, R. L. Dunn, M. S. Litwin, H. M. Sandler, and M. G. Sanda, "Development and validation of the Expanded Prostate Cancer Index Composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer," *Urology*, vol. 56, no. 6, pp. 899–905, 2000.
- [113] D. C. Miller, M. G. Sanda, R. L. Dunn et al., "Long-term outcomes among localized prostate cancer survivors: health-related quality-of-life changes after radical prostatectomy, external radiation, and brachytherapy," *Journal of Clinical Oncology*, vol. 23, no. 12, pp. 2772–2780, 2005.
- [114] S. J. Frank, L. L. Pisters, J. Davis, A. K. Lee, R. Bassett, and D. A. Kuban, "An assessment of quality of life following radical prostatectomy, high dose external beam radiation therapy and brachytherapy iodine implantation as monotherapies for localized prostate cancer," *Journal of Urology*, vol. 177, no. 6, pp. 2151–2156, 2007.
- [115] A. L. Potosky, W. W. Davis, R. M. Hoffman et al., "Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study," *Journal of the National Cancer Institute*, vol. 96, no. 18, pp. 1358–1367, 2004.
- [116] R. M. Hoffman, F. D. Gilliland, D. F. Penson, S. N. Stone, W. C. Hunt, and A. L. Potesky, "Cross-sectional and longitudinal comparisons of health-related quality of life between patients with prostate carcinoma and matched controls," *Cancer*, vol. 101, no. 9, pp. 2011–2019, 2004.
- [117] D. P. Smith, M. T. King, S. Egger et al., "Quality of life three years after diagnosis of localised prostate cancer: population based cohort study," *BMJ*, vol. 339, pp. b4817–b4828, 2009.
- [118] I. J. Korfage, M. L. Essink-Bot, G. J. J. M. Borsboom et al., "Five-year follow-up of health-related quality of life after primary treatment of localized prostate cancer," *International Journal of Cancer*, vol. 116, no. 2, pp. 291–296, 2005.
- [119] B. S. Hoppe, "Erectile function, incontinence, and other quality of life outcomes following proton therapy for prostate cancer in men 60 years old and younger," *Cancer*, vol. 118, no. 18, pp. 4619–4626, 2012.
- [120] S. X. Bian, "Management of prostate cancer in elderly men," *Seminars in Radiation Oncology*, vol. 23, no. 3, pp. 198–205, 2013.
- [121] C. J. Nelson, J. P. Mulhall, and A. J. Roth, "The association between erectile dysfunction and depressive symptoms in men treated for prostate cancer," *Journal of Sexual Medicine*, vol. 8, no. 2, pp. 560–566, 2011.
- [122] Å. R. Helgason, J. Adolfsson, P. Dickman, M. Fredrikson, S. Arver, and G. Steineck, "Waning sexual function - the most important disease-specific distress for patients with prostate cancer," *British Journal of Cancer*, vol. 73, no. 11, pp. 1417–1421, 1996.
- [123] B. Lunenfeld, S. Arver, I. Moncada, D. A. Rees, and H. M. Schulte, "How to help the aging male? Current approaches to hypogonadism in primary care," *The Aging Male*, vol. 15, no. 4, pp. 187–197, 2012.
- [124] L. Incrocci and P. T. Jensen, "Pelvic radiotherapy and sexual function in men and women," *The Journal of Sexual Medicine*, vol. 10, supplement 1, pp. 53–64, 2013.
- [125] M. Alemozaffar, M. M. Regan, M. R. Cooperberg et al., "Prediction of erectile function following treatment for prostate cancer," *Journal of the American Medical Association*, vol. 306, no. 11, pp. 1205–1214, 2011.
- [126] P. I. Karakiewicz, N. Bhojani, A. Neugut et al., "The effect of comorbidity and socioeconomic status on sexual and urinary function and on general health-related quality of life in men treated with radical prostatectomy for localized prostate cancer," *Journal of Sexual Medicine*, vol. 5, no. 4, pp. 919–927, 2008.
- [127] D. P. Lubeck, M. S. Litwin, J. M. Henning, M. L. Stoddard, S. C. Flanders, and P. R. Carroll, "Changes in health-related quality of life in the first year after treatment for prostate cancer: results from caPSURE," *Urology*, vol. 53, no. 1, pp. 180–186, 1999.
- [128] F. Rabbani, A. M. F. Stapleton, M. W. Kattan, T. M. Wheeler, and P. T. Scardino, "Factors predicting recovery of erections after radical prostatectomy," *Journal of Urology*, vol. 164, no. 6, pp. 1929–1934, 2000.

- [129] S. J. Knight and D. M. Latini, "Sexual side effects and prostate cancer treatment decisions. Patient information needs and preferences," *Cancer Journal*, vol. 15, no. 1, pp. 41–44, 2009.
- [130] S. Carter, J. D. Le, and J. C. Hu, "Anatomic and technical considerations for optimizing recovery of sexual function during robotic-assisted radical prostatectomy," *Current Opinion in Urology*, vol. 23, no. 1, pp. 88–94, 2013.
- [131] A. A. Vora, D. Dajani, J. H. Lynch, and K. J. Kowalczyk, "Anatomic and technical considerations for optimizing recovery of urinary function during robotic-assisted radical prostatectomy," *Current Opinion in Urology*, vol. 23, no. 1, pp. 78–87, 2013.
- [132] F. J. Bianco Jr., P. T. Scardino, and J. A. Eastham, "Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta")," *Urology*, vol. 66, no. 5, pp. 83–94, 2005.
- [133] M. S. Litwin, G. Y. Melmed, and T. Nakazon, "Life after radical prostatectomy: a longitudinal study," *Journal of Urology*, vol. 166, no. 2, pp. 587–592, 2001.
- [134] A. Briganti, A. Salonia, A. Gallina et al., "Management of erectile dysfunction after radical prostatectomy in 2007," *World Journal of Urology*, vol. 25, no. 2, pp. 143–148, 2007.
- [135] M. Gacci, A. Ierardi, A. D. Rose et al., "Vardenafil can improve continence recovery after bilateral nerve sparing prostatectomy: results of a randomized, double blind, placebo-controlled pilot study," *Journal of Sexual Medicine*, vol. 7, no. 1, pp. 234–243, 2010.
- [136] E. Sacco, T. Prayer-Galetti, F. Pinto et al., "Urinary incontinence after radical prostatectomy: incidence by definition, risk factors and temporal trend in a large series with a long-term follow-up," *BJU International*, vol. 97, no. 6, pp. 1234–1241, 2006.
- [137] N. Lumen, P. Ost, C. van Praet et al., "Developments in external beam radiotherapy for prostate cancer," *Urology*, vol. 82, no. 1, pp. 5–10, 2013.
- [138] A. Lisbona, D. Averbeck, S. Supiot et al., "IMRT combined to IGRT: increase of the irradiated volume. Consequences?" *Cancer Radiothérapie*, vol. 14, no. 6-7, pp. 563–570, 2010.
- [139] G. Crehange, C. Mirjolet, M. Gauthier et al., "Clinical impact of margin reduction on late toxicity and short-term biochemical control for patients treated with daily on-line image guided IMRT for prostate cancer," *Radiotherapy and Oncology*, vol. 103, no. 2, pp. 244–246, 2012.
- [140] A. Pollack, G. K. Zagars, L. G. Smith et al., "Preliminary results of a randomized radiotherapy dose-escalation study comparing 70 Gy with 78 Gy for prostate cancer," *Journal of Clinical Oncology*, vol. 18, no. 23, pp. 3904–3911, 2000.
- [141] M. J. Zelefsky, E. J. Levin, M. Hunt et al., "Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer," *International Journal of Radiation Oncology Biology Physics*, vol. 70, no. 4, pp. 1124–1129, 2008.
- [142] A. B. Jani, S. D. Parikh, S. Vijayakumar, and J. Gratzle, "Analysis of influence of age on acute and chronic radiotherapy toxicity in treatment of prostate cancer," *Urology*, vol. 65, no. 6, pp. 1157–1162, 2005.
- [143] H. Geinitz, F. B. Zimmermann, R. Thamm, A. Schumertl, R. Busch, and M. Molls, "3D conformal radiation therapy for prostate cancer in elderly patients," *Radiotherapy and Oncology*, vol. 76, no. 1, pp. 27–34, 2005.
- [144] M. Pinkawa, B. Gagel, M. D. Piroth et al., "Erectile dysfunction after external beam radiotherapy for prostate cancer," *European Urology*, vol. 55, no. 1, pp. 227–236, 2009.
- [145] Y. Pardo, F. Guedea, F. Aguiló et al., "Quality-of-life impact of primary treatments for localized prostate cancer in patients without hormonal treatment," *Journal of Clinical Oncology*, vol. 28, no. 31, pp. 4687–4696, 2010.
- [146] K. Rice, J. Hudak, K. Peay et al., "Comprehensive quality-of-life outcomes in the setting of a multidisciplinary, equal access prostate cancer clinic," *Urology*, vol. 76, no. 5, pp. 1231–1238, 2010.
- [147] M. S. Litwin, J. L. Gore, L. Kwan et al., "Quality of life after surgery, external beam irradiation, or brachytherapy for early-stage prostate cancer," *Cancer*, vol. 109, no. 11, pp. 2239–2247, 2007.
- [148] M. J. Resnick, T. Koyama, K. H. Fan et al., "Long-term functional outcomes after treatment for localized prostate cancer," *The New England Journal of Medicine*, vol. 368, no. 5, pp. 436–445, 2013.
- [149] G. J. van der Wielen, M. S. Hoogeman, G. R. Dohle, W. L. J. van Putten, and L. Incrocci, "Dose-volume parameters of the corpora cavernosa do not correlate with erectile dysfunction after external beam radiotherapy for prostate cancer: results from a dose-escalation trial," *International Journal of Radiation Oncology Biology Physics*, vol. 71, no. 3, pp. 795–800, 2008.
- [150] S. A. Mangar, M. R. Sydes, H. L. Tucker et al., "Evaluating the relationship between erectile dysfunction and dose received by the penile bulb: using data from a randomised controlled trial of conformal radiotherapy in prostate cancer (MRC RT01, ISRCTN47772397)," *Radiotherapy and Oncology*, vol. 80, no. 3, pp. 355–362, 2006.
- [151] A. G. Wernicke, R. Valicenti, K. DiEva, C. Houser, and E. Pequignot, "Radiation dose delivered to the proximal penis as a predictor of the risk of erectile dysfunction after three-dimensional conformal radiotherapy for localized prostate cancer," *International Journal of Radiation Oncology Biology Physics*, vol. 60, no. 5, pp. 1357–1363, 2004.
- [152] M. Roach, K. Winter, J. M. Michalski et al., "Penile bulb dose and impotence after three-dimensional conformal radiotherapy for prostate cancer on RTOG 9406: findings from a prospective, multi-institutional, phase I/II dose-escalation study," *International Journal of Radiation Oncology Biology Physics*, vol. 60, no. 5, pp. 1351–1356, 2004.
- [153] D. J. Brenner and E. J. Hall, "Fractionation and protraction for radiotherapy of prostate carcinoma," *International Journal of Radiation Oncology, Biology, Physics*, vol. 43, no. 5, pp. 1095–1101, 2009.
- [154] R. Miralbell, S. A. Roberts, E. Zubizarreta, and J. H. Hendry, "Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5, 969 patients in seven international institutional datasets:  $\alpha/\beta = 1.4$  (0.9–2.2)," *International Journal of Radiation Oncology Biology Physics*, vol. 82, no. 1, pp. e17–e24, 2012.
- [155] H. Quon, C. F. Cheung, and D. A. Loblaw, "Quality of life after hypofractionated concomitant intensity-modulated radiotherapy boost for high-risk prostate cancer," *International Journal of Radiation Oncology Biology Physics*, vol. 83, no. 2, pp. 617–623, 2012.
- [156] S. Namiki, S. Ishidoya, T. Tochigi et al., "Health-related quality of life after intensity modulated radiation therapy for localized prostate cancer: comparison with conventional and conformal radiotherapy," *Japanese Journal of Clinical Oncology*, vol. 36, no. 4, pp. 224–230, 2006.
- [157] D. J. Little, D. A. Kuban, L. B. Levy, G. K. Zagars, and A. Pollack, "Quality-of-life questionnaire results 2 and 3 years

- after radiotherapy for prostate cancer in a randomized dose-escalation study,” *Urology*, vol. 62, no. 4, pp. 707–713, 2003.
- [158] P. A. Kupelian, C. A. Reddy, E. A. Klein, and T. R. Willoughby, “Short-course intensity-modulated radiotherapy (70 GY at 2.5 GY per fraction) for localized prostate cancer: preliminary results on late toxicity and quality of life,” *International Journal of Radiation Oncology Biology Physics*, vol. 51, no. 4, pp. 988–993, 2001.
- [159] K. B. Dieperink, S. Hansen, L. Wagner et al., “Living alone, obesity and smoking: important factors for quality of life after radiotherapy and androgen deprivation therapy for prostate cancer,” *Acta Oncologica*, vol. 51, no. 6, pp. 722–729, 2012.
- [160] M. Bolla, L. Collette, L. Blank et al., “Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial,” *The Lancet*, vol. 360, no. 9327, pp. 103–108, 2002.
- [161] M. R. Cooperberg, G. D. Grossfeld, D. P. Lubeck, and P. R. Carroll, “National practice patterns and time trends in androgen ablation for localized prostate cancer,” *Journal of the National Cancer Institute*, vol. 95, no. 13, pp. 981–989, 2003.
- [162] E. Wibowo and R. J. Wassersug, “The effect of estrogen on the sexual interest of castrated males: implications to prostate cancer patients on androgen-deprivation therapy,” *Critical Reviews in Oncology/Hematology*, vol. 87, no. 3, pp. 224–238, 2013.
- [163] A. Tsujimura, “Role of androgen in the elderly. Problems of androgen deprivation therapy,” *Clinical Calcium*, vol. 23, no. 8, pp. 1185–1190, 2013.
- [164] S. D. Fossa, H. Woehre, K.-H. Kurth et al., “Influence of urological morbidity on quality of life in patients with prostate cancer,” *European Urology*, vol. 31, no. 3, pp. 3–8, 1997.
- [165] K. Dacal, S. M. Sereika, and S. L. Greenspan, “Quality of life in prostate cancer patients taking androgen deprivation therapy,” *Journal of the American Geriatrics Society*, vol. 54, no. 1, pp. 85–90, 2006.
- [166] F. Joly, S. M. H. Alibhai, J. Galica et al., “Impact of androgen deprivation therapy on physical and cognitive function, as well as quality of life of patients with nonmetastatic prostate cancer,” *Journal of Urology*, vol. 176, no. 6, pp. 2443–2447, 2006.
- [167] D. P. Lubeck, G. D. Grossfeld, and P. R. Carroll, “The effect of androgen deprivation therapy on health-related quality of life in men with prostate cancer,” *Urology*, vol. 58, no. 2, pp. 94–99, 2001.
- [168] J. M. Holzbeierlein, M. D. McLaughlin, and J. B. Thrasher, “Complications of androgen deprivation therapy for prostate cancer,” *Current Opinion in Urology*, vol. 14, no. 3, pp. 177–183, 2004.
- [169] A. Descaseaud, J. Chaskalovic, B. Debré, M. Zerbib, and M. Peyromaure, “Sexual function after radical prostatectomy does not affect global patient satisfaction,” *Progres en Urologie*, vol. 14, no. 6, pp. 1177–1180, 2004.
- [170] N. A. Spry, L. Kristjanson, B. Hooton et al., “Adverse effects to quality of life arising from treatment can recover with intermittent androgen suppression in men with prostate cancer,” *European Journal of Cancer*, vol. 42, no. 8, pp. 1083–1092, 2006.
- [171] J. W. Denham, C. Wilcox, D. Joseph et al., “Quality of life in men with locally advanced prostate cancer treated with leuprorelin and radiotherapy with or without zoledronic acid (TROG 03.04 RADAR): secondary endpoints from a randomised phase 3 factorial trial,” *The Lancet Oncology*, vol. 13, no. 12, pp. 1260–1270, 2012.
- [172] P. F. Schellhammer, “An evaluation of bicalutamide in the treatment of prostate cancer,” *Expert Opinion on Pharmacotherapy*, vol. 3, no. 9, pp. 1313–1328, 2002.
- [173] S. Y. Stav and G. Segal, “The role of bicalutamide in the treatment of prostate cancer,” *Harefuah*, vol. 141, no. 4, pp. 379–407, 2002.
- [174] P. Iversen, C. J. Tyrrell, A. V. Kaisary et al., “Casodex (bicalutamide) 150-mg monotherapy compared with castration in patients with previously untreated nonmetastatic prostate cancer: results from two multicenter randomized trials at a median follow-up of 4 years,” *Urology*, vol. 51, no. 3, pp. 389–396, 1998.

## Clinical Study

# Effects of Long-Term Testosterone Therapy on Patients with “Diabesity”: Results of Observational Studies of Pooled Analyses in Obese Hypogonadal Men with Type 2 Diabetes

Ahmad Haider,<sup>1</sup> Aksam Yassin,<sup>2,3,4</sup> Gheorghe Doros,<sup>5</sup> and Farid Saad<sup>4,6</sup>

<sup>1</sup> Private Urology Practice, 27570 Bremerhaven, Germany

<sup>2</sup> Institute for Urology and Andrology, 22846 Norderstedt, Germany

<sup>3</sup> International University, 01067 Dresden, Germany

<sup>4</sup> Research Department, Gulf Medical University, Ajman, UAE

<sup>5</sup> Department of Epidemiology and Statistics, Boston University School of Public Health, Boston, MA 02118, USA

<sup>6</sup> Global Medical Affairs Andrology, Bayer Pharma, 13353 Berlin, Germany

Correspondence should be addressed to Farid Saad; [farid.saad@bayer.com](mailto:farid.saad@bayer.com)

Received 30 October 2013; Revised 23 December 2013; Accepted 24 December 2013; Published 11 March 2014

Academic Editor: Antonio Aversa

Copyright © 2014 Ahmad Haider et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

To investigate effects of long-term testosterone (T) therapy in obese men with T deficiency (TD) and type 2 diabetes mellitus (T2DM), data were collected from two observational, prospective, and cumulative registry studies of 561 men with TD receiving T therapy for up to 6 years. A subgroup of obese hypogonadal men with T2DM was analyzed. Weight, height, waist circumference (WC), fasting blood glucose (FBG), glycated haemoglobin (HbA<sub>1c</sub>), blood pressure, lipid profile, C-reactive protein (CRP), and liver enzymes were measured. A total of 156 obese, diabetic men with T deficiency, aged  $61.17 \pm 6.18$  years, fulfilled selection criteria. Subsequent to T therapy, WC decreased by 11.56 cm and weight declined by 17.49 kg (15.04%). Fasting glucose declined from  $7.06 \pm 1.74$  to  $5.59 \pm 0.94$  mmol/L ( $P < 0.0001$  for all). HbA<sub>1c</sub> decreased from 8.08 to 6.14%, with a mean change of 1.93%. Systolic and diastolic blood pressure, lipid profiles including total cholesterol: HDL ratio, CRP, and liver enzymes all improved ( $P < 0.0001$ ). Long-term T therapy for up to 6 years resulted in significant and sustained improvements in weight, T2DM, and other cardiometabolic risk factors in obese, diabetic men with TD and this therapy may play an important role in the management of obesity and diabetes (*diabesity*) in men with T deficiency.

## 1. Introduction

Obesity has recently been recognized as a chronic disease condition necessitating appropriate medical treatment and not merely a transient condition that can be ameliorated simply with diet and exercise alone [1]. Obesity impacts quality of life and shortens life expectancy. A worldwide increase in the obesity epidemic has been reported. The increase in obesity, coupled with increased insulin resistance (IR) and T2DM, represents a healthcare crisis in developed and developing countries. Obesity is also associated with a host of other comorbidities including sleep apnoea, hypogonadism (testosterone deficiency, TD), dyslipidaemia, and hypertension. The

prevalence of obesity and T2DM in the USA is higher than reported in other parts of the world and obesity is now considered a disease condition to be treated as any other disease conditions. The prevalence of diabetes increased by 7.3% and obesity increased by 7.8% during the past decade [2]. Obesity is associated with increased risk of IR and T2DM [3]. This increased risk was attributed to release of nonesterified fatty acids, glycerol, hormones, proinflammatory cytokines, and other factors from adipose tissue in obese individuals. The risk of developing T2DM may be reduced by 50–60% with a modest weight loss (WL) of 5–7% of body weight [4]. Huang et al. [5] projected the distribution of newly diagnosed, undiagnosed, and established cases of diabetes in the USA



from 2009 to 2034 and estimated that the number of people with diagnosed and undiagnosed, diabetes will increase from 23.7 million to 44.1 million during this period. The obesity distribution in the population without diabetes will remain stable over time with ~65% of individuals of the population being overweight or obese [5]. Seidell et al. [6] reported that visceral fat accumulation is associated with increased insulin and C-peptide and with glucose intolerance [6].

In the early 1970s, Sims et al. [7] coined the term “diabesity” to describe the strong common link between diabetes and obesity, when they exist in the same individual. The risk of T2DM increases with body weight gain and obesity [8–12] and, more importantly, visceral fat accumulation reduces insulin sensitivity and increases IR, thus increasing risk of T2DM [13]. It is estimated that the risk of diabetes worldwide will exceed 171 million and may reach 366 million by the year 2030 [14]. Because increases in obesity are paralleled with increases in T2DM [14], the diagnosis of obesity and T2DM in the same individual presents clinical and therapeutic challenges to healthcare providers [15]. It should be recognized that T2DM complications contribute to cardiovascular disease (CVD), stroke, neuropathy, nephropathy, and retinopathy [16]. On the other hand, obesity confers increased hypertension, dyslipidaemia, stroke, cancer, depression, and obstructive sleep apnoea in addition to T2DM. Thus, the combination of T2DM and obesity in the same individual (diabesity) will have even more complications than either condition alone. The presence of obesity and T2DM in the same individual represents a complex relationship between these conditions. Clearly, it is established that the increased incidence of obesity and T2DM contributes to higher incidence of CVD, hypertension, stroke, cancer, and increased mortality [17, 18]. The frequency of CVD and T2DM increased with increased body mass index (BMI) and WC. This relationship between WC, CVD, and T2DM was noted even in patients with  $\text{BMI} \leq 25 \text{ kg/m}^2$  [17].

Recent studies have provided a critical assessment of the therapeutic options in diabetes and obesity and highlighted the various approaches used to date, including (a) antidiabetics, (b) incretin and glucagon like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase inhibitors, (c) lifestyle modifications, (d) antiobesity agents, and (e) bariatric surgery [1, 19]. For instance, a recent report showed that bariatric surgery resulted in significant and sustained remission and improvement of T2DM and other metabolic factors in severely obese patients [20]. Indeed, some of the therapeutic strategies discussed above will be met with success in some patients while in others it may not. There remains a need for new and innovative alternative approaches to the management of diabetes and obesity. Recently, angiopoietin-like proteins (ANGPTLs) have been suggested as targets for treatment of obesity [21]. It was proposed that suppression of expression of ANGPTL2 and increased expression of ANGPTL6 may represent a therapeutic target for treatment of obesity [21].

Several studies have suggested that TD may contribute to development of obesity, IR, and T2DM and T therapy of men with TD may ameliorate these conditions [22–28]. Men with TD treated with T therapy experienced a

positive effect on visceral obesity, as determined by reduction in body weight (–2.66%), waist-hip ratio (–3.96%), and body fat (–5.65%) when compared to the control group [29]. This treatment also resulted in decreased fasting blood glucose and mean glycated haemoglobin ( $\text{HbA}_{1c}$ ) [29]. Kapoor et al. [27] also demonstrated that T therapy in men with T2DM reduced visceral adiposity and reduced homoeostasis model assessment (HOMA) index,  $\text{HbA}_{1c}$ , and fasting glucose, suggesting improvement in insulin sensitivity and glycaemic control in men with TD and T2DM [27]. Jones et al. [28] examined the effects of T therapy on IR, CVD risk, and symptoms of T deficiency in men with T2DM and/or MetS over a 12-month trial period. T therapy improved glycaemic control and reduced HOMA-IR as well as  $\text{HbA}_{1c}$ , suggesting a beneficial effect of T therapy in men with T2DM [28]. In a study by Aversa et al. [24], in which the effects of T therapy on homoeostasis model assessment-estimated insulin resistance (HOMA-IR), carotid intima media thickness (CIMT), and high-sensitivity C-reactive protein (hsCRP) were investigated in men with TD and metabolic syndrome (MetS), T therapy significantly improved HOMA-IR, CIMT, and hsCRP as compared to the placebo treated group [24]. In another study in men with MetS, Kalinchenko et al. [30] found significant decreases in weight, BMI, WC, and HOMA-IR [30]. The effects of T therapy in 87 diabetic men with coronary artery disease (CAD) were investigated for a period of 12 weeks. T treatment significantly reduced the number of anginal attacks, silent ischaemic episodes, and total ischaemic burden, as compared with the placebo group. Total cholesterol (TC), plasma triglycerides (TG), and HOMA index were also significantly reduced in the T treated group compared to the placebo group, suggesting beneficial effects of T on T2DM complications [31]. In patients with chronic heart failure, T treatment significantly reduced insulin resistance measured by fasting insulin and HOMA-IR [32]. In a recent meta-analysis, Corona et al. [33] showed that T therapy was associated with marked reduction in fasting blood glucose, HOMA-IR, TG, and WC with concomitant increase in high density lipoprotein-cholesterol (HDL), suggesting that T therapy improves metabolic control and may ameliorate central obesity [33].

Several recent reports have shown that long-term T therapy in men with TD has produced significant weight loss, reduction in WC and BMI, as well as marked and significant reduction in total cholesterol, low density lipoprotein-cholesterol (LDL), TG, and increased HDL [23, 25, 34]. Also, marked reductions were noted in fasting glucose,  $\text{HbA}_{1c}$ , the nonspecific inflammatory marker hsCRP, and liver enzymes aspartate aminotransferase (ASA) and alanine aminotransferase (ALA) suggesting improvement in hyperglycemia and reduction in the inflammatory response [23, 25, 34, 35]. The first controlled five-year study using T in men with MetS showed significant decreases in weight, WC, BMI,  $\text{HbA}_{1c}$ , HOMA-IR, total cholesterol, LDL cholesterol, triglycerides, hsCRP, systolic, and diastolic blood pressure, and an increase in HDL [36]. In the current study, we present data on the long-term effects of T therapy in men with “diabesity.”

## 2. Methods and Procedures

This study represents a pooled subgroup analysis of obese hypogonadal men with T2DM from two cumulative registry studies of men, aged between 41 and 73 years (mean  $61.17 \pm 6.18$ ), who were seeking urological consultation in two urologists' offices for various medical conditions such as erectile dysfunction, decreased libido, questions about their T status, or a variety of urological complaints. All subjects included in this study had subnormal plasma total T levels (mean:  $8.9 \pm 1.99$ ; range: 1.63–11.79 nmol/L) and at least mild symptoms of hypogonadism assessed by the Aging Males' Symptoms scale (AMS). All patients had been diagnosed with T2DM prior to seeking urological consultation and treated accordingly by their family physicians with various standard treatment modalities. At their first visit, all men received brief general advice that it would be beneficial if they attempted to lose weight by a healthier diet consisting of more fruits and vegetables and less meat and increasing their physical activity by walking or using the bicycle instead of the car. They were not given any written instructions. All men received treatment with parenteral T undecanoate 1000 mg (Nebido, Bayer Pharma, Berlin, Germany), administered at baseline and 6 weeks and thereafter every 12 weeks for up to 72 months, as described previously [23, 25].

Measurements of anthropometric parameters (height, weight, and waist circumference) were performed and blood samples drawn at baseline and at the majority of visits prior to the next injection of testosterone. Therefore, T levels, measured by standard laboratory measurement, were trough levels at the end of an injection interval. All laboratory measurements for both centres were performed at the same commercial laboratory. Waist circumference (WC) was measured midpoint between the iliac crest and the lowest rib. Since not every measurement was performed at every single visit, values were averaged per patient and year.

Due to the cumulative registry design of the study, the number of subjects decreased over time. New subjects are entered into the database once they have received one year of treatment with T. All 156 subjects were followed for at least one year, 146 for at least two years, 136 for three years, 114 for four years, 105 for five years, and 69 for six years. The declining number of patients reflects duration of treatment but not the dropout rates. On the contrary, adherence to treatment was excellent, and T was only discontinued in two men who were diagnosed with prostate cancer.

## 3. Statistical Analyses

For continuous variables, the mean, median, standard deviation, range, minimum, maximum, and sample size for the overall sample and various groups were reported at each time point. For categorical variables the frequency distribution was reported. We tested the hypotheses regarding change in outcome scores across the study period by fitting a linear mixed effects model to the data. Time (to indicate follow-up interviews) was included as fixed effect in the model. A random effect was included in the model for the intercept. Estimation and test of change in scores were determined by

TABLE 1: Baseline characteristics and measures at the end of the observation period for 156 obese hypogonadal men with type 2 diabetes mellitus treated with testosterone undecanoate for up to 6 years.

|                                 | Baseline           | Endpoint           |
|---------------------------------|--------------------|--------------------|
| Mean age (years)                | $61.17 \pm 6.18$   |                    |
| Anthropometry                   |                    |                    |
| Weight (kg)                     | $113.56 \pm 11.53$ | $97.18 \pm 9.05$   |
| BMI ( $\text{kg}/\text{m}^2$ )  | $36.31 \pm 3.51$   | $31.19 \pm 2.6$    |
| Normal weight (proportion)      | 0                  | 1 (0.6%)           |
| Overweight (proportion)         | 0                  | 48 (30.8%)         |
| Obese (proportion)              | 156 (100%)         | 107 (68.6%)        |
| Waist circumference (cm)        | $114.0 \pm 8.69$   | $102.52 \pm 7.93$  |
| Normal ( $<94$ cm)              | 1 (0.6%)           | 7 (4.5%)           |
| Increased ( $\geq 94$ cm)       | 155 (99.4%)        | 149 (95.5%)        |
| Diabetic parameters             |                    |                    |
| Fasting glucose (mg/dL)         | $128.37 \pm 31.63$ | $101.55 \pm 17.02$ |
| Fasting glucose (mmol/L)        | $7.06 \pm 1.74$    | $5.59 \pm 0.94$    |
| HbA1c                           | $8.08 \pm 0.9$     | $6.14 \pm 0.71$    |
| Other metabolic parameters      |                    |                    |
| Total cholesterol (mg/dL)       | $294.85 \pm 47.65$ | $194.38 \pm 16.79$ |
| Total cholesterol (mmol/L)      | $7.64 \pm 1.23$    | $5.03 \pm 0.43$    |
| HDL cholesterol (mg/dL)         | $56.63 \pm 19.8$   | $67.88 \pm 17.34$  |
| HDL cholesterol (mmol/L)        | $1.47 \pm 0.51$    | $1.76 \pm 0.45$    |
| LDL cholesterol (mg/dL)         | $177.84 \pm 28.34$ | $125.47 \pm 33.05$ |
| LDL cholesterol (mmol/L)        | $4.61 \pm 0.73$    | $3.25 \pm 0.86$    |
| Triglycerides (mg/dL)           | $297.05 \pm 71.25$ | $197.9 \pm 23.24$  |
| Triglycerides (mmol/L)          | $3.36 \pm 0.81$    | $2.24 \pm 0.26$    |
| Systolic blood pressure (mmHg)  | $157.03 \pm 15.46$ | $134.61 \pm 10.21$ |
| Diastolic blood pressure (mmHg) | $93.89 \pm 11.67$  | $79.0 \pm 5.57$    |
| Pulse pressure                  | $63.07 \pm 10.7$   | $55.61 \pm 8.62$   |
| Total cholesterol : HDL ratio   | $6.02 \pm 2.97$    | $3.05 \pm 0.78$    |
| LDL : HDL ratio                 | $3.61 \pm 1.71$    | $1.88 \pm 0.41$    |
| CRP (mg/dL)                     | $3.16 \pm 4.12$    | $0.72 \pm 0.56$    |
| Liver enzymes                   |                    |                    |
| AST                             | $35.55 \pm 13.28$  | $23.94 \pm 8.77$   |
| ALT                             | $39.04 \pm 19.38$  | $26.08 \pm 14.42$  |
| Testosterone                    |                    |                    |
| Testosterone (nmol/L)           | $8.9 \pm 1.99$     | $17.36 \pm 1.92$   |

computing the differences in least square means at baseline versus the score at each follow-up interview. For the correlation study, Pearson correlation was calculated between baseline changes in outcomes at various time points. The significance of each correlation was tested using Fisher's test.

## 4. Results

Table 1 provides the baseline characteristics for 156 obese, diabetic men with TD (mean age  $61.17 \pm 6.18$  years). All 156 subjects had  $\text{BMI} \geq 30 \text{ kg}/\text{m}^2$ . One hundred fifty-five men had  $\text{WC} \geq 94$  cm. Table 1 also contrasts the endpoints achieved with T therapy for most of the parameters described in the baseline characteristics.

TABLE 2: Comorbidities and concomitant medications at baseline for 156 obese hypogonadal men with type 2 diabetes mellitus treated with testosterone undecanoate for up to 6 years.

| Comorbidities   |             |
|---|-------------|
| Hypertension  | 153 (99.4%) |
| Type 2 diabetes   | 156 (100%)  |
| Dyslipidaemia   | 156 (100%)  |
| Coronary artery disease   | 37 (23.7%)  |
| Myocardial infarction   | 19 (12.2%)  |
| Concomitant medications for diabetes at baseline                      |             |
| Metformin   | 36 (23.1%)  |
| Insulin   | 25 (16%)    |
| Sulfonylurea  | 8 (5.1%)    |
| Acarbose  | 2 (1.3%)    |
| Antidiabetic drugs not further specified                              | 51 (32.7%)  |
| Total antidiabetic drugs  | 122 (78.2%) |
| No diabetes drugs (including 2 patients who were "prescribed" a diet) | 29 (18.6%)  |
| No information available  | 9 (5.8%)    |
| Other concomitant medication categories at baseline                   |             |
| Antihypertensives   | 123 (78.8%) |
| Lipid-lowering drugs  | 99 (63.5%)  |

The subjects in this study had several comorbidities. All 156 men had T2DM and dyslipidaemia, 153 men had hypertension, 37 men had a history of CAD, and 19 men had previously had a myocardial infarction. These are shown in Table 2. Table 2 also lists the concomitant medications related to T2DM, hypertension, and dyslipidaemia reported by the patients at baseline.

**4.1. Total Testosterone Levels during the 6-Year Period of Testosterone Treatment.** Total T levels showed a significant rise from  $8.9 \pm 1.99$  nmol/L at the beginning of therapy to above 16 nmol/L within the first year of therapy, and such physiological levels remained constant at this level throughout the course of treatment, as reported previously [23, 25] (data not shown).

**4.2. T Therapy of Obese Diabetic Men with TD Produced Reduction in Waist Circumference (WC).** Figure 1 demonstrates the measured reduction in WC subsequent to T therapy in obese diabetic men with TD. WC declined from  $114 \pm 8.69$  cm (min 89, max 148) to  $102.52 \pm 7.93$  cm (min 82.25, max 121) with a mean reduction of  $11.56 \pm 0.34$  cm over the entire course of treatment ( $P < 0.0001$ ). The reduction in WC was statistically significant at the end of each year compared to the previous year over the first five years ( $P < 0.0001$ ) and had a statistical significance of  $P = 0.0021$  at the end of six compared to five years. At the end of the observation period, 7 patients had achieved a WC below 94 cm.

**4.3. T Therapy of Obese, Diabetic Men with TD Produced Significant Weight Loss (WL).** Figure 2 shows the effects of T

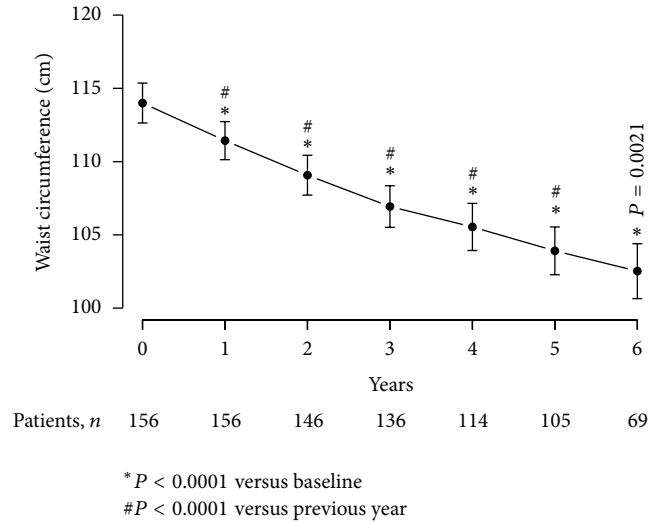


FIGURE 1: Waist circumference (cm) in 156 obese hypogonadal men with type 2 diabetes mellitus treated with testosterone undecanoate injections for up to 6 years.

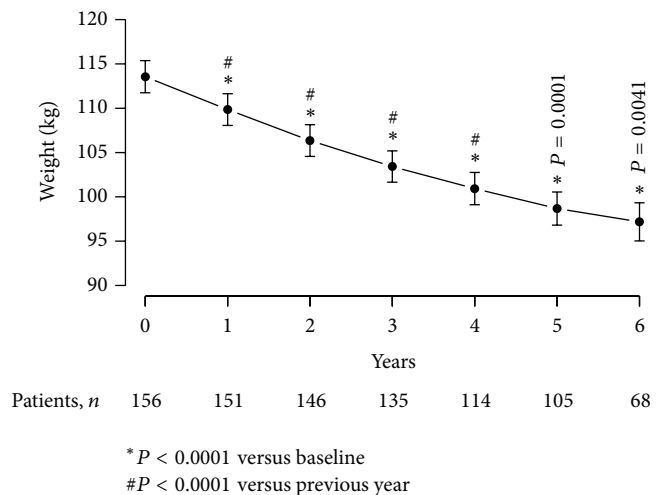


FIGURE 2: Weight (kg) in 156 obese hypogonadal men with type 2 diabetes mellitus treated with testosterone undecanoate injections for up to 6 years.

therapy on the body weight of obese diabetic men with TD over the course of 6 years of therapy. Body weight decreased from  $113.56 \pm 11.53$  kg (minimum: 87, maximum: 141) to  $97.18 \pm 9.04$  kg (min 80, max 118.5) with a mean loss of  $17.49 \pm 0.58$  kg over the course of treatment. This decrease in body weight was statistically significant at the end of each year compared to the previous year over the first five years ( $P < 0.0001$ ) and had a statistical significance of  $P = 0.0041$  at the end of six compared to five years.

**4.4. Percentage Change in Body Weight as a Result of T Therapy of Obese Diabetic Men with TD.** Marked and significant decrease in percentage body weight was noted over the course of T therapy. Over the entire 6-year observation period,

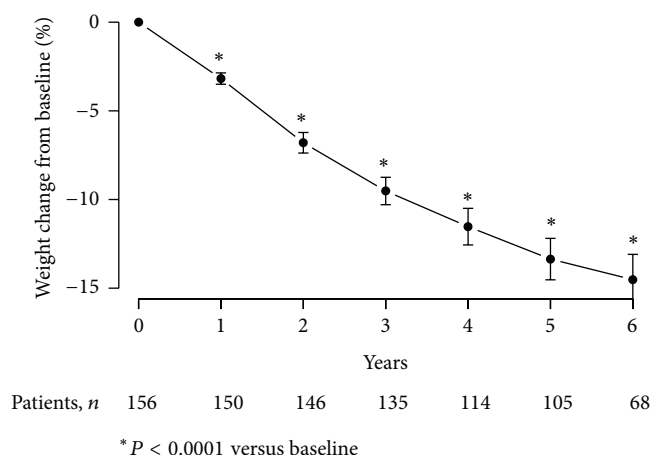


FIGURE 3: Weight change from baseline (%) in 156 obese hypogonadal men with type 2 diabetes mellitus treated with testosterone undecanoate injections for up to 6 years.

patients lost 15.04% of their initial body weight (Figure 3). After one year, patients had lost  $3.1 \pm 0.37\%$  of their initial weight, after two years,  $6.82 \pm 0.37\%$ , after three years,  $9.55 \pm 0.38\%$ , after four years,  $11.78 \pm 0.4\%$ , after five years,  $13.56 \pm 0.41\%$ , and after 6 years,  $15.04 \pm 0.48\%$ . These changes were statistically significant versus baseline ( $P < 0.0001$ ).

**4.5. T Therapy of Obese, Diabetic Men with TD Produced Significant Decline in BMI.** Consistent and progressive decline in BMI was observed over the entire course of treatment with a mean reduction of  $5.59 \pm 0.18 \text{ kg/m}^2$  ( $P < 0.0001$ ) (Figure 4). BMI declined from  $36.31 \pm 3.51$  to  $35.09 \pm 3.44$  after one year,  $33.99 \pm 3.4$  after two years,  $33.03 \pm 3.19$  after three years,  $32.29 \pm 2.97$  after four years,  $31.58 \pm 2.8$  after five years, and  $31.19 \pm 2.6$  after 6 years. The decline in BMI is consistent with the observed reductions in WC and body weight. At the end of the observation period, 48 patients (30.8%) were overweight and one patient (0.6%) had achieved normal weight.

**4.6. T Therapy of Obese, Diabetic Men with TD Improved Blood Glucose Levels.** T therapy of obese, diabetic men with TD resulted in a significant gradual decrease in fasting blood glucose from  $7.06 \pm 1.74 \text{ mmol/L}$  ( $128.37 \pm 31.63 \text{ mg/dL}$ ) to  $5.59 \pm 0.94 \text{ mmol/L}$  ( $101.55 \pm 17.02 \text{ mg/dL}$ ) (Figure 5). The decrease was significant after one year ( $P < 0.0001$ ), further declined after two years ( $P = 0.0178$  versus 12 months), and then reached a plateau with another slight but statistically significant decrease at five years compared to four years ( $P = 0.0246$ ). A decrease of  $1.49 \pm 0.14 \text{ mmol/L}$  ( $27.14 \pm 2.48 \text{ mg/dL}$ ) over the course of six years treatment was noted.

**4.7. Effects of T Treatment of Obese, Diabetic Men with TD on Haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) Levels.** The decrease in fasting blood glucose was accompanied by a marked decrease in HbA<sub>1c</sub> from  $8.08 \pm 0.09\%$  to  $6.14 \pm 0.71\%$  with a mean change of  $1.93 \pm 0.06\%$  ( $P < 0.0001$ ) at the end of the observation

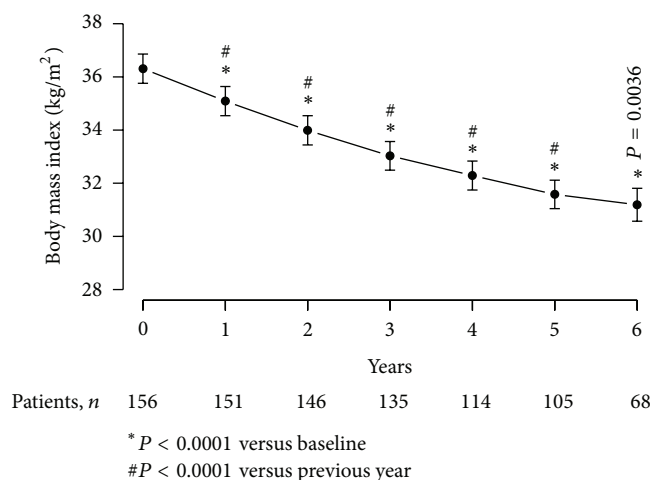


FIGURE 4: Body mass index (BMI,  $\text{kg/m}^2$ ) in 156 obese hypogonadal men with type 2 diabetes mellitus treated with testosterone undecanoate injections for up to 6 years.

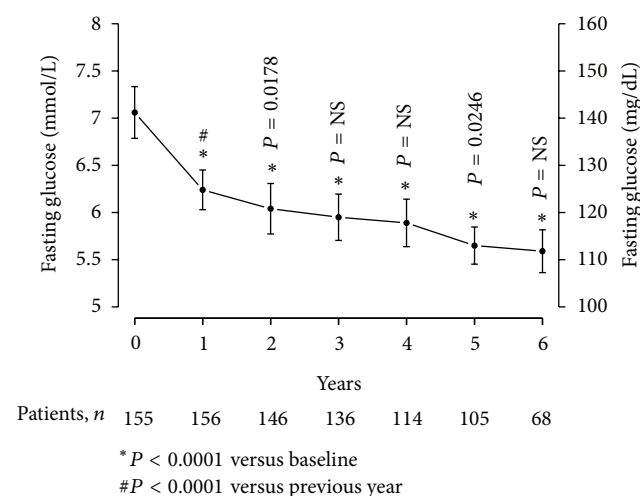


FIGURE 5: Fasting glucose (mg/dL or mmol/L) in 156 obese hypogonadal men with type 2 diabetes mellitus treated with testosterone undecanoate injections for up to 6 years.

period (Figure 6). The decrease in HbA<sub>1c</sub> was progressive and statistically significant after one year ( $P < 0.0001$ ), between two years and one year ( $P < 0.0001$ ), between three and two years ( $P < 0.0001$ ), between four and three years ( $P < 0.0001$ ), and between five and four years ( $P = 0.0003$ ) and approached significance between six and five years ( $P = 0.0635$ ) (Figure 6).

At baseline, 25 subjects (16%) had a HbA<sub>1c</sub> target level of  $\leq 7.0\%$ . At the end of the observation period, 123 men (79%) had reached this goal (Figure 7(a)). At baseline, 12 patients (8%) had a HbA<sub>1c</sub> level of  $\leq 6.5\%$ . At the end of the observation period, 92 men (59%) had achieved this target (Figure 7(b)).

**4.8. T Therapy Improved Systolic and Diastolic Blood Pressure in Obese, Diabetic Men with TD.** T therapy of obese, diabetic



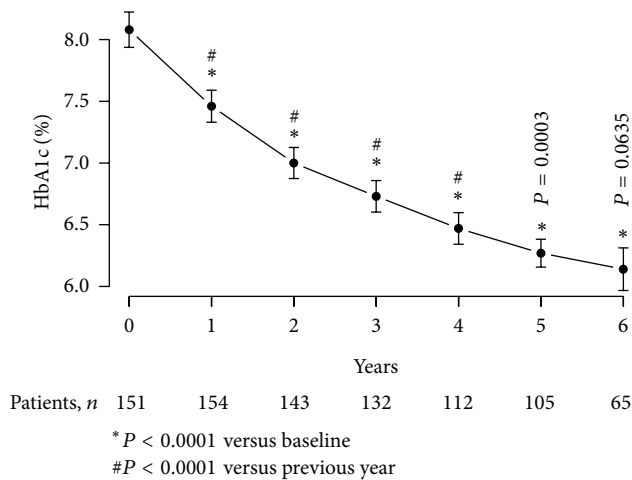


FIGURE 6: HbA<sub>1c</sub> (%) in 156 obese hypogonadal men with type 2 diabetes treated with testosterone undecanoate injections for up to 6 years.

men with TD produced marked and sustained gradual decrease in systolic blood pressure from  $157.03 \pm 15.46$  mmHg to  $134.61 \pm 10.21$  mmHg ( $P < 0.0001$ ) over the course of 6 years of treatment. The mean decrease ( $23.15 \pm 0.83$  mmHg) was significant and progressive over the first three years and reached a plateau at this level over the remaining course of the 6 years of treatment. Similar results were recorded with the diastolic blood pressure which decreased from  $93.89 \pm 11.67$  to  $79 \pm 5.57$  mmHg ( $P < 0.0001$ ) with a mean change of  $15.07 \pm 0.8$  mmHg over the course of treatment (Figure 8). A gradual and progressive decrease was noted over the first three years of treatment and then blood pressure stabilized over the remaining years of treatment.

Another finding was a significant reduction of pulse pressure from  $63.07 \pm 10.7$  (minimum: 35, maximum: 102) to  $55.61 \pm 8.62$  (minimum: 38, maximum: 70). This decrease was statistically significant each year compared to the previous year during the first three years after which it remained stable.

**4.9. T Therapy in Obese, Diabetic Men with TD Improved Lipid Profiles.** As shown in Figure 9, T therapy improved lipid profiles as demonstrated with increase in high density lipoprotein cholesterol (HDL-C) by  $35.03 \pm 5.11\%$  (Figure 9(a)), significant reductions in total cholesterol (TC) by  $32.12 \pm 1.41\%$ , low density lipoprotein cholesterol (LDL-C) by  $25.93 \pm 1.63\%$ , and triglycerides (TG) by  $29.91 \pm 2\%$  (Figure 9(b)). The mean changes in lipid profiles were gradual and progressive and were significant at each year when compared to baseline levels, reaching plateaus between three and four years. The ratio of total cholesterol to HDL cholesterol improved from  $6.02 \pm 2.97$  to  $3.05 \pm 0.78$ . These changes reached a plateau after three years with further slight but not statistically significant decreases.

**4.10. T Therapy in Obese Diabetic Men with TD Reduced the Levels of Inflammatory Biomarkers.** T therapy produced a marked and significant decrease in the concentration of

the nonspecific inflammatory biomarker C-reactive protein (CRP) from  $3.16 \pm 4.12$  to  $0.72 \pm 0.56$  U/L ( $P < 0.0001$  with a plateau after 24 months) and a significant ( $P < 0.0001$ ) mean decrease of  $2.88 \pm 0.28$  over the course of treatment (Figure 10(a)). Moreover, T therapy reduced the concentration of the liver enzyme aspartate transaminase (AST) from  $35.55 \pm 13.28$  to  $23.94 \pm 8.77$  U/L ( $P < 0.0001$  with a plateau after 24 months) and a significant ( $P < 0.0001$ ) mean change of  $12.01 \pm 1.33$  U/L over the course of treatment. Similarly, alanine transaminase (ALT) concentration was reduced from  $39.04 \pm 19.38$  to  $26.08 \pm 14.42$  U/L ( $P < 0.0001$ ) with a plateau after 12 months and significant mean change of  $12.46 \pm 1.83$  U/L over the entire course of treatment, suggesting a reduction in liver fat content, a reduced inflammatory response, and improvement in liver function (Figure 10(b)).

**4.11. T Therapy in Obese Diabetic Men with Total Testosterone below versus above 8 nmol/L.** According to most of the current guidelines for testosterone replacement therapy, levels of total T below 8 nmol/L require treatment whilst levels above this threshold are considered borderline. We therefore analysed whether there were any differences in response in those of our patients who had T levels  $< 8$  nmol/L versus those with T levels  $> 8$  nmol/L and  $< 12$  nmol/L. The results suggest that obese diabetic men in the higher T category respond to T treatment equally well (Table 3).

## 5. Discussion

In this long-term, cumulative, uncontrolled, and observational registry study from two independent sites, we investigated the effects of T therapy on anthropometric parameters, fasting blood glucose (FBG), HbA<sub>1c</sub>, systolic and diastolic blood pressure, lipid profiles, and inflammatory markers in 156 obese, diabetic men with TD. T therapy restored physiological T levels within the first 12 months and T levels were maintained with T therapy throughout the entire 6-year period. Of particular interest, our data demonstrate that T therapy in obese, diabetic men with TD produced significant and marked WL in 100% of all obese, diabetic patients. The WL subsequent to T therapy was gradual, progressive, and sustainable for the course of 6 years of treatment. The WL was significant and was associated with considerable and marked reductions in WC and BMI, suggesting that T therapy in obese, diabetic men results in improvement in metabolic function and probably behavioral changes with increased energy and motivation and physical activity that are translated into changes in body composition, which are accompanied by increases in lean body mass and reduction in fat mass, as discussed previously [22, 23, 25].

Over the entire observation period of 72 months, the longest follow-up reported to date, T therapy produced marked reductions in WC and BMI, consistent with the hypothesis that T is an anabolic hormone required for maintenance of muscle mass and regulation of adipogenesis [25]. It is of interest to note that the magnitude of changes over time in the obese, diabetic men was marked, progressive, and significant when compared with baseline data. These findings

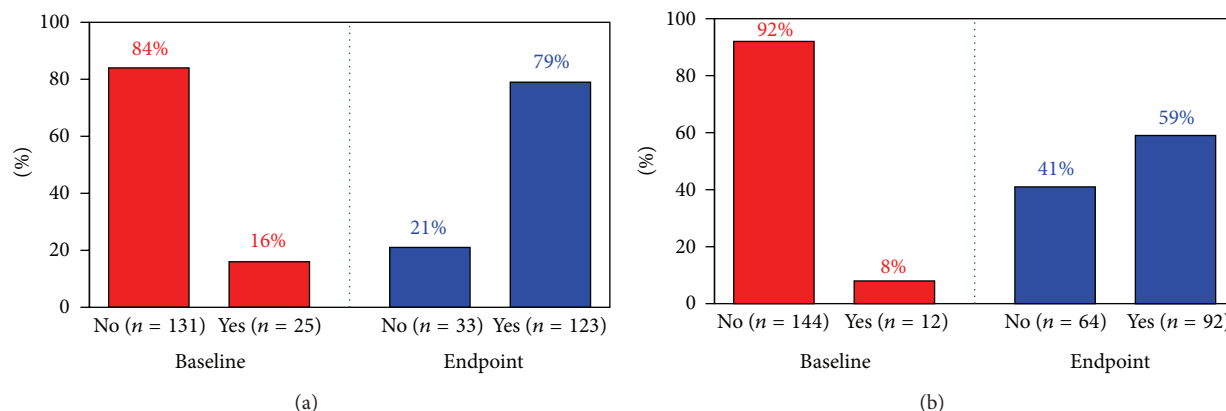


FIGURE 7: Patients reaching HbA<sub>1c</sub> target of  $\leq 7\%$  (a) and  $\leq 6.5\%$  (b) at baseline and end of observation time after treatment with testosterone undecanoate injections for up to 6 years.

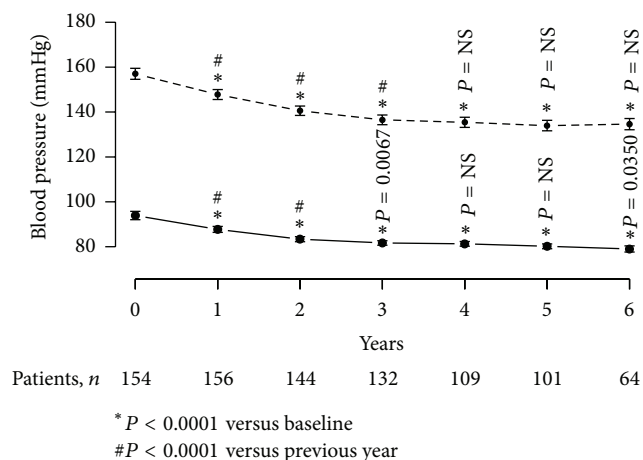


FIGURE 8: Systolic (dotted line) and diastolic (continuous line) blood pressure (mmHg) in 156 obese hypogonadal men with type 2 diabetes treated with testosterone undecanoate injections for up to 6 years.

are not surprising since it is known that T promotes myogenesis and inhibits adipogenesis and regulates carbohydrate, lipid, and protein metabolism [25]. Thus, the changes in body composition noted in this study are attributed to T regulation of the metabolic processes in muscle and adipose tissues as well as functional metabolism.

It is important to point out that all these hypogonadal, obese men had been diagnosed with T2DM and received standard treatment by their family physician prior to initiation of T therapy. The mean baseline for HbA<sub>1c</sub> in this study was 8.08% and only 25 men had an HbA<sub>1c</sub>  $\leq 7.0\%$ , suggesting an overall poor control prior to T therapy. Interestingly, however, T therapy produced marked decrease in fasting blood glucose and HbA<sub>1c</sub>, suggesting that T therapy ameliorates hyperglycemia and IR in subjects with T2DM, consistent with previous reports [25]. These findings are also congruent with those reported in the IPASS study [37] in

which 1438 men with TD were treated with T and followed up for up to 12 months suggesting similar reductions in glucose and HbA<sub>1c</sub>, particularly in patients with a poor HbA<sub>1c</sub> control [37].

We also noted a meaningful reduction in systolic and diastolic blood pressure in response to T therapy. That T therapy improves hypertension in patients with TD is of interest, but limited data are available. It is possible that T modulates arterial blood pressure, through a variety of mechanisms, such as direct effects on the heart, the kidney, and the vessels, as well as the endothelium [38, 39]. Our data are consistent with previous work in obese, hypogonadal, and diabetic men in which blood pressure was shown to decrease favorably in response to therapy with an oral T formulation [29, 40].

Men with prostate cancer who were treated with androgen deprivation therapy (ADT) showed increased arterial stiffness [41, 42]. In our study, we observed a significant decrease of pulse pressure. Elevated pulse pressure is associated with an increase in large artery stiffness and recognized as an independent risk factor for CVD [43]. Our results are consistent with a placebo-controlled study that demonstrated a reduction in arterial stiffness, measured by use of the augmentation index, following T therapy [44].

CRP, a nonspecific marker of inflammation, was markedly reduced over the course of T therapy in obese, diabetic men with TD. Since it has been shown that WL significantly reduces plasma C-reactive protein (CRP) concentration [45], it is likely that the reduced weight reestablishes a new equilibrium with attenuated inflammatory responses and reduced CRP levels. It has been suggested that CRP concentration was significantly and directly associated with change in systolic blood pressure (SBP) and WC but inversely associated with HDL cholesterol [46]. Since T therapy improved both systolic blood pressure and reduced WC in this cohort of obese, diabetic men, it is not surprising that CRP levels were significantly reduced.

In addition, we noted a marked reduction in the activities of several liver enzymes, used as markers of nonalcoholic fatty

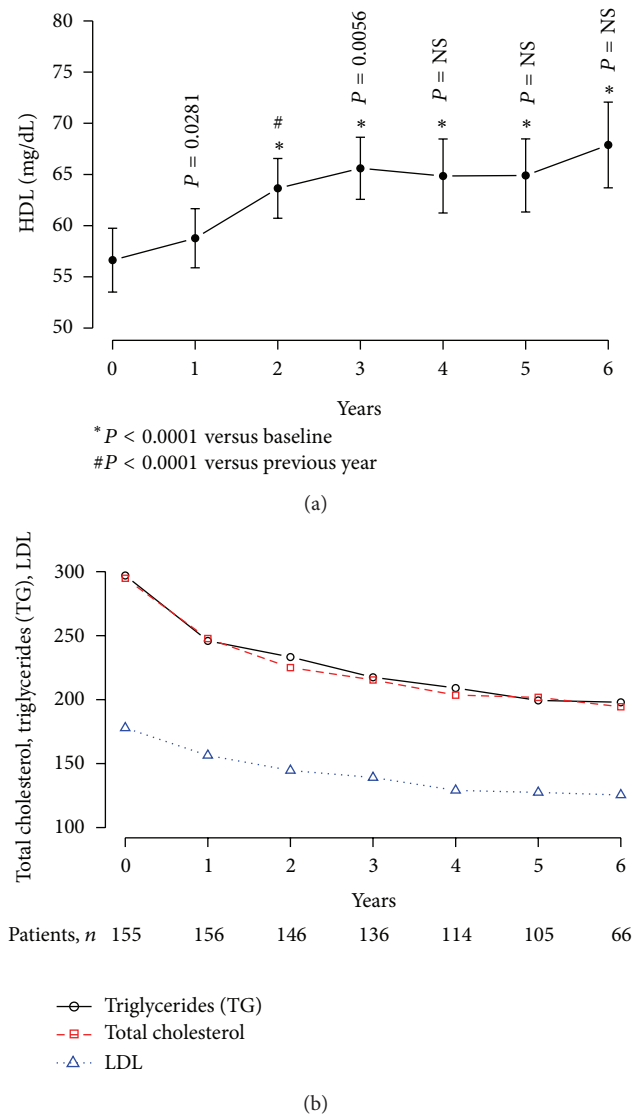


FIGURE 9: Changes in lipids (mg/dL) in 156 obese hypogonadal men with type 2 diabetes treated with testosterone undecanoate injections for up to 6 years. HDL cholesterol (a). Total cholesterol, LDL cholesterol, and triglycerides (b).

liver disease (NAFLD) and liver function, suggesting that T therapy reduces liver fat content and attenuates the inflammatory response and improves various physiological functions. Our findings are consistent with the work by Hoyos et al. [44] who showed a reduction in liver fat content assessed by diagnostic imaging [44]. Taken together, these findings strongly suggest that normalizing T levels in obese men with TD ameliorates a host of MetS components and reduces inflammation, thus reducing the risk of cardiometabolic diseases.

It is of interest to note that, in this group of obese, diabetic men with TD, T therapy markedly and significantly reduced total cholesterol (TC) levels and this diminution was very pronounced and sustained over the entire 6-year period of T treatment. Further, we noted that long-term T therapy

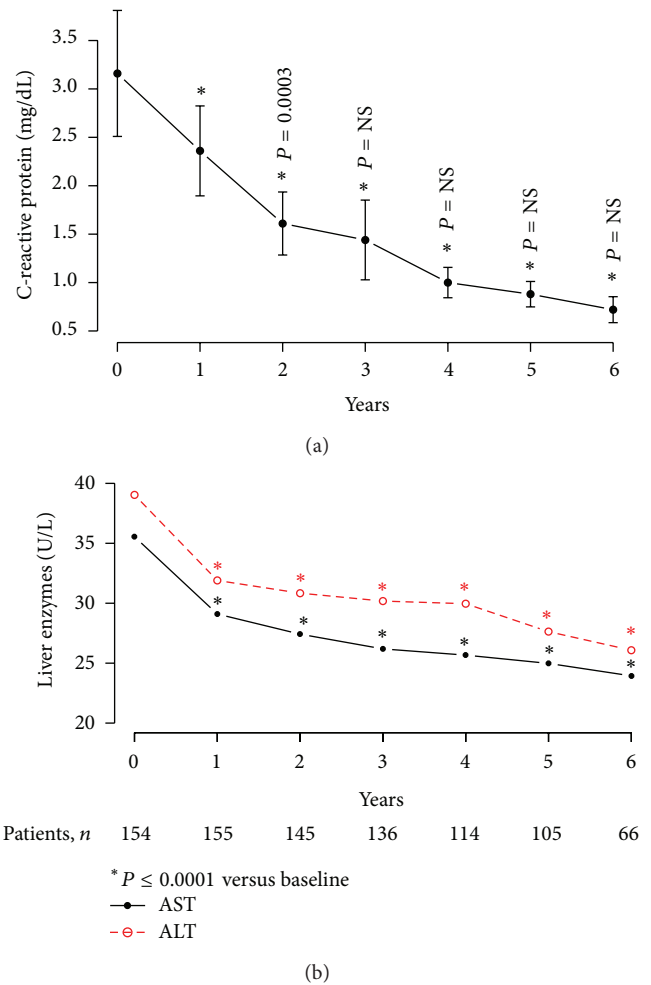


FIGURE 10: (a) C-reactive protein (mg/dL); (b) liver enzymes aspartate transaminase and alanine transaminase (U/L) in 156 obese hypogonadal men with type 2 diabetes treated with testosterone undecanoate injections for up to 6 years.

reduced LDL throughout the treatment period, and LDL levels were maintained at low levels throughout the course of treatment. The clinical implication of this observation is that reduction in LDL correlates with reduced CVD risk. Further, T therapy not only reduced the levels of LDL and TC but also produced small yet significant increases in HDL levels. Moreover, the ratio of total cholesterol to HDL cholesterol dropped from  $>6$  to  $<3.5$ . These findings suggest that T therapy of obese, diabetic men with TD may reduce CVD risk and increase health benefits, such as improved lipid profiles. Another important observation in this study was the marked and significant reduction in triglycerides (TGs) in response to T therapy in these obese, diabetic men with TD. Since visceral fat storage depends on accumulation of TGs, thus, in men with TD, it is expected that increased lipid accumulation will contribute to obesity and T therapy is expected to produce reduction in body weight, WC, and BMI [23, 25]. Finally, a closer look at the per cent reduction in the lipids concentrations (TC, LDL, and TGs) indicated that the reductions approach 30%, a value similar to that attained by

TABLE 3: Changes in anthropometric and metabolic parameters in subgroups of obese hypogonadal men with type 2 diabetes and total testosterone &lt;8 nmol/L versus total testosterone &gt;8 nmol/L and &lt;12 nmol/L after treatment with testosterone undecanoate for up to 6 years.

|   | T < 8 nmol/L (n = 53) | T > 8 nmol/L (n = 103) |
|---|-----------------------|------------------------|
| Mean age (years)                            | 61.43 ± 7.78          | 60.96 ± 5.24           |
| Anthropometry                               |                       |                        |
| Decrease in weight (kg)                     | 16.05 ± 1.01          | 18.42 ± 0.71           |
| Weight reduction from baseline (%)          | 13.75 ± 0.84          | 15.88 ± 0.58           |
| Decrease in BMI (kg/m <sup>2</sup> )        | 5.06 ± 0.32           | 5.94 ± 0.22            |
| Decrease in waist circumference (cm)        | 12.84 ± 0.64          | 10.77 ± 0.36           |
| Diabetic parameters                         |                       |                        |
| Decrease in fasting glucose (mg/dL)         | 32.31 ± 5.19          | 24.4 ± 2.42            |
| Decrease in HbA1c (%)                       | 1.98 ± 0.09           | 1.9 ± 0.07             |
| Other metabolic parameters                  |                       |                        |
| Decrease in total cholesterol (mg/dL)       | 94.99 ± 8.72          | 106.21 ± 4.04          |
| Increase in HDL cholesterol (mg/dL)         | 14.87 ± 3.08          | 10.78 ± 1.3            |
| Decrease in LDL cholesterol (mg/dL)         | 51.28 ± 5.29          | 44.07 ± 2.83           |
| Decrease in triglycerides (mg/dL)           | 107.73 ± 12.23        | 98.55 ± 5.64           |
| Decrease in systolic blood pressure (mmHg)  | 22.11 ± 1.56          | 23.57 ± 0.97           |
| Decrease in diastolic blood pressure (mmHg) | 9.21 ± 1.41           | 18.29 ± 0.88           |
| Testosterone                                |                       |                        |
| Increase in testosterone (nmol/L)           | 11.45 ± 0.54          | 6.37 ± 0.37            |

use of statins in men with dyslipidaemia. This is an important finding and warrants further investigations.

Obesity is a public health threat and its prevalence continues to increase worldwide [44, 47]. Obesity is associated with numerous comorbidities including T2DM, hypertension, stroke, and coronary artery disease [48]. From a global health policy perspective, the increased prevalence of T2DM and obesity epidemics represents a warning salvo for all healthcare systems. Evidence is accumulating suggesting that WL improves insulin sensitivity and  $\beta$ -cell function [49, 50]. It has been suggested that a loss of approximately 5–7% of body weight reduces the risk of developing diabetes by roughly 58% [4, 51]. The potential benefits of a moderate 5–10% WL in high risk patients with a cluster of atherothrombotic proinflammatory abnormalities associated with hypertriglyceridaemic waist have been proposed by Després et al. [52]. The authors suggested that visceral obesity leads to T2DM, dyslipidaemia, and hypertension, which result in increased risk and development of CVD, and a 5–10% WL can be very beneficial for improving health status and this should be pursued by behavioral therapy, exercise, diet, and pharmacotherapy [52].

The role of obesity in development of TD, T2DM, and inflammation is complex and involves a bidirectional and integrated variety of endocrine factors that results in increased IR, decreased T secretion, and increased inflammatory cytokines [53–56]. Increased levels of circulating free fatty acids and blood glucose result in triglyceride formation and storage, thus increasing visceral and subcutaneous fat mass. This further promotes additional release of free fatty acids into the circulation due to activation of lipases. Increased glucose is taken up by the liver. The increased sugar and fat uptake by the liver impairs the ability of insulin to regulate gluconeogenesis and activate glycogen

synthesis. Inflammatory cytokine expression is increased which contributes to the development of insulin resistance. A recent study by Phillips and Perry [57] suggested that reduced inflammatory status increases the likelihood of metabolic health, particularly among obese subjects. Schnell et al. [58] showed that treatment which reduced inflammation, as assessed by CRP levels, was also associated with reductions in HbA<sub>1c</sub> in diabetic individuals. Most studies have shown that HbA<sub>1c</sub> control is not sustainable [59, 60]. However, we observed that T therapy produced significant and sustained reduction in HbA<sub>1c</sub>, suggesting that normalizing T levels reduces inflammation and restores glycaemic control [25].

The prevalence of T2DM is attributed, in part, to the increased prevalence of obesity combined with aging [14, 61]. The increased prevalence of obesity together with diabetes in the same individuals, henceforth referred to as “diabesity,” has also been reported, and individuals with “diabesity” exhibited higher risks of CVD [62, 63]. Obesity is also associated with increased expression of inflammatory cytokines. These inflammatory cytokines contribute to the impairment of insulin action and increased IR [64]. In a recent study of middle-aged individuals without glucose lowering medication the contributions of IR and hyperglycaemia to the development of subclinical atherosclerosis were attributed to a large extent to abdominal adiposity [65]. These findings suggest that weight management and prevention of weight gain in adulthood are critical for management of IR, obesity, and CVD. Casanueva et al. [18] reported that abdominal obesity was strongly associated with CVD and diabetes, even in patients who may be considered lean based on BMI assessment.

It is well recognized that adipose tissue is a unique endocrine organ which produces proinflammatory cytokines and free fatty acids that may promote development of IR and



therefore will contribute to the development of atherosclerosis and CVD through hyperglycemia, inflammation, dyslipidaemia, and hypertension [65–67]. We believe that T therapy may confer health benefits since it results in significant and sustained WL in individuals with abdominal adiposity, as suggested previously [68]. One of the key measures of WL is the reduction in WC [69]. In fact, some studies have suggested that WC may be a risk factor for all-cause mortality [69, 70], incident CVD, and diabetes [17, 71]. Tseng [72] suggested that BMI and WC may be used as determinants of CAD in men with T2DM. Since T therapy produces significant reductions in WC, we believe that T therapy may provide significant health benefits in obese and diabetic patients with TD and may improve cardiometabolic function and reduce the risk of CVD.

Therapeutic approaches to treatment of obesity and diabetes include bariatric surgery, which were reported to be successful in management of this condition, producing rapid and durable weight loss, reductions in CVD events and overall mortality, and sustained remission of diabetes in most patients [73, 74]. However, bariatric surgery is not indicated for all obese diabetic patients and only select patients undergo this procedure, and thus this may be considered to be a limitation, given the large number of obese/diabetic patients.

Several other therapeutic approaches have also been used as potential treatment for diabetes, including sulfonylureas, thiazolidinediones, metformin, and insulin. However, with the exception of metformin, many of these agents result in weight gain and may increase IR risk. Alternative approaches also include the development of stable glucagon like peptide 1 (GLP-1) receptor agonists, which increase insulin secretion and suppress glucagon secretion and appetite [75]. GLP-1 is an effective agent in improving glycaemic control, when administered subcutaneously in patients with T2DM [76, 77]. Also the use of dipeptidyl peptidase inhibitors (DPP-4) to increase the intracellular level of endogenous GLP-1 has been proposed [78]. DPP4 inhibitors do not cause WL but instead are “weight neutral” [78]. These approaches were considered advantageous in treating diabetes when compared with the thiazolidinediones or sulfonylureas which result in weight gain.

T is well known to regulate a host of metabolic functions in liver, adipose tissue, muscles, coronary arteries, and the heart. Thus, it is not surprising that T therapy reduces the risk of CVD. An inverse relationship exists between T and obesity and TD is associated with dyslipidaemia, atherosclerosis, cardiovascular diseases, MetS, and diabetes (for review cf. Kelly et al. [54–56]). Several studies have suggested an association between reduced T levels and visceral obesity and diabetes. Visceral fat accumulation in men was positively associated with IR, hyperglycaemia, and C-peptide and is negatively associated with T levels [6]. The proportion of men with TD was increased in men with T2DM [79]. A significant association between TD and BMI and WC was noted in 355 male patients with T2DM (mean age 58 years) [27]. These findings suggest that WC and BMI in diabetic patients are associated with increased obesity. These findings are further supported by the work of Hackett et al. [35].

A number of studies have shown that T therapy in diabetic men with TD reduced body weight, WC, and body fat and reduced fasting blood glucose and HbA1c [24, 27–33]. These findings support the data presented in this study and suggest that T therapy may be a novel therapeutic approach to the management of T2DM and obesity in men with “diabesity.”

It should be pointed out that a number of studies have evaluated several drugs approved for management of diabetes and obesity with some positive outcome, albeit the efficacy of these drugs in maintaining WL or sustained weight loss remains debatable. Dyson [80] summarized the findings from studies on lifestyle, diet, and behavioral interventions on WL and WL maintenance. Based on a systematic review and meta-analysis, the authors suggested that all lifestyle interventions have a modest but significant effect on WL ranging between 1 and 4.9 kg in the overweight and obese subjects [80]. The authors concluded that exercise alone results in a moderate effect but is more effective when combined with dietary interventions. It was strongly suggested that behavioral therapy is an effective approach when combined with diet and exercise [80]. The diabetes prevention program (DPP) research group investigated the long-term safety and tolerability of metformin, along with WL, and change in WC during the diabetic prevention program (DPP) in a randomized double-blind clinical trial followed by a 7–8-year open-label extension [81]. Metformin treatment resulted in modest WL and WC, when compared with placebo. Most importantly, the magnitude of WL during the 2-year period was dependent on patients’ adherence to treatment. During the open follow-up period, WL remained significantly greater in the metformin group than in the placebo group. In a double-blind clinical trial, Smith et al. [82] investigated the effects of lorcaserin together with diet and exercise and counseling in a large number of obese or overweight adults over a period of 52 weeks. After one year of treatment, approximately 47.5% of patients who received lorcaserin lost 5% or more of their body weight ( $\sim 5.8 \pm 0.2$  kg) [82]. Interestingly, even in the treatment group, some weight gain was noted over the course of the second year of treatment. When treatment was discontinued, patients regained the weight lost over the course of the year. Gadde et al. [83] investigated the effects of oral phentermine and topiramate on WL in overweight or obese patients with several comorbidities such as hypertension, dyslipidaemia, diabetes, or abdominal obesity. The authors suggested that the combination of phentermine and topiramate, with office-based lifestyle interventions, might be a valuable treatment for obesity. In a subanalysis of the aforementioned study, the investigators could show reductions of 70.5% and 78.7% in the annualised incidence rate of T2DM [84]. Astrup et al. [63] investigated the effects of liraglutide over a two-year period and assessed the effects of this drug when coupled with diet and exercise on mean change in BW and WC in obese patients. The findings of this study indicated that liraglutide, together with diet and exercise, provides sustained WL over 2 years, with improvements in obesity associated metabolic and cardiovascular risk factors [63]. Chilton and colleagues [68] analysed data comparing orlistat or lorcaserin to lifestyle

modifications (placebo) with sibutramine, rimonabant, or metformin on changes in WC and dropout rates attributed to adverse events of these agents. The authors suggested that orlistat significantly reduced WC by 6.96 cm when compared to placebo at 6 and 12 months. Lorcaserin also reduced WC and was more effective than that of other interventions at 12 months. Approximately 6.5% of patients on orlistat and 5.4% of those on lorcaserin discontinued their treatment due to adverse events at 12 months. The authors suggested that orlistat should be combined with lifestyle interventions in the treatment of obesity.

Thus, while a number of drugs, combined with behavioral and lifestyle changes, are shown to have moderate effect on WL and maintenance of weight loss, our data suggest that T therapy in obese diabetic men has a profound effect on WL and WC and this is irrespective of diet and exercise or behavioral counseling. This is meaningful, since the WL and the reduction in WC were observed over a long period of followup. We believe that since obesity is associated with hypogonadism (TD) and may, in fact, cause TD, long-term T treatment in hypogonadal men results in continuous improvements in weight and WC and may be an effective tool for weight management in obese men. The reduction in WL and WC with T-undecanoate in more than 500 hypogonadal men [23, 34] appears to be superior when compared to data published with other drugs, in combination with lifestyle and behavioural interventions.

Our study is the first to report 6-year data of T therapy in hypogonadal obese men with T2DM, showing a progressive and sustainable reduction of HbA<sub>1c</sub> levels. This result seems to be highly favorable when compared to any other reported interventions where maintaining glycaemic control over a prolonged period of time appears extremely difficult to achieve, even with a modern generation of T2DM drugs [59, 85, 86]. Moreover, the findings that a large proportion of patients reach HbA<sub>1c</sub> targets appear to be unique in comparison to other studies reported in the literature. Most testosterone studies in men with T2DM and/or metabolic syndrome have been performed over a relatively short period of time. Hackett et al. [35], in their 18-month study, found the marked decrease in HbA<sub>1c</sub> during the last 12 months of their study [35], indicating that these effects may take some time to occur.

As shown in the United Kingdom Prospective Diabetes Study (UKPDS), HbA<sub>1c</sub> levels were not maintained over time even with intensive control treatment [59, 85]. Similarly, glycaemic control as assessed by fasting blood glucose and HbA<sub>1c</sub> were not maintained over time with treatment with rosiglitazone, metformin, or glyburide monotherapy [60]. Similar trends were noted in HbA<sub>1c</sub> after treatment with liraglutide [86]. These findings suggest that control of hyperglycemia is not maintained over time by these pharmacotherapeutic agents. In contrast, the data from our study showed that T therapy consistently lowered HbA<sub>1c</sub>, and the reduced HbA<sub>1c</sub> and fasting blood glucose were maintained at the lower level and we did not observe any return to higher levels during the 72 months of T treatment. These findings are further supported by a recent study in which T therapy in diabetic patients was shown to reduce mortality, which

could be explained in part by the positive effects of T on cardiometabolic function [87].

Because, six years ago when this study was commenced, we did not anticipate changes in diabetic parameters in response to T therapy, comedication was only assessed at baseline. The initial mean HbA<sub>1c</sub> of 8.08% and the small proportion of men within HbA<sub>1c</sub> targets at baseline indicated that the hyperglycemia in these patients was not very well controlled. The lack of assessment of antidiabetic treatment on the outcome of T therapy may represent a potential limitation of this study. It is important to note that a recent study by Hackett et al. [88] reported a marked reduction in HbA<sub>1c</sub> as a result of T therapy, in addition to standard antidiabetic treatment. The reduction in HbA<sub>1c</sub> in the cohort of poorly controlled patients was 0.41% by 6 weeks and was maintained at 18 and 30 weeks of treatment, respectively [88]. In this well-controlled study, there were no changes in antidiabetic medications. These findings are congruent with our observations.

Hypertension and obesity are common comorbidities in patients with T2DM. Thus, any pharmacotherapy that not only ameliorates hyperglycemia, but also improves blood pressure and reduces adipogenesis would be of interest. The prevalence of hypertension is higher in patients with T2DM and ~60% of patients diagnosed exhibit arterial hypertension. This is attributed to (i) hyperinsulinaemia, (ii) increased sympathetic tone, and (iii) increased renin-angiotensin-aldosterone system activity [89]. Our findings suggest that T therapy not only improves lipid profiles, but also improves hyperglycemia and blood pressure. This is a novel finding and merits further exploration.

One of the limitations of this study is the nature of the registry design. This combined two-center, open-label observational study was not a randomized controlled study and therefore may limit the scope of interpretation of the presented findings. Simply, obese and diabetic subjects were treated in a urology clinical setting. This may introduce unintended bias since many of the subjects are seeking medical treatment of various urological conditions. Another potential limitation is that we used total T levels and not free T levels, in combination with signs and symptoms, to evaluate TD (hypogonadism). An additional limitation was that the patients in these registries had a number of different comorbidities. Since our results were not foreseen when the study was designed and commenced six years ago, we did not assess the duration of T2DM, neither was a continued assessment of potential changes in comedications performed. Therefore, we did not have the possibility to assess whether there were any cases of remission of T2DM (defined as HbA<sub>1c</sub> < 6.0% without antidiabetic medications for at least one year).

Another limitation is that we did not assess behavioral and lifestyle changes, that is, changes in nutritional and exercise habits. Since weight loss had not been expected, we did not consider the use of questionnaires or other methods to measure dietary changes or changes in physical activity.

In summary, the findings of this study demonstrate that long-term treatment with T-undecanoate in obese men with diabetes and TD restored physiological T levels and

produced marked and significant WL and reduced WC and BMI. Further, T treatment significantly reduced fasting blood glucose and HbA<sub>1c</sub> levels. Of equal importance, T therapy significantly reduced total cholesterol, LDL cholesterol, and triglycerides and increased HDL cholesterol levels and improved systolic and diastolic blood pressure. T therapy also reduced the levels of inflammatory markers, suggesting reduction in the inflammation response. These findings strongly suggest that T therapy of obese, diabetic men improves glycaemic control and lipid profiles and may prove useful in reducing the risk of CVD. These findings further suggest that long-term T treatment of diabetic obese men with TD may produce important clinical benefits in men with "diabesity." One unique aspect of this study is that it followed up diabetic obese men with TD for a period of 6 years, which is the longest reported duration of T treatment to date. We suggest that T therapy in obese diabetic men may prove useful in management of men with "diabesity."

## Conflict of Interests

Ahmad Haider and Aksam Yassin have received compensation for data entry for the present study from Bayer Pharma. Gheorghe Doros has received compensation for statistical analyses for the present study from Bayer Pharma. Farid Saad is a full-time employee of Bayer Pharma.

## References

- [1] S. Colagiuri, "Diabesity: therapeutic options," *Diabetes, Obesity and Metabolism*, vol. 12, no. 6, pp. 463–473, 2010.
- [2] S. M. Haffner, "Relationship of metabolic risk factors and development of cardiovascular disease and diabetes," *Obesity*, vol. 14, supplement 3, pp. 121S–127S, 2006.
- [3] S. E. Kahn, R. L. Hull, and K. M. Utzschneider, "Mechanisms linking obesity to insulin resistance and type 2 diabetes," *Nature*, vol. 444, no. 7121, pp. 840–846, 2006.
- [4] J. Tuomilehto, J. Lindström, J. G. Eriksson et al., "Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance," *New England Journal of Medicine*, vol. 344, no. 18, pp. 1343–1350, 2001.
- [5] E. S. Huang, A. Basu, M. O'Grady, and J. C. Capretta, "Projecting the future diabetes population size and related costs for the U.S," *Diabetes Care*, vol. 32, no. 12, pp. 2225–2229, 2009.
- [6] J. C. Seidell, P. Bjorntorp, L. Sjostrom, H. Kvist, and R. Sannerstedt, "Visceral fat accumulation in men is positively associated with insulin, glucose, and C-peptide levels, but negatively with testosterone levels," *Metabolism*, vol. 39, no. 9, pp. 897–901, 1990.
- [7] E. A. H. Sims, E. Danforth Jr., and E. S. Horton, "Endocrine and metabolic effects of experimental obesity in man," *Recent Progress in Hormone Research*, vol. 29, pp. 457–496, 1973.
- [8] G. A. Colditz, W. C. Willett, A. Rotnitzky, and J. E. Manson, "Weight gain as a risk factor for clinical diabetes mellitus in women," *Annals of Internal Medicine*, vol. 122, no. 7, pp. 481–486, 1995.
- [9] A. E. Field, E. H. Coakley, A. Must et al., "Impact of overweight on the risk of developing common chronic diseases during a 10-year period," *Archives of Internal Medicine*, vol. 161, no. 13, pp. 1581–1586, 2001.
- [10] C. L. Hart, D. J. Hole, D. A. Lawlor, and G. Davey Smith, "How many cases of Type 2 diabetes mellitus are due to being overweight in middle age? Evidence from the Midspan prospective cohort studies using mention of diabetes mellitus on hospital discharge or death records," *Diabetic Medicine*, vol. 24, no. 1, pp. 73–80, 2007.
- [11] K. M. V. Narayan, J. P. Boyle, T. J. Thompson, E. W. Gregg, and D. F. Williamson, "Effect of BMI on lifetime risk for diabetes in the U.S," *Diabetes Care*, vol. 30, no. 6, pp. 1562–1566, 2007.
- [12] S. G. Wannamethee, A. G. Shaper, and M. Walker, "Overweight and obesity and weight change in middle aged men: impact on cardiovascular disease and diabetes," *Journal of Epidemiology and Community Health*, vol. 59, no. 2, pp. 134–139, 2005.
- [13] C. T. Montague and S. O'Rahilly, "The perils of portliness: causes and consequences of visceral adiposity," *Diabetes*, vol. 49, no. 6, pp. 883–888, 2000.
- [14] S. Wild, G. Roglic, A. Green, R. Sicree, and H. King, "Global Prevalence of Diabetes: estimates for the year 2000 and projections for 2030," *Diabetes Care*, vol. 27, no. 5, pp. 1047–1053, 2004.
- [15] A. H. Mokdad, E. S. Ford, B. A. Bowman et al., "Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001," *Journal of the American Medical Association*, vol. 289, no. 1, pp. 76–79, 2003.
- [16] American Diabetes Association web site 2011, <http://www.diabetes.org/diabetes-basics/diabetes-statistics/?loc=DropDownDB-stats>.
- [17] B. Balkau, J. E. Deanfield, J.-P. Després et al., "International day for the evaluation of abdominal obesity (IDEA): a study of waist circumference, cardiovascular disease, and diabetes mellitus in 168 000 primary care patients in 63 countries," *Circulation*, vol. 116, no. 17, pp. 1942–1951, 2007.
- [18] F. F. Casanueva, B. Moreno, R. Rodríguez-Azaredo et al., "Relationship of abdominal obesity with cardiovascular disease, diabetes and hyperlipidaemia in Spain," *Clinical Endocrinology*, vol. 73, no. 1, pp. 35–40, 2010.
- [19] R. R. Henry, R. Chilton, and W. T. Garvey, "New options for the treatment of obesity and type 2 diabetes mellitus (narrative review)," *Journal of Diabetes and Its Complications*, vol. 27, no. 5, pp. 508–518, 2013.
- [20] S. A. Brethauer, A. Aminian, H. Romero-Talamás et al., "Can diabetes be surgically cured? Long-term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus," *Annals of Surgery*, vol. 258, no. 4, pp. 628–637, 2013.
- [21] T. Kadomatsu, M. Tabata, and Y. Oike, "Angiopoietin-like proteins: emerging targets for treatment of obesity and related metabolic diseases," *FEBS Journal*, vol. 278, no. 4, pp. 559–564, 2011.
- [22] F. Saad, "Androgen therapy in men with testosterone deficiency: can testosterone reduce the risk of cardiovascular disease?" *Diabetes Metabolism Research and Reviews*, vol. 28, supplement 2, pp. 52–59, 2012.
- [23] F. Saad, A. Haider, G. Doros, and A. Traish, "Long-term treatment of hypogonadal men with testosterone produces substantial and sustained weight loss," *Obesity*, vol. 21, no. 10, pp. 1975–1981, 2013.
- [24] A. Aversa, R. Bruzziches, D. Francomano et al., "Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study," *Journal of Sexual Medicine*, vol. 7, no. 10, pp. 3495–3503, 2010.



- [25] A. M. Traish, A. Haider, G. Doros, and F. Saad, "Long-term testosterone therapy in hypogonadal men ameliorates elements of the metabolic syndrome: an observational, long-term registry study," *International Journal of Clinical Practice*, 2013.
- [26] G. Hackett, "Testosterone and the heart," *International Journal of Clinical Practice*, vol. 66, no. 7, pp. 648–655, 2012.
- [27] D. Kapoor, E. Goodwin, K. S. Channer, and T. H. Jones, "Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes," *European Journal of Endocrinology*, vol. 154, no. 6, pp. 899–906, 2006.
- [28] T. H. Jones, S. Arver, H. M. Behre et al., "Testosterone replacement in hypogonadal men with Type 2 diabetes and/or metabolic syndrome (the TIMES2 study)," *Diabetes Care*, vol. 34, no. 4, pp. 828–837, 2011.
- [29] M. A. Boyanov, Z. Boneva, and V. G. Christov, "Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency," *Aging Male*, vol. 6, no. 1, pp. 1–7, 2003.
- [30] S. Y. Kalinchenko, Y. A. Tishova, G. J. Mskhalaya, L. J. G. Gooren, E. J. Giltay, and F. Saad, "Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study," *Clinical Endocrinology*, vol. 73, no. 5, pp. 602–612, 2010.
- [31] A. Cornoldi, G. Caminiti, G. Marazzi et al., "Effects of chronic testosterone administration on myocardial ischemia, lipid metabolism and insulin resistance in elderly male diabetic patients with coronary artery disease," *International Journal of Cardiology*, vol. 142, no. 1, pp. 50–55, 2010.
- [32] G. Caminiti, M. Volterrani, F. Iellamo et al., "Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure," *Journal of the American College of Cardiology*, vol. 54, no. 10, pp. 919–927, 2009.
- [33] G. Corona, M. Monami, G. Rastrelli et al., "Testosterone and metabolic syndrome: a meta-analysis study," *Journal of Sexual Medicine*, vol. 8, no. 1, pp. 272–283, 2011.
- [34] A. A. Yassin and G. Doros, "Testosterone therapy in hypogonadal men results in sustained and clinically meaningful weight loss," *Clinical Obesity*, vol. 3, no. 3–4, pp. 73–83, 2013.
- [35] G. Hackett, N. Cole, M. Bhartia et al., "Testosterone replacement therapy with long-acting testosterone undecanoate improves sexual function and quality-of-life parameters vs. placebo in a population of men with type 2 diabetes," *Journal of Sexual Medicine*, vol. 10, no. 6, pp. 1612–1627, 2013.
- [36] D. Francomano, A. Ilacqua, R. Bruzziches et al., "Effects of 5-year treatment with testosterone undecanoate on lower urinary tract symptoms in obese men with hypogonadism and metabolic syndrome," *Urology*, vol. 83, no. 1, pp. 167–174, 2014.
- [37] M. Zitzmann, A. Mattern, J. Hanisch et al., "IPASS: a study on the tolerability and effectiveness of injectable testosterone undecanoate for the treatment of male hypogonadism in a worldwide sample of 1,438 men," *Journal of Sexual Medicine*, vol. 10, no. 2, pp. 579–588, 2013.
- [38] J. F. Reckelhoff, "Gender differences in the regulation of blood pressure," *Hypertension*, vol. 37, no. 5, pp. 1199–1208, 2001.
- [39] R. K. Dubey, S. Oparil, B. Imthurn, and E. K. Jackson, "Sex hormones and hypertension," *Cardiovascular Research*, vol. 53, no. 3, pp. 688–708, 2002.
- [40] J.-Y. Li, J.-C. Zhu, J.-T. Dou et al., "Effects of androgen supplementation therapy on partial androgen deficiency in the aging male: a preliminary study," *Aging Male*, vol. 5, no. 1, pp. 47–51, 2002.
- [41] J. C. Smith, S. Bennett, L. M. Evans et al., "The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer," *Journal of Clinical Endocrinology and Metabolism*, vol. 86, no. 9, pp. 4261–4267, 2001.
- [42] F. Dockery, C. J. Bulpitt, S. Agarwal, M. Donaldson, and C. Rajkumar, "Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia," *Clinical Science*, vol. 104, no. 2, pp. 195–201, 2003.
- [43] A. M. Dart and B. A. Kingwell, "Pulse pressure—a review of mechanisms and clinical relevance," *Journal of the American College of Cardiology*, vol. 37, no. 4, pp. 975–984, 2001.
- [44] C. M. Hoyos, B. J. Yee, C. L. Phillips et al., "Body compositional and cardiometabolic effects of testosterone therapy in obese men with severe obstructive sleep apnoea: a randomized placebo-controlled trial," *European Journal of Endocrinology*, vol. 167, no. 4, pp. 531–541, 2012.
- [45] C. Richard, P. Couture, S. Desroches, and B. Lamarche, "Effect of the Mediterranean diet with and without weight loss on markers of inflammation in men with metabolic syndrome," *Obesity*, vol. 21, no. 1, pp. 51–57, 2013.
- [46] S. K. Musani, R. S. Vasan, A. Bidulescu et al., "Aldosterone, C-reactive protein, and plasma B-type natriuretic peptide are associated with the development of metabolic syndrome and longitudinal changes in metabolic syndrome components: findings from the Jackson Heart Study," *Diabetes Care*, vol. 36, no. 10, pp. 3084–3092, 2013.
- [47] D. Withrow and D. A. Alter, "The economic burden of obesity worldwide: a systematic review of the direct costs of obesity," *Obesity Reviews*, vol. 12, no. 2, pp. 131–141, 2011.
- [48] D. P. Guh, W. Zhang, N. Bansback, Z. Amarsi, C. L. Birmingham, and A. H. Anis, "The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis," *BMC Public Health*, vol. 9, article 88, 2009.
- [49] B. H. Goodpaster, D. E. Kelley, R. R. Wing, A. Meier, and F. L. Thaete, "Effects of weight loss on regional fat distribution and insulin sensitivity in obesity," *Diabetes*, vol. 48, no. 4, pp. 839–847, 1999.
- [50] K. M. Utzschneider, D. B. Carr, S. M. Barsness, S. E. Kahn, and R. S. Schwartz, "Diet-induced weight loss is associated with an improvement in  $\beta$ -cell function in older men," *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 6, pp. 2704–2710, 2004.
- [51] R. F. Hamman, R. R. Wing, S. L. Edelstein et al., "Effect of weight loss with lifestyle intervention on risk of diabetes," *Diabetes Care*, vol. 29, no. 9, pp. 2102–2107, 2006.
- [52] J.-P. Després, I. Lemieux, and D. Prud'homme, "Treatment of obesity: need to focus on high risk abdominally obese patients," *British Medical Journal*, vol. 322, no. 7288, pp. 716–720, 2001.
- [53] S. A. Saboor Aftab, S. Kumar, and T. M. Barber, "The role of obesity and type 2 diabetes mellitus in the development of male obesity-associated secondary hypogonadism," *Clinical Endocrinology*, vol. 78, no. 3, pp. 330–337, 2013.
- [54] D. M. Kelly and T. H. Jones, "Testosterone: a vascular hormone in health and disease," *Journal of Endocrinology*, vol. 217, no. 3, pp. 47–71, 2013.



- [55] D. M. Kelly and T. H. Jones, "Testosterone: a metabolic hormone in health and disease," *Journal of Endocrinology*, vol. 217, no. 3, pp. R25–R45, 2013.
- [56] P. M. Rao, D. M. Kelly, and T. H. Jones, "Testosterone and insulin resistance in the metabolic syndrome and T2DM in men," *Nature Reviews Endocrinology*, vol. 9, no. 8, pp. 479–493, 2013.
- [57] C. M. Phillips and I. J. Perry, "Does inflammation determine metabolic health status in obese and nonobese adults?" *Journal of Clinical Endocrinology and Metabolism*, 2013.
- [58] O. Schnell, I. Amann-Zalan, Z. Jelsovsky et al., "Changes in A1C levels are significantly associated with changes in levels of the cardiovascular risk biomarker hs-CRP: results from the SteP study," *Diabetes Care*, vol. 36, no. 7, pp. 2084–2089, 2013.
- [59] R. Turner, "Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34)," *The Lancet*, vol. 352, no. 9131, pp. 854–865, 1998.
- [60] S. E. Kahn, S. M. Haffner, M. A. Heise et al., "Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy," *New England Journal of Medicine*, vol. 355, no. 23, pp. 2427–2443, 2006.
- [61] G. Tharakan, T. Tan, and S. Bloom, "Emerging therapies in the treatment of 'diabetes': beyond GLP-1," *Trends in Pharmacological Sciences*, vol. 32, no. 1, pp. 8–15, 2011.
- [62] A. Astrup and N. Finer, "Redefining type 2 diabetes: 'Diabetes' or 'obesity dependent diabetes mellitus'?" *Obesity Reviews*, vol. 1, no. 2, pp. 57–59, 2000.
- [63] A. Astrup, R. Carraro, N. Finer et al., "Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide," *International Journal of Obesity*, vol. 36, no. 6, pp. 843–854, 2012.
- [64] K. E. Wellen and G. S. Hotamisligil, "Inflammation, stress, and diabetes," *Journal of Clinical Investigation*, vol. 115, no. 5, pp. 1111–1119, 2005.
- [65] K. B. Gast, J. W. Smit, M. den Heijer, N. E. O. study group et al., "Abdominal adiposity largely explains associations between insulin resistance, hyperglycemia and subclinical atherosclerosis: the NEO study," *Atherosclerosis*, vol. 229, no. 2, pp. 423–429, 2013.
- [66] F. Giacco and M. Brownlee, "Oxidative stress and diabetic complications," *Circulation Research*, vol. 107, no. 9, pp. 1058–1070, 2010.
- [67] B. Gustafson, "Adipose tissue, inflammation and atherosclerosis," *Journal of Atherosclerosis and Thrombosis*, vol. 17, no. 4, pp. 332–341, 2010.
- [68] M. Chilton, A. Dunkley, P. Carter et al., "The effect of anti-obesity drugs on waist circumference: a mixed treatment comparison," *Diabetes, Obesity and Metabolism*, 2013.
- [69] S. Czernichow, A.-P. Kengne, E. Stamatakis, M. Hamer, and G. D. Batty, "Body mass index, waist circumference and waist-hip ratio: which is the better discriminator of cardiovascular disease mortality risk? Evidence from an individual-participant meta-analysis of 82864 participants from nine cohort studies," *Obesity Reviews*, vol. 12, no. 9, pp. 680–687, 2011.
- [70] A. Boillot, S. Zoungas, P. Mitchell et al., "Obesity and the microvasculature: a systematic review and meta-analysis," *PLoS ONE*, vol. 8, no. 2, Article ID e52708, 2013.
- [71] E. J. Jacobs, C. C. Newton, Y. Wang et al., "Waist circumference and all-cause mortality in a large US cohort," *Archives of Internal Medicine*, vol. 170, no. 15, pp. 1293–1301, 2010.
- [72] C.-H. Tseng, "Body mass index and waist circumference as determinants of coronary artery disease in Taiwanese adults with type 2 diabetes mellitus," *International Journal of Obesity*, vol. 30, no. 5, pp. 816–821, 2006.
- [73] L. Sjöström, K. Narbro, C. D. Sjöström et al., "Effects of bariatric surgery on mortality in Swedish obese subjects," *New England Journal of Medicine*, vol. 357, no. 8, pp. 741–752, 2007.
- [74] H. Buchwald and D. M. Oien, "Metabolic/bariatric surgery worldwide 2008," *Obesity Surgery*, vol. 19, no. 12, pp. 1605–1611, 2009.
- [75] L. L. Baggio and D. J. Drucker, "Biology of incretins: GLP-1 and GIP," *Gastroenterology*, vol. 132, no. 6, pp. 2131–2157, 2007.
- [76] J. F. Todd, J. P. H. Wilding, C. M. B. Edwards, F. A. Khan, M. A. Ghatei, and S. R. Bloom, "Glucagon-like peptide-1 (GLP-1): a trial of treatment in non-insulin-dependent diabetes mellitus," *European Journal of Clinical Investigation*, vol. 27, no. 6, pp. 533–536, 1997.
- [77] G. Tharakan, T. Tan, and S. Bloom, "Emerging therapies in the treatment of 'diabetes': Beyond GLP-1," *Trends in Pharmacological Sciences*, vol. 32, no. 1, pp. 8–15, 2011.
- [78] I. Raz, M. Hanefeld, L. Xu, C. Caria, D. Williams-Herman, and H. Khatami, "Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus," *Diabetologia*, vol. 49, no. 11, pp. 2564–2571, 2006.
- [79] S. Dhindsa, S. Prabhakar, M. Sethi, A. Bandyopadhyay, A. Chaudhuri, and P. Dandona, "Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes," *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 11, pp. 5462–5468, 2004.
- [80] P. A. Dyson, "The therapeutics of lifestyle management on obesity," *Diabetes, Obesity and Metabolism*, vol. 12, no. 11, pp. 941–946, 2010.
- [81] The Diabetes Prevention Program Research Group, "Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study," *Diabetes Care*, vol. 35, no. 4, pp. 731–737, 2012.
- [82] S. R. Smith, N. J. Weissman, C. M. Anderson et al., "Multicenter, placebo-controlled trial of lorcaserin for weight management," *New England Journal of Medicine*, vol. 363, no. 3, pp. 245–256, 2010.
- [83] K. M. Gadde, D. B. Allison, D. H. Ryan et al., "Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial," *The Lancet*, vol. 377, no. 9774, pp. 1341–1352, 2011.
- [84] W. T. Garvey, D. H. Ryan, M. Look et al., "Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study," *American Journal of Clinical Nutrition*, vol. 95, no. 2, pp. 297–308, 2012.
- [85] R. Turner, "Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)," *The Lancet*, vol. 352, no. 9131, pp. 837–853, 1998.
- [86] M. A. Nauck, "A critical analysis of the clinical use of incretin-based therapies: the benefits by far outweigh the potential risks," *Diabetes Care*, vol. 36, no. 7, pp. 2126–2132, 2013.
- [87] V. Muraleedharan, H. Marsh, D. Kapoor et al., "Testosterone deficiency is associated with increased risk of mortality and

testosterone replacement improves survival in men with type 2 diabetes,” *European Journal of Endocrinology*, vol. 169, no. 6, pp. 725–733, 2013.

- [88] G. Hackett, N. Cole, M. Bhartia et al., “Testosterone replacement therapy improves metabolic parameters in hypogonadal men with type 2 diabetes but not in men with coexisting depression: the BLAST study,” *The Journal of Sexual Medicine*, 2013.
- [89] O. Schnell, W. Otter, and E. Standl, “The Munich Myocardial Infarction Registry: translating the European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD) guidelines on diabetes, pre-diabetes, and cardiovascular disease into clinical practice,” *Diabetes care*, vol. 32, pp. S326–330, 2009.

## Review Article

# The Interplay between Magnesium and Testosterone in Modulating Physical Function in Men

**Marcello Maggio,<sup>1,2</sup> Francesca De Vita,<sup>1</sup> Fulvio Lauretani,<sup>1</sup> Antonio Nouvenne,<sup>2</sup> Tiziana Meschi,<sup>1,2</sup> Andrea Ticinesi,<sup>1</sup> Ligia J. Dominguez,<sup>3</sup> Mario Barbagallo,<sup>3</sup> Elisabetta Dall'Aglia,<sup>1,2</sup> and Gian Paolo Ceda<sup>1,2</sup>**

<sup>1</sup> Section of Geriatrics, Department of Clinical and Experimental Medicine, University of Parma, Via Gramsci 14, 43100 Parma, Italy

<sup>2</sup> Geriatric Rehabilitation Department, University-Hospital of Parma, Via Gramsci 14, 43100 Parma, Italy

<sup>3</sup> Department of Internal Medicine and Medical Specialties (DIMIS), University of Palermo, Piazza delle Cliniche 2, 90127 Palermo, Italy

Correspondence should be addressed to Marcello Maggio; [marcellogiuseppe.maggio@unipr.it](mailto:marcellogiuseppe.maggio@unipr.it)

Received 24 November 2013; Revised 20 January 2014; Accepted 20 January 2014; Published 3 March 2014

Academic Editor: Lorenzo Maria Donini

Copyright © 2014 Marcello Maggio et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The role of nutritional status as key factor of successful aging is very well recognized. Among the different mechanisms by which nutrients may exert their beneficial effects is the modulation of the hormonal anabolic milieu, which is significantly reduced with aging. Undernutrition and anabolic hormonal deficiency frequently coexist in older individuals determining an increased risk of mobility impairment and other adverse outcomes. Mineral assessment has received attention as an important determinant of physical performance. In particular, there is evidence that magnesium exerts a positive influence on anabolic hormonal status, including Testosterone, in men. In this review we summarize data from observational and intervention studies about the role of magnesium in Testosterone bioactivity and the potential underlying mechanisms of this relationship in male subjects. If larger studies will confirm these pivotal data, the combination of hormonal and mineral replacements might be adopted to prevent or delay the onset of disability in the elderly.

## 1. Biological Role of Magnesium

Magnesium is an essential ion involved in multiple fundamental physiologic functions in humans [1]. As part of the activated MgATP complex, magnesium is involved in the pathways generating adenosine triphosphate (ATP) and energy in mitochondria, electron transport chain and complex subunits, and oxygen detoxification. Magnesium is also a cofactor in over 300 enzymatic reactions and biological processes, including protein and nucleic acid synthesis, and neuromuscular excitability [1].

Circulating magnesium exists in three forms. The metabolically active free ionized fraction (magnesium ion) is the most represented, accounting up to 60–70% of the total serum magnesium. Other main serum forms include the protein-bound (25% and 8% bound to albumin and globulin, resp.) and the chelated magnesium fraction (12%) [2].

The most represented reservoir of magnesium in human body is the mineral phase of the bone that accounts for about 64% of total magnesium. The remaining amount is located in the intracellular (34%) and extracellular spaces (1%). The intracellular magnesium concentration is fundamental to ensure the most important cellular and metabolic activities [3]. Indeed, the rapid requirements of this cation are usually met by intracellular stores that more quickly exchange magnesium with intracellular fluids.

Because of the lack of clinical tests available for assessing total-body magnesium content, the serum magnesium concentration remains the most clinically reliable test.

Adequate serum magnesium levels (normal ranges: 0.75–0.95 mmol/L or 1.7–2.5 mg/dL) seem to be critical in ensuring the normal cellular homeostasis [1, 2]. Magnesium status is influenced by dietary intake, absorption in the gastrointestinal tract, renal excretion, and tissue uptake and utilization

(e.g., cardiac and skeletal muscle tissue) [4]. To guarantee an optimal magnesium homeostasis the recommended intake from dietary sources is estimated in 420 and 320 mg/day for healthy men and women, respectively [5]. Food-rich magnesium sources are cereals, green leafy vegetables, seeds, nuts, cocoa, and seafood [6]. However, the definition of magnesium deficiency is notoriously complex. Magnesium serum concentrations below the laboratory reference range of <1.8 mg/dL are currently used to define some degree of magnesium depletion. However, this cut-off value could be not necessarily related to a pathophysiologic state of deficiency, because low intracellular magnesium has been documented even in patients with serum magnesium concentrations >1.8 mg/dL [7].

## 2. Magnesium and Muscle Function in Young Trained Individuals

Magnesium has been the most investigated mineral involved in muscle function. The beneficial effects of magnesium on skeletal muscle and physical performance are linked to its known actions on energetic metabolism (phosphorylation processes and reactions requiring ATP, energy utilization and transfer, and transmembrane transport) which have enormous implications in muscle contraction [1]. In fact, dietary magnesium deprivation is associated with increased oxygen requirements to complete submaximal exercise and reduced endurance performance [8].

Magnesium administration elicited the reductions in heart rate, ventilation, oxygen uptake, and carbon dioxide production during submaximal work [9, 10]. In male athletes, 25 days of magnesium (390 mg/d), with a 3 wk washout, increased peak oxygen uptake and total work output during work capacity tests [11]. Similarly, in physically active collegians, magnesium supplementation significantly improved endurance performance and oxygen utilization [12]. In a depletion-repletion experiment in 10 postmenopausal women (aged 45–71), dietary magnesium (320 versus 180 mg/d) improved magnesium balance, erythrocyte and skeletal muscle magnesium concentrations, heart rate, and oxygen consumption during submaximal exercise [13].

It is not surprising that most of the current observational and intervention studies have been conducted on athlete subjects. In young men participating at 7-week strength training program, supplemental magnesium was capable of significantly improving muscle strength and power [14]. The gain in muscle strength occurred at dietary magnesium intake higher than 250 mg/d and was even more evident at 500 mg/d (exceeding the recommended dietary allowance, RDA) [14]. However, magnesium supplementation per se does not affect work performance in magnesium-replete trained individuals [15]. Dietary surveys reveal a magnesium intake equaling or exceeding the RDA for male athletes [16]. In female athletes it tends to be 60% to 65% of the current recommendation. Regardless of sex, athletes competing in sports requiring weight classifications or esthetic components tend to consume up to 30–55% of the magnesium RDA [17]. Serum magnesium levels may also be reduced during

intense and/or long-term exercise [18] leading to latent fatigue and decreased endurance [19], similarly to what has been observed during the condition of zinc deficiency [20].

These lines of evidence led to consider magnesium as potentially limiting element for human physical performance, creating the rationale for the routine use of magnesium supplementation during intense endurance exercise.

## 3. Age-Related Changes in Magnesium Levels and Physical Performance

Suboptimal magnesium status is a frequent condition in older persons. The most common cause of magnesium deficit is the low dietary magnesium intake [21]. This is a well-represented phenomenon in older population, occurring in up to 10–15% of community-dwelling older subjects [22]. The typical western diet, highly rich in processed foods and deficient in green vegetables and whole grain, may also contribute to an inadequate magnesium intake.

The magnesium requirement for older population does not differ from young and adult subjects. However, data from the National Health and Nutrition Examination Survey (NHANES) III show an average daily magnesium intake dramatically below the recommended RDA, approximately of 225 mg/day in men and 166 mg/day in women [5].

A suboptimal magnesium status may also result from altered magnesium absorption and/or increased urinary loss [23]. Polypharmacotherapy (loop diuretics, digitals, and proton pump inhibitors) as well as a wide range of clinical conditions (HIV, type 2 diabetes, alcoholism, and cardiovascular diseases) plays additional important roles in lowering magnesium levels [24–26].

However, the magnesium deficiency is more difficult to be detected in the elderly population. In fact the pauperization of intracellular stores is not usually accompanied by a parallel decline in magnesium serum concentrations that tend to remain more stable, within the normal range [27]. The deficiency of magnesium at cellular level and in the body stores is crucial for maintaining the skeletal muscle efficiency. It is very well known that sarcopenia (recently defined by consensus documents as the presence of both low muscle mass and low muscle function (strength or performance)) [28–30] frequently leads to a condition of decreased physiological reserve, increased vulnerability to stressors, and adverse outcomes, known as “frailty” [31]. The frail status is a strong predictor of mortality, independent of traditional indicators of disease [32]. Despite the role of magnesium in muscle integrity and function, there are few data in this regard in the elderly. In a representative cohort of 1138 older men, Dominguez and colleagues [33] using data from the InCHIANTI Study showed a significant, independent, and strong positive relationship between circulating magnesium levels and measures of muscle performance (hand grip strength, lower-leg muscle power, knee extension torque, and ankle extension strength). These authors suggested the need of identifying serum magnesium cut-off values to attain the best possible physical function. These data suggest the



potential contribution of low magnesium status, frequently observed in the elderly, to the reduced physical performance.

#### **4. The Concept of Nutritional Modulation of Anabolic Hormonal Status in Older Men**

In healthy adult subjects, changes in food consumption and utilization may induce homeostatic adaptations that redistribute nutrients without affecting muscle function and physical performance. During the aging process the body energy delivery system could be impaired because of the decline in physiological reserves and the disruption of metabolic pathways, and sarcopenia may arise. Physiological, psychological, and hormonal systems interact to determine the energy need. Macronutrients are essential to provide the body structure to perform work. Minerals are fundamental to enable the use of macronutrients for all physiological processes. In fact, an insufficient qualitative and quantitative nutrient intake is one of the multiple causes of loss of muscle mass, decreased physical performance, and adverse outcomes [34]. Anabolic hormones, whose levels decrease with age, play an important role in maintaining the optimal body energy delivery. In older persons, the occurrence of a single mild hormonal derangement is rarely observed. More frequently there is a simultaneous anabolic hormonal deficiency [Testosterone (T), Dehydroepiandrosterone (DHEA), estradiol (E2), growth hormone-Insulin-like Growth Factor-1 (GH-IGF-1), and vitamin D] which is part of “multiple hormonal dysregulation” [35]. These hormones interplay in ensuring overall anabolic state and induce the satellite cell activation together with exercise and muscle hypertrophy [35]. The simultaneous presence of low levels of Testosterone, together with DHEAS and IGF-1, has a strong effect on all-cause mortality in older men [36]. Experimental data confirm that hormonal therapies, singularly or in combination, may improve body composition and physical performance [37–41]. The nutrients (especially the minerals magnesium, selenium, and zinc) and the anabolic hormones, especially T and IGF-1, seem to interact. The combination of nutritional and hormonal strategies in frail undernourished older people determines a more effective reduction in the number of hospitalizations, the time to hospital admission, and the days of hospital stay [42, 43]. The specific actions of both micronutrients and hormones at skeletal muscle level have led to the hypothesis of an interaction of these factors in ensuring optimal physical performance [44]. This novel concept could have important clinical implications in the elderly, who are more prone to a disruption of the anabolic/catabolic equilibrium and undernutrition. The use of specific mineral supplements may represent a sort of preventive measure of mobility impairment.

#### **5. Changes in Testosterone Secretion with Age and Implications in Skeletal Muscle Function**

Testosterone is the most important male sex steroid, synthesized by the Leydig cells of the testes (95%) and derived by

peripheral adrenal androgens conversion for the remaining 5% [45].

In men, up to 44–65% of the circulating plasma T is bound to sex hormone binding globulin (SHBG) and 33–54% to albumin, and approximately 2–3% is available as a free form. The free fraction of circulating T plus albumin-bound T represents the amount of biologically active T (Bio-T) that more accurately reflects the clinical androgen state of the subject [46]. Total T levels progressively decrease from the age of 35, by 1% per year. The decline is more pronounced for Bio-T, 2% per year [45], especially in untreated depressed men [47, 48]. The causes of the age-related fall in total and Bio-T levels include a decrease in testicular function and a disruption of hypothalamic-pituitary axis. This peculiar phenomenon of the ageing process involves the GnRH secretion and activity (reduced amplitude of the peaks, attenuation of the circadian rhythm, and reduced sensitivity to negative feedback), the pituitary gland (reduced gonadotropin response to GnRH), and the Leydig cells (reduced response to human chorionic gonadotropin, HCG) [49].

Other mechanisms such as the increased SHBG levels and T aromatization (increased activity aromatase in adipose tissue) as well as the reduced bioconversion of T into dihydrotestosterone could also concur to impair T biological activity with age [50, 51]. Some authors hypothesize that the age-related decline in androgenic activity could be related to the reduced DHEA secretion, which is an important precursor of T [52]. Finally, qualitative changes in signaling transduction (reduced T receptors expression and/or impaired T binding capacity in the liver, brain, and prostate) should be also accounted for [53, 54].

The anabolic, anticatabolic, and neurotrophic effects of T administration on muscle are well known and extensively studied.

Observational studies on castrated animals [55] and adult men [56, 57] show that low T levels are associated with a reduction in lean body mass and muscle strength and other negative changes in body composition.

In a very recent cross-sectional analysis of 250 patients, 70 years or older, Ucak et al. [58] have found a negative impact of “compensated” or “subclinical” hypogonadism (defined as mild biochemical alterations accompanied by signs and symptoms of T deficiency) [59] on physical function, mood, cognitive, and nutritional status.

Intervention studies on elderly subjects have documented beneficial effects of T on counteracting the age-related changes of body composition and physical function [60–62]. T exerts direct influence on lean body mass and strength [63, 64], whereas equivocal evidence is available on the effects of T on physical performance and quality of life [35].

The anabolic effects of T are even more evident in older subjects with mobility limitation.

In 209 community-dwelling men with low T levels (100 to 350 ng/dL [3.5 to 12.1 nmol/L]) from Testosterone in Older Men (TOM) with Mobility Limitations Trial, the daily T gel therapy for 6 months improved both leg-press and chest-press strength and stair-climbing power [65]. Testosterone may also influence muscle metabolism by improving haemoglobin levels in older men with mild anaemia [66, 67].

In women, skeletal muscle tissue seems to be sensitive to the anabolic action of androgens [68]. However, the impact of T administration on full physical function has not been fully studied. The precise molecular mechanisms underlying these observed physical changes in men are likely to include specific T effects on adipocytes and skeletal muscle cell receptors. The binding of T to its receptors could lead to the stimulation of lipolysis and protein synthesis [41, 69]. Finally, several lines of evidence support the hypothesis of permissive effects of T on the differentiation of the precursor stromal cells into muscular line [70].

## 6. The Interplay between Magnesium and Testosterone in Physical Function

The hypothesis of a link between magnesium and T has been tested in pivotal experiences using magnesium supplementation in adult subjects. Brilla and Conte investigated the combined role of magnesium supplementation and exercise on T levels [71]. A simple zinc-magnesium nutritional formulation (30 mg zinc monomethionine aspartate, 450 mg magnesium aspartate, and 10.5 mg of vitamin B-6) was able to improve T levels of athletes engaging in intense physical activity compared to placebo (132.1 to 176.3 pg/mL versus 141 to 126.6 pg/mL). The highest levels of T were found in those athletes both exercising and receiving magnesium supplementation. Moreover, significant differences in muscle strength via torque measurements and functional power were noted between the 2 groups (189.9 to 211 Nm at 180°/s and 316.5 to 373.7 Nm at 300°/s versus 204.2 to 209.1 Nm at 180°/s and 369.5 to 404.3 Nm at 300°/s). These data have been confirmed in a recent study performed on young subjects, where 4-week magnesium supplementation (magnesium sulfate 10 mg/kg/d) and exercise increase free and total T concentrations at exhaustion before and after supplementation compared to resting levels [72, 73]. There are limited data about the relationship between magnesium and T in study population, especially of older subjects. Maggio and colleagues [74] in 399 older men  $\geq 65$  years ( $74.18 \pm 6.43$  mean age  $\pm$  SD) from the InCHIANTI Study documented for the first time the strong and positive association between magnesium levels and total T and total IGF-1 levels. Interestingly, the relationship between magnesium and T was independent of body mass index, IL-6, DHEAS, SHBG, insulin, total IGF-1, grip strength, Parkinson's disease, and chronic heart failure. Because of the cross-sectional nature of the study the authors could not establish a cause-effect relationship between magnesium and T levels. This finding led the authors to perform a pilot single-center, randomized, placebo-controlled, single-blind intervention study. 46 elderly hospitalized male subjects (21 in the treatment group), aged 65 years or older, with magnesium serum levels  $< 2.5$  mg/dL, were randomly assigned to magnesium sulfate treatment (1 g/mL of ion  $Mg^{++}$  diluted in 250 cc of normal saline solution) or placebo (250 cc of saline solution) [75]. The active product or placebo was in a single intravenous dose administered in about 30 minutes. Testosterone, IGF-1, SHBG, and C-reactive protein (CRP) concentrations were

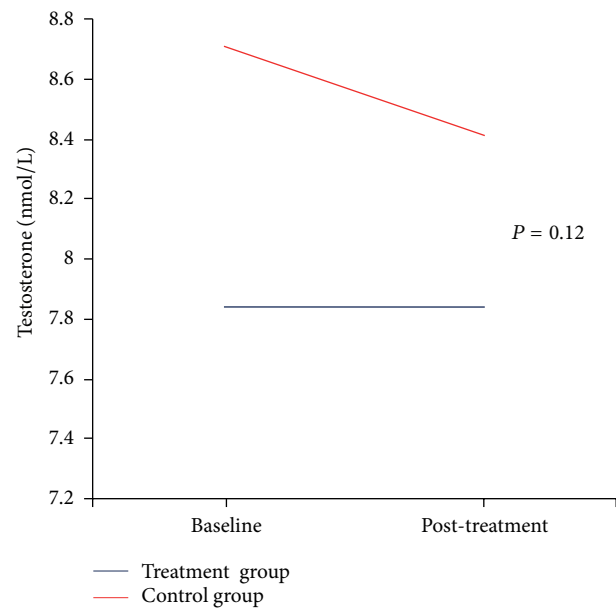


FIGURE 1: Changes in Testosterone levels at baseline and after treatment. Changes in the average Testosterone levels (nmol/L) before (baseline) and after (post-treatment) magnesium sulfate administration (blue line) and placebo (red line). The difference in total Testosterone levels between the 2 groups touched the statistical significance ( $P = 0.12$ ).

evaluated before and after treatment. All measurements were performed at the Laboratory of the University-Hospital of Parma. Baseline characteristics between intervention and control groups were analyzed by *t*-test. Paired *t*-test was used to examine and to compare the response trends between the two groups at baseline and after treatment. As expected, magnesium sulfate administration induced a significant increase in serum magnesium levels ( $\Delta 1.28 \pm 0.61$ ) compared to placebo ( $\Delta -0.03 \pm 0.14$ ) ( $P < 0.001$ ). Interestingly, total T levels remained substantially unchanged ( $\Delta 0.01 \pm 0.80$ ) in the intervention group while they were significantly decreased in the placebo group ( $\Delta -0.03 \pm 0.14$ ). The difference in total T levels between the 2 groups touched the statistical significance ( $P = 0.12$ ) (Figure 1). No differences were appreciated in bioavailable T (Bio-T), IGF-1, and SHBG concentrations. In this preliminary analysis no differences in CRP levels were observed between the two groups at baseline. The adjustment for CRP levels at baseline did not affect the relationship between magnesium and total T [75].

These preliminary data in humans are supported by experimental studies in animal models.

Interestingly, magnesium supplementation has been shown to have an apparent beneficial effect on male gonadal system, as observed in a very recent study performed on sexually mature male rats [76]. Chandra et al. evaluated the morphological, cytological, and functional changes in testis after magnesium administration. Interestingly, the authors showed significant enhancing in steroidogenic enzymes, namely,  $\Delta 5\beta$ -hydroxysteroid dehydrogenase and  $17\beta$ -hydroxysteroid dehydrogenase, activities at moderate

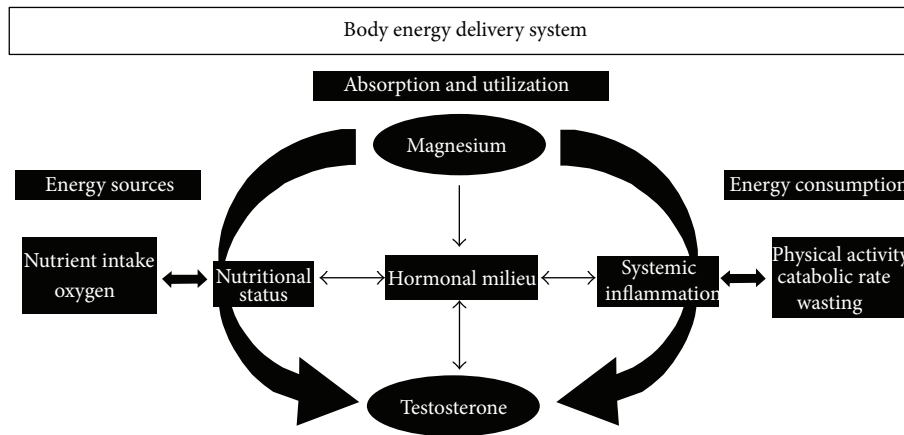


FIGURE 2: Relationship between Testosterone and magnesium, potential underlying mechanisms and clinical implications. The aging process is frequently characterized by an impaired homeostatic reserve due to an imbalance between energy assumption (left side) and utilization and consumption (middle and right sides). The activity of anabolic hormones, where T plays a central role, is influenced by mineral status (magnesium), along with caloric and protein intake. The systemic inflammation, which negatively influences magnesium and T and is in turn downregulated by these 2 factors.

and high dose of magnesium that resulted in increased serum T levels [76]. This phenomenon was followed by a progressive development in cytoarchitecture of genital organs without significant changes in quantitative spermatogenesis. The results were remarkably more evident in the groups treated for a longer period and at high doses of magnesium. In mice, dietary magnesium depletion seems to target apical cells within caput epididymis [77]. Moreover, in older male dromedary camel, the age-related decline in plasma T concentrations has been associated with a disruption of the mechanisms controlling normal cation distribution (including magnesium) in the testis, epididymis, and accessory glands [78].

## 7. The Role of Inflammation in the Interplay between Magnesium and Testosterone Levels

We can account for different factors influencing both T and magnesium concentration in adult and elderly men. Particular attention deserves the role of inflammation, which is a negative modulator of both these factors.

Inflammatory cytokines act as inhibitory factors at pituitary (on the secretion of LH) and testicular level (reduction of T secretion and sensitivity of T to LH) [79], contributing to the development of hypogonadism.

Higher levels of inflammatory markers and low T concentration are strong predictors of frailty, disability, and cardiovascular events [80, 81] that negatively influence the muscle mass [82].

In older men, there is a steeper decline of T levels during a proinflammatory postoperative status (also known as “acute postoperative frailty”) [83].

However, short-term T administration seems in turn to reduce systemic inflammatory cytokines including TNF- $\alpha$ , IL-6, and IL-1 $\beta$  [84] and to increase the anti-inflammatory cytokine IL-10 [85]. In a similar manner,

magnesium seems to be fundamental in maintaining the threshold of antioxidant capacity and the control of oxidative stress [1]. Moreover, there is evidence of impaired overall antioxidant capacity and low-grade inflammation in magnesium-deficient cultured human and animals cells [86]. Inadequate intracellular magnesium may reduce the mitochondrial efficiency and increase the production of reactive oxygen species (ROS), determining structural and functional impairment of proteins [87] and DNA [88]. Interestingly, magnesium and T were found to be lower during systemic inflammation, and conditions associated with both increased ROS, oxygen-derived free radicals, oxygen peroxide production, and impaired antioxidant enzyme expression and activity [89, 90].

Multiple changes in physiological pathways could be identified as pathogenic factors in several age-related phenomena including sarcopenia, frailty, disability, or altered immune response and chronic diseases. Therefore, during the aging process, where lower anabolic hormones, increased proinflammatory cytokines, and impaired nutritional status frequently coexist, combined strategies could have important clinical implications [91] (Figure 2).

## 8. Biomolecular Mechanisms Underlying the Relationship between Magnesium and Testosterone

In the recent years biomolecular interactions between T, SHBG, and magnesium have been studied by high performance liquid chromatography (HPLC) [92]. Excoffon and colleagues [92] provided evidence of a magnesium-mediated variation in the T-SHBG affinity. The change in magnesium levels inside the biological serum concentration range (0.75–0.95 mM) could lead to an enhancement of the Bio-T. In fact, the affinity of T to SHBG seems to change slightly with the magnesium concentration. Magnesium binds SHBG in a nonspecific mode, leading to an uncompetitive inhibition

with T in binding SHBG and to a subsequent enhancement of Bio-T availability. The binding is accompanied by a magnesium release (or uptake) with a corresponding heat effect around in magnitude 17 kJ/mol [92].

SHBG is a homodimer comprising 373 amino acid residues for each monomer that transports the sex steroids in the blood and also regulating their activity in target cells [93]. Interestingly, each monomer of SHBG contains three metal-binding sites, one calcium-binding and two zinc-binding, [94, 95], that are divalent cations as well as magnesium. This data supports, at molecular level, the role of magnesium in modulating T bioactivity.

Guillaume's group investigated the role of magnesium on both the T-serum albumin binding process and the T displacement to its human serum albumin (HSA) binding cavity by DHEA. Serum albumin binds to T with low affinity [46]. In particular DHEA and T seem to bind to the same HSA site. DHEA has been shown to displace T to its HSA binding site. The authors observed *in vitro* that adequate magnesium concentrations displaced T from its HSA binding site [96, 97] and hypothesized the opportunity of testing *in vivo* the effects of magnesium supplementation, during DHEA treatment, on the Bio-T rate.

## 9. Conclusions

The ageing process seems to be at least partly due to the defect of anabolic hormones, low-grade inflammation, reduced physical activity, and a poor quality of nutrition. The permissive role that several micronutrients, such as magnesium, might exert on the serum concentration and the biological activity of T could be of undoubted interest for future clinical approaches. Male individuals with impaired magnesium status and T deficiency (accurately assessed) could benefit from magnesium and/or T treatment targeting physical performance. Future randomized clinical trials adopting synergistic treatments could lead to improving the effectiveness of T treatment, in preventing mobility limitation and adverse outcomes in older men.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

## References

- [1] M. Barbagallo and L. J. Dominguez, "Magnesium and aging," *Current Pharmaceutical Design*, vol. 16, no. 7, pp. 832–839, 2010.
- [2] N.-E. Saris, E. Mervaala, H. Karppanen, J. A. Khawaja, and A. Lewenstam, "Magnesium: an update on physiological, clinical and analytical aspects," *Clinica Chimica Acta*, vol. 294, no. 1-2, pp. 1–26, 2000.
- [3] R. A. Reinhart, "Magnesium metabolism: a review with special reference to the relationship between intracellular content and serum levels," *Archives of Internal Medicine*, vol. 148, no. 11, pp. 2415–2420, 1988.
- [4] F. I. Wolf and A. Cittadini, "Chemistry and biochemistry of magnesium," *Molecular Aspects of Medicine*, vol. 24, no. 1-3, pp. 3–9, 2003.
- [5] E. S. Ford and A. H. Mokdad, "Dietary magnesium intake in a national sample of US adults," *The Journal of Nutrition*, vol. 133, no. 9, pp. 2879–2882, 2003.
- [6] J. R. Marier, "Magnesium content of the food supply in the modern-day world," *Magnesium*, vol. 5, no. 1, pp. 1–8, 1986.
- [7] R. K. Rude, A. Stephen, and J. Nadler, "Determination of red blood cell intracellular free magnesium by nuclear magnetic resonance as an assessment of magnesium depletion," *Magnesium and Trace Elements*, vol. 10, no. 2-4, pp. 117–121, 1991.
- [8] H. C. Lukaski, "Vitamin and mineral status: effects on physical performance," *Nutrition*, vol. 20, no. 7-8, pp. 632–644, 2004.
- [9] S. W. Golf, S. Bender, and J. Grüttner, "On the significance of magnesium in extreme physical stress," *Cardiovascular Drugs and Therapy*, vol. 12, no. 2, pp. 197–202, 1998.
- [10] L. Vecchiet, G. Pieralisi, M. L. D'Ovidio et al., "Effects of magnesium supplementation on maximal and submaximal effort," in *Magnesium and Physical Activity*, L. Vecchiet, Ed., pp. 227–237, Parthenon, London, UK, 1995.
- [11] R. K. Rude, "Magnesium metabolism and deficiency," *Endocrinology and Metabolism Clinics of North America*, vol. 22, no. 2, pp. 377–395, 1993.
- [12] L. R. Brilla and K. B. Gunther, "Effect of magnesium supplementation on exercise time to exhaustion," *Medicine, Exercise, Nutrition and Health*, vol. 4, pp. 230–233, 1995.
- [13] H. C. Lukaski and F. H. Nielsen, "Dietary magnesium depletion affects metabolic responses during submaximal exercise in postmenopausal women," *The Journal of Nutrition*, vol. 132, no. 5, pp. 930–935, 2002.
- [14] S. Terblanche, T. D. Noakes, S. C. Dennis, D. Marais, and M. Eckert, "Failure of magnesium supplementation to influence marathon running performance or recovery in magnesium-replete subjects," *International Journal of Sport Nutrition*, vol. 2, no. 2, pp. 154–164, 1992.
- [15] L. R. Brilla and T. F. Haley, "Effect of magnesium supplementation on strength training in humans," *Journal of the American College of Nutrition*, vol. 11, no. 3, pp. 326–329, 1992.
- [16] H. C. Lukaski, "Prevention and treatment of magnesium deficiency in athletes," in *Magnesium and Physical Activity*, L. Vecchiet, Ed., pp. 211–226, Parthenon, London, UK, 1995.
- [17] J. F. Hickson Jr., J. Schrader, and L. C. Trischler, "Dietary intakes of female basketball and gymnastics athletes," *Journal of the American Dietetic Association*, vol. 86, no. 2, pp. 251–253, 1986.
- [18] A. L. Buchman, C. Keen, J. Commisso et al., "The effect of a marathon run on plasma and urine mineral and metal concentrations," *Journal of the American College of Nutrition*, vol. 17, no. 2, pp. 124–127, 1998.
- [19] L. R. Brilla and V. P. Lombardi, "Magnesium in sports physiology and performance," in *Sports Nutrition: Minerals and Electrolytes. An American Chemical Society Monograph*, C. V. Kies and J. A. Driskell, Eds., pp. 139–177, CRC Press, Boca Raton, Fla, USA, 1995.
- [20] A. Córdova and F. J. Navas, "Effect of training on zinc metabolism: changes in serum and sweat zinc concentrations in sportsmen," *Annals of Nutrition & Metabolism*, vol. 42, no. 5, pp. 274–282, 1998.
- [21] Y. N. Berner, F. Stern, Z. Polyak, and Y. Dror, "Dietary intake analysis in institutionalized elderly: a focus on nutrient density," *The Journal of Nutrition, Health and Aging*, vol. 6, no. 4, pp. 237–242, 2002.
- [22] J. E. Morley, "Anorexia of aging: physiologic and pathologic," *The American Journal of Clinical Nutrition*, vol. 66, no. 4, pp. 760–763, 1997.



- [23] M. Barbagallo, M. Belvedere, and L. J. Dominguez, "Magnesium homeostasis and aging," *Magnesium Research*, vol. 22, no. 4, pp. 235–246, 2009.
- [24] A. L. Lameris, L. A. Monnens, R. J. Bindels, and J. G. Hoenderop, "Drug-induced alterations in  $Mg^{2+}$  homeostasis," *Clinical Science*, vol. 123, no. 1, pp. 1–14, 2012.
- [25] T. Cundy and A. Dissanayake, "Severe hypomagnesaemia in long-term users of proton-pump inhibitors," *Clinical Endocrinology*, vol. 69, no. 2, pp. 338–341, 2008.
- [26] E. J. Hoorn, J. van der Hoek, R. A. de Man, E. J. Kuipers, C. Bolwerk, and R. Zietse, "A case series of proton pump inhibitor-induced hypomagnesemia," *American Journal of Kidney Diseases*, vol. 56, no. 1, pp. 112–116, 2010.
- [27] M. Barbagallo, R. K. Gupta, L. J. Dominguez, and L. M. Resnick, "Cellular ionic alterations with age: relation to hypertension and diabetes," *Journal of the American Geriatrics Society*, vol. 48, no. 9, pp. 1111–1116, 2000.
- [28] A. J. Cruz-Jentoft, J. P. Baeyens, J. M. Bauer et al., "Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People," *Age and Ageing*, vol. 39, no. 4, pp. 412–423, 2010.
- [29] I. H. Rosenberg, "Sarcopenia: origins and clinical relevance," *The Journal of Nutrition*, vol. 127, no. 5, pp. 990S–991S, 1997.
- [30] M. Muscaritoli, S. D. Anker, J. Argilés et al., "Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics," *Clinical Nutrition*, vol. 29, no. 2, pp. 154–159, 2010.
- [31] J. E. Morley, B. Vellas, G. A. van Kan et al., "Frailty consensus: a call to action," *Journal of the American Medical Directors Association*, vol. 14, no. 6, pp. 392–397, 2013.
- [32] S. A. Bridenbaugh and R. W. Kressig, "Quantitative gait disturbances in older adults with cognitive impairments," *Current Pharmaceutical Design*, 2013.
- [33] L. J. Dominguez, M. Barbagallo, F. Lauretani et al., "Magnesium and muscle performance in older persons: the InCHIANTI study," *The American Journal of Clinical Nutrition*, vol. 84, no. 2, pp. 419–426, 2006.
- [34] T. Cederholm, A. Nouvenne, A. Ticinesi et al., "The role of malnutrition in older persons with mobility limitations," *Current Pharmaceutical Design*, 2013.
- [35] M. Maggio, F. Lauretani, F. de Vita et al., "Multiple hormonal dysregulation as determinant of low physical performance and mobility in older persons," *Current Pharmaceutical Design*, 2013.
- [36] M. Maggio, F. Lauretani, G. P. Ceda et al., "Relationship between low levels of anabolic hormones and 6-year mortality in older men: the aging in the chianti area (InCHIANTI) study," *Archives of Internal Medicine*, vol. 167, no. 20, pp. 2249–2254, 2007.
- [37] K. T. Brill, A. L. Weltman, A. Gentili et al., "Single and combined effects of growth hormone and testosterone administration on measures of body composition, physical performance, mood, sexual function, bone turnover, and muscle gene expression in healthy older men," *The Journal of Clinical Endocrinology & Metabolism*, vol. 87, no. 12, pp. 5649–5657, 2002.
- [38] O. Ragnarsson, M. G. Burt, K. K. Ho, and G. Johannsson, "Effect of short-term GH and testosterone administration on body composition and glucose homeostasis in men receiving chronic glucocorticoid therapy," *European Journal of Endocrinology*, vol. 168, no. 2, pp. 243–251, 2013.
- [39] K. Nimptsch, E. A. Platz, W. C. Willett, and E. Giovannucci, "Association between plasma 25-OH vitamin D and testosterone levels in men," *Clinical Endocrinology*, vol. 77, no. 1, pp. 106–112, 2012.
- [40] F. Sattler, S. Bhasin, J. He et al., "Testosterone threshold levels and lean tissue mass targets needed to enhance skeletal muscle strength and function: the HORMA trial," *The Journals of Gerontology A*, vol. 66, no. 1, pp. 122–129, 2011.
- [41] R. J. Urban, Y. H. Bodenbun, C. Gillison et al., "Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis," *American Journal of Physiology*, vol. 269, no. 5, pp. E820–E826, 1995.
- [42] I. M. Chapman, R. Visvanathan, A. J. Hammond et al., "Effect of testosterone and a nutritional supplement, alone and in combination, on hospital admissions in undernourished older men and women," *The American Journal of Clinical Nutrition*, vol. 89, no. 3, pp. 880–889, 2009.
- [43] C. Piantadosi, R. Visvanathan, V. Naganathan et al., "The effect of testosterone and a nutritional supplement on hospital admissions in under-nourished, older people," *BMC Geriatrics*, vol. 11, article 66, 2011.
- [44] M. Maggio, F. De Vita, F. Lauretani et al., "IGF-1, the cross road of the nutritional, inflammatory and hormonal pathways to frailty," *Nutrients*, vol. 5, no. 10, pp. 4184–4205, 2013.
- [45] R. Arianayagam, M. Arianayagam, S. McGrath, and P. Rashid, "Androgen deficiency in the aging man," *Australian Family Physician*, vol. 39, no. 10, pp. 752–755, 2010.
- [46] P. Emadi-Konjin, J. Bain, and I. L. Bromberg, "Evaluation of an algorithm for calculation of serum "Bioavailable" testosterone (BAT)," *Clinical Biochemistry*, vol. 36, no. 8, pp. 591–596, 2003.
- [47] H. A. Feldman, C. Longcope, C. A. Derby et al., "Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study," *The Journal of Clinical Endocrinology & Metabolism*, vol. 87, no. 2, pp. 589–598, 2002.
- [48] M. Maggio, C. Cattabiani, F. Lauretani et al., "The concept of multiple hormonal dysregulation," *Acta Bio-Medica*, vol. 81, no. 1, pp. 19–29, 2010.
- [49] J. D. Veldhuis, "Aging and hormones of the hypothalamo-pituitary axis: gonadotropic axis in men and somatotrophic axes in men and women," *Ageing Research Reviews*, vol. 7, no. 3, pp. 189–208, 2008.
- [50] J. D. Veldhuis, "Recent insights into neuroendocrine mechanisms of aging of the human male hypothalamic-pituitary-gonadal axis," *Journal of Andrology*, vol. 20, no. 1, pp. 1–17, 1999.
- [51] G. P. Ceda, L. Denti, G. Ceresini, W. Torsiglieri, A. R. Hoffman, and G. Valenti, "The effects of aging on the secretion of the common alpha-subunit of the glycoprotein hormones in men," *Journal of the American Geriatrics Society*, vol. 39, no. 4, pp. 353–358, 1991.
- [52] E.-E. Baulieu, "Androgens and aging men," *Molecular and Cellular Endocrinology*, vol. 198, no. 1–2, pp. 41–49, 2002.
- [53] M. T. Haren, M. J. Kim, S. H. Tariq, G. A. Wittert, and J. E. Morley, "Andropause: a quality-of-life issue in older males," *Medical Clinics of North America*, vol. 90, no. 5, pp. 1005–1023, 2006.
- [54] K. Krithivas, S. M. Yurgalevitch, B. A. Mohr et al., "Evidence that the CAG repeat in the androgen receptor gene is associated with the age-related decline in serum androgen levels in men," *Journal of Endocrinology*, vol. 162, no. 1, pp. 137–142, 1999.

- [55] C. D. Kochakian, "Comparison of protein anabolic property of various androgens in the castrated rat," *American Journal of Physiology*, vol. 160, no. 1, pp. 53–61, 1950.
- [56] L. Katznelson, J. S. Finkelstein, D. A. Schoenfeld, D. I. Rosenthal, E. J. Anderson, and A. Klibanski, "Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism," *The Journal of Clinical Endocrinology & Metabolism*, vol. 81, no. 12, pp. 4358–4365, 1996.
- [57] M. Maggio, F. Lauretani, G. P. Ceda et al., "Association between hormones and metabolic syndrome in older Italian men," *Journal of the American Geriatrics Society*, vol. 54, no. 12, pp. 1832–1838, 2006.
- [58] S. Ucak, O. Basat, and G. Karatemiz, "Functional and nutritional state in elderly men with compensated hypogonadism," *Journal of the American Medical Directors Association*, vol. 14, no. 6, pp. 433–436, 2013.
- [59] E. Giannetta, D. Gianfrilli, F. Barbagallo, A. M. Isidori, and A. Lenzi, "Subclinical male hypogonadism," *Best Practice & Research Clinical Endocrinology & Metabolism*, vol. 26, no. 4, pp. 539–550, 2012.
- [60] C. Wang, R. S. Swerdloff, A. Iranmanesh et al., "Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men," *The Journal of Clinical Endocrinology & Metabolism*, vol. 85, no. 8, pp. 2839–2853, 2000.
- [61] P. Marin, S. Holmang, C. Gustanoffson et al., "Androgen treatment of abdominally obese men," *Obesity Research & Clinical Practice*, vol. 1, no. 4, pp. 245–251, 1993.
- [62] S. Bhasin, T. G. Travison, T. W. Storer et al., "Effect of testosterone supplementation with and without a dual 5 $\alpha$ -reductase inhibitor on fat-free mass in men with suppressed testosterone production: a randomized controlled trial," *Journal of the American Medical Association*, vol. 307, no. 9, pp. 931–939, 2012.
- [63] M. Sheffield-Moore, E. L. Dillon, S. L. Casperson et al., "A randomized pilot study of monthly cycled testosterone replacement or continuous testosterone replacement versus placebo in older men," *The Journal of Clinical Endocrinology & Metabolism*, vol. 96, no. 11, pp. E1831–E1837, 2011.
- [64] S. Bhasin, O. M. Calof, T. W. Storer et al., "Drug insight: testosterone and selective androgen receptor modulators as anabolic therapies for chronic illness and aging," *Nature Clinical Practice. Endocrinology & Metabolism*, vol. 2, no. 3, pp. 146–159, 2006.
- [65] T. G. Travison, S. Basaria, T. W. Storer et al., "Clinical meaningfulness of the changes in muscle performance and physical function associated with testosterone administration in older men with mobility limitation," *The Journals of Gerontology A*, vol. 66, no. 10, pp. 1090–1099, 2011.
- [66] L. Ferrucci, M. Maggio, S. Bandinelli et al., "Low testosterone levels and the risk of anemia in older men and women," *Archives of Internal Medicine*, vol. 166, no. 13, pp. 1380–1388, 2006.
- [67] M. Maggio, P. J. Snyder, G. P. Ceda et al., "Is the haematopoietic effect of testosterone mediated by erythropoietin? The results of a clinical trial in older men," *Andrology*, vol. 1, no. 1, pp. 24–28, 2013.
- [68] M. Sheffield-Moore, D. Paddon-Jones, S. L. Casperson et al., "Androgen therapy induces muscle protein anabolism in older women," *The Journal of Clinical Endocrinology & Metabolism*, vol. 91, no. 10, pp. 3844–3849, 2006.
- [69] X. Xu, G. de Pergola, and P. Bjorntorp, "The effects of androgens on the regulation of lipolysis in adipose precursor cells," *Endocrinology*, vol. 126, no. 2, pp. 1229–1234, 1990.
- [70] A. M. Traish and N. Kim, "Weapons of penile smooth muscle destruction: androgen deficiency promotes accumulation of adipocytes in the corpus cavernosum," *The Aging Male*, vol. 8, no. 3–4, pp. 141–146, 2005.
- [71] L. R. Brilla and V. Conte, "Effects of a novel zinc-magnesium formulation on hormones and strength," *Journal of Exercise Physiology Online*, vol. 3, no. 4, pp. 26–36, 2000.
- [72] V. Cinar, Y. Polat, A. K. Baltaci, and R. Mogulkoc, "Effects of magnesium supplementation on testosterone levels of athletes and sedentary subjects at rest and after exhaustion," *Biological Trace Element Research*, vol. 140, no. 1, pp. 18–23, 2011.
- [73] A. C. Fry, W. J. Kraemer, and L. T. Ramsey, "Pituitary-adrenal-gonadal responses to high-intensity resistance exercise over-training," *Journal of Applied Physiology*, vol. 85, no. 6, pp. 2352–2359, 1998.
- [74] M. Maggio, G. P. Ceda, F. Lauretani et al., "Magnesium and anabolic hormones in older men," *International Journal of Andrology*, vol. 34, no. 6, part 2, pp. e594–e600, 2011.
- [75] F. De Vita, F. Lauretani, G. P. Ceda, T. Cederholm, L. Lind, and M. Maggio, "Vitamin D and endothelial vasodilation in older individuals," in *Proceedings of the 7th International Conference of the Society on Sarcopenia, Cachexia and Wasting Disorders (SCWD '13)*, pp. 9–11, Kobe, Japan, December 2013.
- [76] A. K. Chandra, P. Sengupta, H. Goswami, and M. Sarkar, "Effects of dietary magnesium on testicular histology, steroidogenesis, spermatogenesis and oxidative stress markers in adult rats," *Indian Journal of Experimental Biology*, vol. 51, no. 1, pp. 37–47, 2013.
- [77] P. Vernet, A. Britan, E. Gueux, A. Mazur, and J. R. Drevet, "Dietary magnesium depletion does not promote oxidative stress but targets apical cells within the mouse caput epididymidis," *Biochimica et Biophysica Acta*, vol. 1675, no. 1–3, pp. 32–45, 2004.
- [78] A. A. Al-Qarawi, H. A. Abdel-Rahman, M. S. El-Belely, and S. A. El-Mougy, "Age-related changes in plasma testosterone concentrations and genital organs content of bulk and trace elements in the male dromedary camel," *Animal Reproduction Science*, vol. 62, no. 4, pp. 297–307, 2000.
- [79] D. I. Spratt, P. Cox, J. Orav, J. Moloney, and T. Bigos, "Reproductive axis suppression in acute illness is related to disease severity," *The Journal of Clinical Endocrinology & Metabolism*, vol. 76, no. 6, pp. 1548–1554, 1993.
- [80] M. Maggio, J. M. Guralnik, D. L. Longo, and L. Ferrucci, "Interleukin-6 in aging and chronic disease: a magnificent pathway," *The Journals of Gerontology A*, vol. 61, no. 6, pp. 575–584, 2006.
- [81] S. Stenholm, M. Maggio, F. Lauretani et al., "Anabolic and catabolic biomarkers as predictors of muscle strength decline: the InCHIANTI study," *Rejuvenation Research*, vol. 13, no. 1, pp. 3–11, 2010.
- [82] L. A. Schaap, S. M. F. Pluijm, D. J. H. Deeg, and M. Visser, "Inflammatory markers and loss of muscle mass (Sarcopenia) and strength," *The American Journal of Medicine*, vol. 119, no. 6, pp. 526.e9–526.e17, 2006.
- [83] M. Maggio, G. P. Ceda, G. de Cicco et al., "Acute changes in circulating hormones in older patients with impaired ventricular function undergoing on-pump coronary artery bypass grafting," *Journal of Endocrinological Investigation*, vol. 28, no. 8, pp. 711–719, 2005.

- [84] C. J. Malkin, P. J. Pugh, R. D. Jones, D. Kapoor, K. S. Chan-ner, and T. H. Jones, "The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men," *The Journal of Clinical Endocrinology & Metabolism*, vol. 89, no. 7, pp. 3313–3318, 2004.
- [85] S. M. Liva and R. R. Voskuhl, "Testosterone acts directly on CD4<sup>+</sup> T lymphocytes to increase IL-10 production," *The Journal of Immunology*, vol. 167, no. 4, pp. 2060–2067, 2001.
- [86] B. F. Dickens, W. B. Weglicki, Y.-S. Li, and I. T. Mak, "Magnesium deficiency in vitro enhances free radical-induced intra-cellular oxidation and cytotoxicity in endothelial cells," *FEBS Letters*, vol. 311, no. 3, pp. 187–191, 1992.
- [87] J. Liu, E. Head, A. M. Gharib et al., "Memory loss in old rats is associated with brain mitochondrial decay and RNA/DNA oxidation: partial reversal by feeding acetyl-L-carnitine and/or R- $\alpha$ -lipoic acid," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 4, pp. 2356–2361, 2002.
- [88] K. R. Short, M. L. Bigelow, J. Kahl et al., "Decline in skeletal muscle mitochondrial function with aging in humans," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 15, pp. 5618–5623, 2005.
- [89] Y. Rayssiguier, J. Durlach, E. Gueux, E. Rock, and A. Mazur, "Magnesium and ageing—I. Experimental data: importance of oxidative damage," *Magnesium Research*, vol. 6, no. 4, pp. 369–378, 1993.
- [90] Y. Yang, Z. Wu, Y. Chen et al., "Magnesium deficiency enhances hydrogen peroxide production and oxidative damage in chick embryo hepatocyte in vitro," *BioMetals*, vol. 19, no. 1, pp. 71–81, 2006.
- [91] C. Franceschi, M. Bonafè, S. Valensin et al., "Inflamm-aging: an evolutionary perspective on immunosenescence," *Annals of the New York Academy of Sciences*, vol. 908, pp. 244–254, 2000.
- [92] L. Excoffon, Y. C. Guillaume, M. C. Woronoff-Lemsi, and C. André, "Magnesium effect on testosterone-SHBG association studied by a novel molecular chromatography approach," *Journal of Pharmaceutical and Biomedical Analysis*, vol. 49, no. 2, pp. 175–180, 2009.
- [93] M. Maggio, G. P. Ceda, F. Lauretani et al., "SHBG, sex hormones, and inflammatory markers in older women," *The Journal of Clinical Endocrinology & Metabolism*, vol. 96, no. 4, pp. 1053–1059, 2011.
- [94] G. V. Avvakumov, I. Grishkovskaya, Y. A. Muller, and G. L. Hammond, "Crystal structure of human sex hormone-binding globulin in complex with 2-methoxyestradiol reveals the molecular basis for high affinity interactions with C-2 derivatives of estradiol," *The Journal of Biological Chemistry*, vol. 277, no. 47, pp. 45219–45225, 2002.
- [95] G. V. Avvakumov, Y. A. Muller, and G. L. Hammond, "Steroid-binding specificity of human sex hormone-binding globulin is influenced by occupancy of a zinc-binding site," *The Journal of Biological Chemistry*, vol. 275, no. 34, pp. 25920–25925, 2000.
- [96] C. André, A. Xicluna, J.-F. Robert, M. Thomassin, and Y.-C. Guillaume, "Reanalysis of the testosterone displacement from its HSA binding site by DHEA using competitive Langmuir isotherm," *Talanta*, vol. 65, no. 3, pp. 814–818, 2005.
- [97] C. André, A. Berthelot, J. F. Robert, M. Thomassin, and Y. C. Guillaume, "Testimony of the correlation between DHEA and bioavailable testosterone using a biochromatographic concept: effect of two salts," *Journal of Pharmaceutical and Biomedical Analysis*, vol. 33, no. 5, pp. 911–921, 2003.

## Clinical Study

# Health-Related Quality of Life and Quality of Sexual Life in Obese Subjects

**Eleonora Poggiogalle,<sup>1</sup> Luca Di Lazzaro,<sup>1</sup> Alessandro Pinto,<sup>1</sup> Silvia Migliaccio,<sup>2</sup> Andrea Lenzi,<sup>1</sup> and Lorenzo M. Donini<sup>1</sup>**

<sup>1</sup> Medical Pathophysiology, Food Science and Endocrinology Section, Department of Experimental Medicine, "Sapienza" University of Rome, Piazzale Aldo Moro 5, 00185 Rome, Italy

<sup>2</sup> Department of Movement, Human and Health Sciences, University of Rome "Foro Italico", 00195 Rome, Italy

Correspondence should be addressed to Eleonora Poggiogalle; [eleonora.poggiogalle@gmail.com](mailto:eleonora.poggiogalle@gmail.com)

Received 16 October 2013; Revised 12 January 2014; Accepted 13 January 2014; Published 23 February 2014

Academic Editor: Francesco Mattace Raso

Copyright © 2014 Eleonora Poggiogalle et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The increased prevalence of obesity represents, currently, one of the major public health issues, due to its consequences on physical and psychological health status as well as on the psychosocial functioning. As defined by the World Health Organization, sexual health is "a state of physical, emotional, mental, and social well-being in relation to sexuality." The aim of the present study was to explore the relationship between sexual life in obese subjects and quality of life, psychological status, and disability. *Methods.* 95 obese subjects were recruited from June 2012 to February 2013 and underwent physical examination and measures for the assessment of quality of life, sexual life, psychological status, and disability. *Results.* In obese subjects sexual life was related to gender, age, psychological status, disability, and quality of life. *Conclusion.* As obesity is a multifactorial disease, and is accompanied by multiple comorbidities, it is difficult to identify a single causative factor responsible for the impairment of sexual life in obese subjects; thus, a thorough, multidimensional evaluation including sexual function assessment should be performed in obese people.

## 1. Introduction

The increased prevalence of obesity represents, currently, one of the major public health issues, due to its consequences on physical and psychological health status as well as on psychosocial functioning [1–3]. On one hand, chronic diseases associated with excess fat are well known and documented [1, 2]; on the other hand, evidence is relatively scarce with respect to quality of life—including sexual life—in obese subjects [4, 5].

As defined by the World Health Organization, sexual health is "a state of physical, emotional, mental, and social well-being in relation to sexuality" [6]. Sexual dysfunction encompasses clinical syndromes that impair sexual functioning such as sexual aversion, dysfunctional sexual arousal and vaginismus in females, and erectile dysfunction and premature ejaculation in males [7].

Studies exist reporting that obese men and women tend to have greater problems in their sexual life when compared

to their lean counterparts [8, 9]. A number of obesity-related comorbidities, such as dyslipidemia, hypertension, type 2 diabetes, and depression, are associated with sexual dysfunction [9–12]; hence, it is difficult to identify the role of obesity *per se* in the development of sexual dysfunction. Potential mechanisms explaining the association between obesity and sexual dysfunction include: endothelial dysfunction, metabolic syndrome and diabetes, endocrine disorders, obstructive sleep apnea syndrome, physical disability, and social and psychosocial problems [5].

Overweight and obesity have been identified as risk factors for sexual dysfunction only in men [4, 13, 14], whereas the relationship between female sexual function and excess fat remains to be better clarified [15–19].

Few studies described the impairment of quality of life in obese subjects [20]; sexual functioning is a determinant of quality of life, and excess fat could play a pivotal role also in the quality of sexual life [21, 22]. The aim of the present study was to explore the relationship between sexual life in



obese subjects and quality of life, psychological status, and disability.

## 2. Materials and Methods

**2.1. Study Population.** Participants were recruited from June 2012 to February 2013 among outpatients referring to the High Specialization Centre for the Care of Obesity (named “CASCO”) at the Department of Experimental Medicine—Pathophysiology, Food Science and Endocrinology Section, Policlinico Umberto I—Sapienza University of Rome, Italy. Inclusion criteria were BMI  $\geq 30$  Kg/m<sup>2</sup> and age ranging from 15 to 69 years. Oral and written informed consent was obtained from all the participants. The study was approved by the local ethics committee.

**2.2. Demographics and Clinical Status.** Medical history, with particular attention to obesity-related complications (insulin resistance, type 2 diabetes, hypertension, dyslipidemia, thyroid dysfunction, cardiovascular, osteoarticular, respiratory, gastrointestinal, and psychiatric diseases) and medication use, as well as demographic, social, and cultural information (age, gender, job, and education level), and smoking habits were obtained.

**2.3. Anthropometric Measurements.** All the subjects underwent physical examination. Anthropometric measurements were gathered following the procedures described in the Standard Manual for Anthropometric Measures [23]. Body weight was measured using a SECA scale (Hamburg, Germany) to the nearest 0.1 kg; height was measured using a SECA stadiometer (Hamburg, Germany) to the nearest 0.5 cm. Body mass index (BMI = body weight/height squared) was calculated. Skinfold thicknesses were measured using a Harpenden Skinfold Caliper (British Indicators Ltd, St Albans, Herts, UK), to the nearest 0.2 mm. Body composition fat mass (FM) and fat-free mass (FFM) were estimated by bioelectrical impedance analysis (BIA) using a single-frequency 50 kHz analyzer STA—BIA (Akern Bioresarch SRL, Pontassieve, FL, Italy). Measurements were performed following standardized procedures [24]. Estimation of FM and FFM by BIA was obtained using gender-specific BIA prediction equations developed by Sun et al. [25].

**2.4. Measures for the Assessment of Quality of Life, Sexual Life, Psychological Status, and Disability.** All the participants underwent the administration of four questionnaires.

(i) The Laval questionnaire—Italian version [26] consists of 44 items distributed in 6 domains: symptoms, activity/mobility, personal hygiene/clothing, emotions, social interaction, and sexual life (items n. 12 and 37). Each domain is scored on a 7-point Likert scale, higher scores corresponding to a better quality of life.

(ii) The O.R.Well-97 questionnaire [27] is composed of 18 items; for each item the patient is asked to score on a 4-point Likert scale the occurrence and/or severity of the symptom (occurrence) and the subjective relevance of the symptom-related impairment in one's own life (relevance). The items

are related to three different areas: symptoms, discomfort, and impact of obesity on familial relationship, role functioning, and social network. We selected the items n. 2, 10, and 11 regarding sexual life.

(iii) The SCL-90 (Symptom Checklist-90) [28] is a scale including 90 questions exploring the presence and the severity of psychological symptoms occurred in the last week. Dimensions explored are somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychotism. Each answer is scored on a 5-point Likert scale. For the evaluation of sexual life, we selected the items n. 5, 21, 69, 84.

(iv) The TSD-OC (SIO obesity-related disability) test [29] is a questionnaire developed by the Italian Society of Obesity (SIO); it is made of 36 items divided into 7 sections: pain, rigidity, activities of daily living, housework, outdoor activities, occupational activities, and social life. Each question is answered using a visual analogue scale, with a score ranging from 0 (absence of difficulty) to 10 (the highest degree of disability) for each item.

**2.5. Statistics.** After the verification of the normal distribution of the variables, *t*-test was performed to describe differences between means of the groups. A linear regression analysis (Pearson's *r*) was performed to verify the association among continuous variables. Differences were considered to be statistically significant for  $P < 0.05$ . Statistical analysis was performed using SPSS 10.0 statistical software (SPSS Inc. Wacker Drive, Chicago, IL, USA).

## 3. Results

95 subjects (25 men and 70 women) were enrolled. Participants' demographic and clinical characteristics are summarized in Tables 1 and 2.

**3.1. Sexual Life and Demographics.** Men reported better scores than women in the domain “Sexual life” of the Italian version of the Laval questionnaire ( $P < 0.05$ ). Analogous differences were reported in the scores obtained at the items n. 5; 21; 69; 84 of the SCL-90 questionnaire ( $P < 0.05$ ).

A statistically significant relationship was found between age and scores at the selected items (n. 5; 21; 69; 84) of the SCL-90 scale addressed to sexual life ( $r = 0.24$ ,  $P < 0.05$ ); no significant differences were observed between genders and related to smoking habits.

**3.2. Sexual Life and Anthropometric Parameters.** Statistically significant correlations emerged between waist circumference ( $r = 0.33$ ,  $P < 0.05$ ) and the scores obtained for items n. 12 and 37 in the “Sexual life” domain of the Laval questionnaire—Italian version. The relationship between BMI and scores was obtained at the specific items about sexual life (n. 2; 10; 11) of the O.R.Well-97 questionnaire ( $r = 0.24$ ,  $P < 0.05$ ).

**3.3. Sexual Life and Clinical Status (Table 3).** Subjects suffering from cardiovascular diseases had a worse sexual life

TABLE 1: Demographic and clinical characteristics.

|                                | Total sample | Males        | Females      | P  |
|--------------------------------|--------------|--------------|--------------|----|
| Population Study (no.)         | 95           | 25           | 70           |    |
| Age (years)                    | 44.2 ± 13.5  | 41.1 ± 13.9  | 45.3 ± 13.3  | ** |
| BMI (Kg/m <sup>2</sup> )       | 41.2 ± 8.2   | 43.9 ± 11.0  | 40.3 ± 6.4   | *  |
| Waist circumference (cm)       | 118.4 ± 14.3 | 131.4 ± 20.2 | 113.8 ± 12.1 | ** |
| Fat mass—BIA (%)               | 43.9 ± 4.8   | 39.8 ± 6.0   | 45.4 ± 4.3   | ** |
| Fat mass—anthropometry (%)     | 44.3 ± 6.2   | 40.2 ± 8.5   | 45.8 ± 5.8   | *  |
| Obesity-related diseases       |              |              |              |    |
| Type 2 diabetes mellitus (no.) | 10           | 4            | 6            |    |
| Cardiovascular disease (no.)   | 10           | 3            | 7            |    |
| Hypertension (no.)             | 31           | 8            | 23           |    |
| Osteoarticular disease (no.)   | 40           | 9            | 31           |    |
| Respiratory disease (no.)      |              |              |              |    |
| Total (no.)                    | 28           | 8            | 20           |    |
| OSAS (no.)                     | 19           | 6            | 13           |    |
| Hypogonadism (no.)             | 3            | 3            |              |    |
| Medications                    |              |              |              |    |
| CPAP therapy (no.)             | 5            | 1            | 4            |    |
| ACE inhibitors (no.)           | 9            | 2            | 7            |    |
| ARB (no.)                      | 13           | 4            | 9            |    |

\*  $P < 0.05$ ; \*\*  $P < 0.01$ .

BMI: body mass index; Fat mass—anthropometry: assessed by the measurement of skinfold thicknesses (Lohman et al. [23]); fat mass—BIA: assessed through bioimpedance electric analysis; OSAS: obstructive sleep apnea syndrome; ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blockers; CPAP: continuous positive airway pressure.

( $P < 0.05$ ). No significant association was observed between sexual life and the remaining diseases or medication use.

**3.4. Sexual Life and Quality of Life.** In obese subjects a statistically significant relationship was shown between scores corresponding to the items n. 12 and 37 of the “Sexual life” domain, the total score of the Laval questionnaire—Italian version ( $r = 0.65$ ;  $P < 0.01$ ), and the other single domains of the same questionnaire: “activity-mobility”, “Symptoms”, and “Emotions” ( $P < 0.01$ ), as well as total score ( $r = -0.61$ ,  $P < 0.01$ ) and scores of “Occurrence” ( $P < 0.01$ ) and “Relevance” ( $P < 0.01$ ) at the O.R.Well-97 questionnaire ( $r = -0.61$ ,  $P < 0.01$ ).

**3.5. Sexual Life and Psychic Discomfort.** Scores of the “Sexual life” domain of the Laval questionnaire—Italian version were statistically significantly correlated with the total score at the SCL-90 questionnaire and its single domains: “Somatization”, “Obsessive-compulsive”, “Interpersonal sensitivity”, “Depression”, “Anxiety”, “Hostility”, “Phobic anxiety”, “Paranoid ideation”, and “Psychoticism” (all:  $P < 0.01$ ).

**3.6. Disability.** Scores regarding the “Sexual life” domain of the Laval questionnaire—Italian version were statistically significantly correlated with the total score at the TSD-OC test ( $r = -0.64$ ,  $P < 0.01$ ) and scores at its single domains: “Pain”, “Rigidity”, “Activities of daily living”, “Housework”, “Outdoor activities”, “Occupational activities”, and “Social life” (all:  $P < 0.01$ ).

## 4. Discussion

In the present study, in obese subjects sexual life was related to gender, age, psychological status, disability, and quality of life.

We observed that sexual life in obese men was better than obese women; moreover, sexual life was influenced by age in our study population. These findings are in agreement with data provided by Laumann et al. [30], showing a greater prevalence of sexual dysfunctions in women (43%) when compared to men (31%); in addition, authors found a positive relationship between age and erectile dysfunction and lack of sexual desire in men, whereas women reported a reduction of sexual disturbances with ageing. From data analysis, in our study population, no differences related to gender emerged with respect to age and sexual life, but this finding may be due to differences in the male and female sample size (men were only 25).

In our study, we showed an inverse relationship between sexual life and BMI, and sexual life and waist circumference. With respect to men, our results are consistent with a number of previous studies [13, 18, 21, 31], demonstrating the association between obesity and erectile dysfunction, with obvious consequences in the global sexuality. In accordance with data in our study, Morotti et al. [32] observed an impairment in sexual function in overweight and obese women when compared with their lean counterparts. In a paper by [33], even though a negative relationship was found between body weight and sexual function, no association appeared between central fat distribution and sexual dysfunction. In contrast,

TABLE 2: Correlations between sexual life domain (at Laval questionnaire, SCL-90 test, and O.R.WELL questionnaire) and quality of life, psychological status, and disability.

|                            | Laval questionnaire<br>Items: 12-37 | SCL-90 Test<br>Items: 5-21-69-84 | O.R.Well questionnaire<br>Items: 2-10-11 |
|----------------------------|-------------------------------------|----------------------------------|--|
| Age                        | -0.18                               | 0.24*                            | -0.03                                    |
| Body composition           |                                     |                                  |  |
| Waist circumference        | 0.33*                               | -0.21                            | 0.02                                     |
| Fat mass—anthropometry     | -0.11                               | 0.23                             | 0.15                                     |
| Fat mass—BIA               | -0.12                               | 0.17                             | 0.18                                     |
| BMI                        | -0.11                               | -0.03                            | 0.24*                                    |
| Laval questionnaire        |                                     |                                  |  |
| Total Score                | 0.65**                              | -0.62**                          | -0.51**                                  |
| Activity-mobility          | 0.70**                              | -0.52**                          | -0.51**                                  |
| Symptoms                   | 0.55**                              | -0.51**                          | -0.37**                                  |
| Emotions                   | 0.68**                              | -0.67**                          | -0.48**                                  |
| O.R.Well-97 questionnaire  |                                     |                                  |  |
| Total score                | -0.61**                             | 0.63**                           | 0.77**                                   |
| Incidence                  | -0.51**                             | 0.56**                           | 0.69**                                   |
| Relevance                  | -0.62**                             | 0.63**                           | 0.76**                                   |
| SCL-90 test                |                                     |                                  |  |
| Global score index         | -0.65**                             | 0.82**                           | 0.49**                                   |
| Somatization               | -0.58**                             | 0.57**                           | 0.37**                                   |
| Obsessive-compulsive       | -0.60**                             | 0.68**                           | 0.49**                                   |
| Interpersonal sensitivity  | -0.59**                             | 0.80**                           | 0.50**                                   |
| Depression                 | -0.68**                             | 0.77**                           | 0.51**                                   |
| Anxiety                    | -0.61**                             | 0.73**                           | 0.41**                                   |
| Phobic anxiety             | -0.42**                             | 0.68**                           | 0.34**                                   |
| Paranoid ideation          | -0.49**                             | 0.74**                           | 0.38**                                   |
| TSD-OC test                |                                     |                                  |  |
| Total score                | -0.64**                             | 0.49**                           | 0.44**                                   |
| Pain                       | -0.60**                             | 0.49**                           | 0.38**                                   |
| Stiffness                  | 0.62**                              | 0.55**                           | 0.42**                                   |
| Activities of daily living | -0.30**                             | 0.23*                            | 0.19                                     |
| Housework                  | -0.55**                             | 0.43**                           | 0.28**                                   |
| Outdoor activities         | -0.61**                             | 0.41**                           | 0.37**                                   |
| Occupational activity      | -0.50**                             | 0.39**                           | 0.37**                                   |
| Social life                | -0.51**                             | 0.45**                           | 0.48**                                   |

\*  $P < 0.05$ ; \*\*  $P < 0.01$ 

Legend: BMI: body mass index; TSD-OC test: Italian Society of Obesity test for obesity-related disabilities; fat mass—anthropometry: assessed by the measurement of skinfold thicknesses (Lohman et al. [23]); fat mass—BIA: assessed through bioimpedance analysis.

in our study, waist circumference negatively correlated with sexual function, and it seems to be in line with the association between increased BMI and reduced sexual health, both showing a relationship between adiposity indices and sexual dysfunction.

In line with our results, cardiovascular disease was demonstrated to influence sexual function in both males and females [34]. Neurovascular factors seem to have a causal role linking cardiovascular disease and sexual dysfunction in both genders [35], but the evaluation of these peculiar causative aspects was beyond the objective of our study.

A relevant finding in the present study was the strict relationship between sexual life and the global quality of

life. This connection has been previously described in obese individuals [36, 37]. Moreover, independently of body weight, in a large sample of subjects [30], poor physical and emotional quality of life was associated to a higher prevalence of sexual dysfunction in both the genders, and, in a sort of vicious cycle, an impaired sexual function was connected to a diminished individual and social quality of life.

Another important observation in our study was the association of sexual life and mental health, consistently with extant literature [22, 38–40]. In addition, in a number of studies, the association between obesity and psychological distress has been described [41, 42]. In particular, in our sample of obese subjects, the obesity-related psychological

TABLE 3: Sexual life defined through Laval questionnaire and clinical status.

|                         | Total score | Laval questionnaire         |         |         |
|-------------------------|-------------|-----------------------------|---------|---------|
|                         |             | Score in sexual life domain | Item 12 | Item 37 |
| Type 2 diabetes         |             |                             |         |         |
| +                       | 4.4 ± 1     | 4.8 ± 2                     | 4.4 ± 2 | 5.0 ± 2 |
| –                       | 4.5 ± 1     | 4.7 ± 2                     | 4.0 ± 2 | 5.2 ± 2 |
| Cardiovascular diseases |             |                             |         |         |
| +                       | 4.0 ± 1     | 3.8 ± 1*                    | 3.2 ± 2 | 4.4 ± 2 |
| –                       | 4.6 ± 1     | 4.8 ± 2                     | 4.2 ± 2 | 5.3 ± 2 |
| Hypertension            |             |                             |         |         |
| +                       |             |                             |         |         |
| –                       |             |                             |         |         |
| Osteoarticular diseases |             |                             |         |         |
| +                       | 4.4 ± 1     | 4.4 ± 2                     | 3.9 ± 2 | 4.6 ± 2 |
| –                       | 4.6 ± 1     | 5.0 ± 1                     | 4.2 ± 2 | 5.7 ± 2 |
| Respiratory diseases    |             |                             |         |         |
| +                       | 4.3 ± 1     | 4.6 ± 2                     | 4.0 ± 2 | 4.7 ± 2 |
| –                       | 4.6 ± 1     | 4.7 ± 2                     | 4.1 ± 2 | 5.4 ± 2 |

\*  $P < 0.05$ .

distress, as well as other psychological characteristics in obese subjects, may account for the positive relationship between psychic discomfort and sexual dysfunction in our study.

An interesting aspect explored in our study was the relationship between sexual dysfunction and disability in obese individuals. Functional disability in osteoarticular and neurologic diseases is known to affect sexual function. In our study, we reported that obesity-related disability, assessed through a specific tool (the TSD-OC test), was related to sexual dysfunction.

The main limitation to our study was the evaluation of sexual life and dysfunction-assessed using single items from different tools, without exploring the underlying disturbances. However, the aim of our study was to investigate the presence of sexual discomfort related to obesity, independently of any other potential cause. Another limitation is represented by the composition of the study sample that was not homogeneous in terms of gender. Sexual dysfunction takes different forms in men and women but the small size, in particular of the male subgroup, may account for the impossibility to perform separate analysis to identify gender-related differences in correlations between sexual life and quality of life, psychological status, and disability. Finally, probably due to the small sample, we did not find any correlation between sexual life and smoking habits, medication use, or hypogonadism.

## 5. Conclusion

As obesity is a multifactorial disease and is accompanied by multiple comorbidities, it is difficult to identify a single causative factor responsible for the impairment of sexual life in obese subjects; thus, a thorough, multidimensional evaluation including sexual function assessment should be performed in obese people.

Obesity is a disabling disease with significant sequelae in multiple domains [43], and our results suggest the need of awareness toward obesity-related disability and its impact on sexual life in obese subjects.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

## References

- [1] T. L. S. Visscher and J. C. Seidell, "The public health impact of obesity," *Annual Review of Public Health*, vol. 22, pp. 355–375, 2001.
- [2] S. B. Wyatt, K. P. Winters, and P. M. Dubbert, "Overweight and obesity: prevalence, consequences, and causes of a growing public health problem," *The American Journal of the Medical Sciences*, vol. 331, no. 4, pp. 166–174, 2006.
- [3] R. M. Puhl and C. A. Heuer, "Obesity stigma: important considerations for public health," *American Journal of Public Health*, vol. 100, no. 6, pp. 1019–1028, 2010.
- [4] T. S. Han, A. Tajar, T. W. O'Neill et al., "Impaired quality of life and sexual function in overweight and obese men: the European male ageing study," *European Journal of Endocrinology*, vol. 164, no. 6, pp. 1003–1011, 2011.
- [5] S. H. Larsen, G. Wagner, and B. L. Heitmann, "Sexual function and obesity," *International Journal of Obesity*, vol. 31, no. 8, pp. 1189–1198, 2007.
- [6] World Health Organization, "Defining sexual health," WHO, 2006, [http://www.who.int/reproductivehealth/topics/sexual\\_health/sh\\_definitions/en/index.html](http://www.who.int/reproductivehealth/topics/sexual_health/sh_definitions/en/index.html).
- [7] World Health Organization, "Sexual health issues," PAHO/WHO, 2000, [http://www.who.int/reproductivehealth/topics/sexual\\_health/issues/en/](http://www.who.int/reproductivehealth/topics/sexual_health/issues/en/).



- [8] K. Esposito and D. Giugliano, "Obesity, the metabolic syndrome, and sexual dysfunction," *International Journal of Impotence Research*, vol. 17, no. 5, pp. 391–398, 2005.
- [9] G. Marchesini, S. Natale, F. Tiraferri et al., "The burden of obesity on everyday life: a role for osteoarticular and respiratory diseases," *Diabetes, Nutrition & Metabolism*, vol. 16, no. 5–6, pp. 284–290, 2003.
- [10] N. Amidu, W. K. B. A. Owiredo, H. Alidu, C. Sarpong, C. K. Gyasi-Sarpong, and L. Quaye, "Association between metabolic syndrome and sexual dysfunction among men with clinically diagnosed diabetes," *Diabetology & Metabolic Syndrome*, vol. 5, no. 1, article 42, 2013.
- [11] D. Morrison, M. Aitchison, D. T. Connelly, and F. S. Mair, "Sexual dysfunction in cardiovascular disease," *British Medical Journal*, vol. 343, article d4437, 2011.
- [12] A. I. El-Sakka, "Erectile dysfunction, depression, and ischemic heart disease: does the existence of one component of this triad necessitate inquiring the other two? (CME)," *The Journal of Sexual Medicine*, vol. 8, no. 4, pp. 937–940, 2011.
- [13] K. Esposito and D. Giugliano, "Obesity, the metabolic syndrome, and sexual dysfunction in men," *Clinical Pharmacology & Therapeutics*, vol. 90, no. 1, pp. 169–173, 2011.
- [14] G. Corona, G. Rastrelli, E. Maseroli, G. Forti, and M. Maggi, "Sexual function of the ageing male," *Best Practice & Research Clinical Endocrinology & Metabolism*, vol. 27, no. 4, pp. 581–601, 2013.
- [15] N. Bajos, K. Wellings, C. Laborde, and C. Moreau, "Sexuality and obesity, a gender perspective: results from French national random probability survey of sexual behaviours," *British Medical Journal*, vol. 340, article c2573, 2010.
- [16] G. F. Yaylali, S. Tekekoglu, and F. Akin, "Sexual dysfunction in obese and overweight women," *International Journal of Impotence Research*, vol. 22, no. 4, pp. 220–226, 2010.
- [17] S. Kirchengast, B. Hartmann, D. Gruber, and J. Huber, "Decreased sexual interest and its relationship to body build in postmenopausal women," *Maturitas*, vol. 23, no. 1, pp. 63–71, 1996.
- [18] T. Lue, R. Basson, R. Rosen, F. Giuliano, S. Khoury, and F. Montorsi, *Sexual Medicine: Sexual Dysfunction in Men and Women*, 2nd International Consultation on Sexual Dysfunction, Health Publication, Paris, France, 2004.
- [19] W. M. Edwards and E. Coleman, "Defining sexual health: a descriptive overview," *Archives of Sexual Behavior*, vol. 33, no. 3, pp. 189–195, 2004.
- [20] R. L. Kolotkin, K. Meter, and G. R. Williams, "Quality of life and obesity," *Obesity Reviews*, vol. 2, no. 4, pp. 219–229, 2001.
- [21] D. B. Sarwer, J. C. Spitzer, T. A. Wadden et al., "Sexual functioning and sex hormones in persons with extreme obesity and seeking surgical and nonsurgical weight loss," *Surgery for Obesity and Related Diseases*, vol. 9, no. 6, pp. 997–1007, 2013.
- [22] H. M. Tan, S. F. Tong, and C. C. K. Ho, "Men's health: sexual dysfunction, physical, and psychological health—is there a link?" *The Journal of Sexual Medicine*, vol. 9, no. 3, pp. 663–671, 2012.
- [23] T. G. Lohman, A. F. Roche, and R. Martorell R, *Anthropometric Standardization Reference Manual*, EDRA, Milan, Italy, 1992.
- [24] R. F. Kushner, "Bioelectrical impedance analysis: a review of principles and applications," *Journal of the American College of Nutrition*, vol. 11, no. 2, pp. 199–209, 1992.
- [25] S. S. Sun, W. C. Chumlea, S. B. Heymsfield et al., "Development of bioelectrical impedance analysis prediction equations for body composition with the use of a multicomponent model for use in epidemiologic surveys," *The American Journal of Clinical Nutrition*, vol. 77, no. 2, pp. 331–340, 2003.
- [26] L. M. Donini, E. Poggiogalle, L. Di Lazzaro et al., "Validation of the Italian version of the Laval Questionnaire: health-related quality of life in obese subjects," *Eating and Weight Disorders*. In press.
- [27] E. Mannucci, V. Ricca, E. Barciulli et al., "Quality of life and overweight: the obesity related well-being (Orwell 97) questionnaire," *Addictive Behaviors*, vol. 24, no. 3, pp. 345–357, 1999.
- [28] L. R. Derogatis, *Symptom Checklist-90-R: Administration, Scoring and Procedures Manual*, National Computer System, Minneapolis, Minn, USA, 3rd edition, 1994.
- [29] L. M. Donini, A. Brunani, A. Sirtori et al., "Assessing disability in morbidly obese individuals: the Italian Society of Obesity test for obesity-related disabilities," *Disability and Rehabilitation*, vol. 33, no. 25–26, pp. 2509–2518, 2011.
- [30] E. O. Laumann, A. Paik, and R. C. Rosen, "Sexual dysfunction in the United States: prevalence and predictors," *The Journal of the American Medical Association*, vol. 281, no. 6, pp. 537–544, 1999.
- [31] M. Diaz-Arjonilla, M. Schwarcz, R. S. Swerdloff, and C. Wang, "Obesity, low testosterone levels and erectile dysfunction," *International Journal of Impotence Research*, vol. 21, no. 2, pp. 89–98, 2009.
- [32] E. Morotti, B. Battaglia, R. Paradisi et al., "Body mass index, Stunkard Figure Rating Scale, and sexuality in young Italian women: a pilot study," *The Journal of Sexual Medicine*, vol. 10, no. 4, pp. 1034–1043, 2013.
- [33] K. Esposito, M. Ciotola, F. Giugliano et al., "Association of body weight with sexual function in women," *International Journal of Impotence Research*, vol. 19, no. 4, pp. 353–357, 2007.
- [34] S. L. Archer, F. S. Gragasini, L. Webster, D. Bochinski, and E. D. Michelakis, "Aetiology and management of male erectile dysfunction and female sexual dysfunction in patients with cardiovascular disease," *Drugs & Aging*, vol. 22, no. 10, pp. 823–844, 2005.
- [35] Y. Ma and Z. Yang, "Cardiovascular disease may lead to female sexual dysfunction," *Medical Hypotheses*, vol. 72, no. 4, p. 482, 2009.
- [36] R. H. Moore, D. B. Sarwer, J. A. Lavenberg et al., "Relationship between sexual function and quality of life in obese persons seeking weight reduction," *Obesity*, vol. 21, no. 10, pp. 1966–1974, 2013.
- [37] D. B. Sarwer, M. Lavery, and J. C. Spitzer, "A review of the relationships between extreme obesity, quality of life, and sexual function," *Obesity Surgery*, vol. 22, no. 4, pp. 668–676, 2012.
- [38] A. M. Smith, K. Patrick, W. Heywood et al., "Body mass index, sexual difficulties and sexual satisfaction among people in regular heterosexual relationships: a population-based study," *Internal Medicine Journal*, vol. 42, no. 6, pp. 641–651, 2012.
- [39] J. S. McCall-Hosenfeld, S. A. Jaramillo, C. Legault et al., "Correlates of sexual satisfaction among sexually active postmenopausal women in the women's health initiative-observational study," *Journal of General Internal Medicine*, vol. 23, no. 12, pp. 2000–2009, 2008.
- [40] A. Nicolosi, E. D. Moreira Jr., M. Villa, and D. B. Glasser, "A population study of the association between sexual function, sexual satisfaction and depressive symptoms in men," *Journal of Affective Disorders*, vol. 82, no. 2, pp. 235–243, 2004.

- [41] A. Algul, M. A. Ates, U. B. Semiz et al., "Evaluation of general psychopathology, subjective sleep quality, and health-related quality of life in patients with obesity," *The International Journal of Psychiatry in Medicine*, vol. 39, no. 3, pp. 297–312, 2009.
- [42] E. Mannucci, M. L. Petroni, N. Villanova, C. M. Rotella, G. Apolone, and G. Marchesini, "Clinical and psychological correlates of health-related quality of life in obese patients," *Health and Quality of Life Outcomes*, vol. 8, article 90, 2010.
- [43] M. Reuser, L. G. Bonneux, and F. J. Willekens, "Smoking kills, obesity disables: a multistate approach of the US health and retirement survey," *Obesity*, vol. 17, no. 4, pp. 783–789, 2009.

## Review Article

# Benign Prostatic Hyperplasia: A New Metabolic Disease of the Aging Male and Its Correlation with Sexual Dysfunctions

**Giovanni Corona,<sup>1</sup> Linda Vignozzi,<sup>2</sup> Giulia Rastrelli,<sup>2</sup> Francesco Lotti,<sup>2</sup> Sarah Cipriani,<sup>2</sup> and Mario Maggi<sup>2</sup>**

<sup>1</sup> Endocrinology Unit, Medical Department, Azienda Usl, Maggiore-Bellaria Hospital, Bologna, Italy

<sup>2</sup> Sexual Medicine Andrology Unit, Department of Experimental, Clinical and Biomedical Sciences, University of Florence, Viale Pieraccini 6, 50139 Florence, Italy

Correspondence should be addressed to Mario Maggi; [m.maggi@dfc.unifi.it](mailto:m.maggi@dfc.unifi.it)

Received 26 October 2013; Accepted 5 December 2013; Published 13 February 2014

Academic Editor: Antonio Aversa

Copyright © 2014 Giovanni Corona et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Metabolic syndrome (MetS) is a well-recognized cluster of cardiovascular (CV) risk factors including obesity, hypertension, dyslipidemia, and hyperglycaemia, closely associated with an increased risk of forthcoming cardiovascular disease and type 2 diabetes mellitus. Emerging evidence indicates that benign prostate hyperplasia (BPH) and its related lower urinary tract symptoms (LUTS) represent other clinical conditions frequently observed in subjects with MetS. Several modifiable factors involved in MetS determinism, such as inadequate diet, lack of physical exercise, and smoking and drinking behaviours are emerging as main contributors to the development of BPH. The pathogenetic mechanisms underlying the connection between MetS and BPH have not been completely clarified. MetS and its components, hypogonadism, and prostate inflammation probably play an important role in inducing BPH/LUTS. Although historically considered as a “normal” consequence of the aging process, BPH/LUTS should now be faced proactively, as a preventable disorder of the elderly. Type of diet and level of physical activity are now considered important factors affecting prostate health in the aging male. However, whether physical exercise, weight loss, and modifications of dietary habit can really alter the natural history of BPH/LUTS remains to be determined. Further research is advisable to better clarify these points.

## 1. Introduction

Time is an absolute dimension which ranks events as past, present, and future. Since biological aging is the accumulation and stratification of time-associated changes in a person, aging is an inevitable phenomenon, and, as such, it must be accepted. Because rejuvenation is impossible, the health-care intervention in aging should be focused on formatting this biological process as an acceptable lifetime season and, therefore, as healthy as possible. We strongly believe that acting on modifiable factors—such as going to the primary care doctor routinely, a healthy diet, or smoking cessation—can reduce an individual's absolute propensity to aging. In contrast, chronic morbidities—such as cardiovascular diseases (CVD), type 2 diabetes mellitus (T2DM), osteoarthritis, and mental disabilities—are conditions that seniors often

face as they age and that impair their enjoyment of this late lifetime season. Low-grade inflammation is supposed to represent the common determinant underlying almost all the aforementioned, age-related, and degenerative health conditions [1]. In fact, almost 10 years ago, Time magazine, on its cover, labeled inflammation as “The Secret Killer” for human health (<http://content.time.com/time/magazine/article/0,9171,993419,00.html>). However, inflammation per se is a beneficial reaction of the body, and its innate immune system, to an injurious stimulus, recognized 2000 years ago in the pioneering work of Celsius.

The concept of metabolic syndrome (MetS) was introduced almost 60 years ago, but only recently it was recognized as a valid construct to cluster some common medical disorders—such as visceral obesity, glucose intolerance, hypertension, and dyslipidemia—which increase the odds for

CVD and T2DM [2]. Even in the case of MetS, chronic, low-grade inflammation is considered, in concert with insulin resistance, the milestone of the syndrome. In the male, three other bothersome, age-related conditions were recently proposed as new factors often associated with MetS [2–4]. They are hypogonadism, erectile dysfunction (ED), and benign prostate hyperplasia (BPH). These age-associated medical conditions have a relatively high socioeconomic burden and are generally not regarded as preventable ailments. In contrast, we strongly believe that their impact on male aging can be halted by lifestyle changes or at least buffered by available medications. In this study we will overview pathogenetic interconnections between BPH, inflammation, MetS and hypogonadism, highlighting possible interventions to prevent their negative effect on men's health. In fact, several modifiable factors, such as inadequate diet, lack of physical exercise, and smoking and drinking behaviors, are emerging as main contributors to the development of MetS and its related disorders, including BPH.

## 2. BPH/LUTS and Hypogonadism

Androgens play an essential role in the development and growth of the entire male genital tract and in particular of the prostate, stimulating *differentiation* and *proliferation* of both the epithelial and the stromal compartments of the gland. Androgens acts through activation of androgen receptor (AR), which is expressed in both prostatic stromal and epithelial cells.

**2.1. Androgens and Prostate Differentiation.** The differentiating and growth-promoting actions of androgens are exerted starting in early embryonic life and still persist in adulthood and senescence. In fetal life, the AR-induced differentiation and branching morphogenesis was deeply explored by the Cunha laboratory, which demonstrated the role of androgens in mesenchyme cell-induced prostatic development [5, 6]. Cunha et al. [7, 8] found that androgens could stimulate prostatic epithelial development and growth interacting with AR within the stromal tissue, under the influence of specific growth factors. This concept was originally based on tissue recombinant experiments, composed of wild-type stromal cells and AR-deficient epithelium from the testicular feminization mouse. During prostatic development, several growth factors, termed andromedins (IGF-1, EGF, and several FGF-related proteins), have been proposed to be the paracrine mediators of these androgen-induced, stromal-mediated, generation of prostatic epithelial buds, and subsequent ductal elongation and branching morphogenesis [9]. In the adult prostate, AR expression drives basal epithelial cells of the glands into differentiation to generate intermediate cells and into terminal differentiated luminal cells [10]. As a caveat of these prodifferentiating actions of androgens, recent studies indicate that hypogonadism is associated with a more aggressive phenotype of prostate cancer [11].

**2.2. Androgens and Prostate Growth.** Besides differentiation, another biological action of androgens in the prostate is to

promote growth [12], which is essentially orchestrated in three distinct waves. The first growth wave is completed at birth, when the average weight of the prostate is about 1.5 grams. Prostatic development at this stage is a clear function of androgen signaling and is dependent on the function of the fetal testis. After a quiescent phase, at puberty—under the influence of increasing testosterone—the second wave starts: the prostate size reaches approximately 10 grams at early puberty and almost double that around the age of twenty [13]. Thereafter, the size of the prostate remains constant until midlate adulthood. At that time, in contrast to the pubertal growth phase which involves the entire gland, often there is a third selective growth phase, involving one of the three anatomically distinct prostate zones, the periurethral one, and which gives rise to BPH. BPH is a condition extremely prevalent in male adulthood and senescence, affecting 42% of men in the fifth decade to almost 90% in men older than 80 years [14]. BPH is essentially a histological diagnosis, characterized by hyperproliferation of the stromal and, to a lesser extent, of the epithelial compartment of the prostate, which can be clinically manifested as benign prostate enlargement (BPE), in almost half of the cases, or, less often, as benign prostate obstruction (BPO). The latter two clinical entities are characterized by progressive development of symptoms (lower urinary tract symptoms, LUTS), that are derived from prostate enlargement to the point where urination becomes difficult (BPE) or impaired (BPO), due to mechanical pressure on the bladder and urethra. Approximately 25% of men in their 50s and 80% of men in their 70s have clinically significant LUTS. However, not all men with BPH develop LUTS. In addition, not all men with LUTS have BPH as the underlying cause, because they are not disease-specific, being often multifactorial.

Although an increased androgen signaling is clearly implicated in the first two waves of prostate growth, its role in the third phase, BPH, is a matter of debate. In fact, a clear dose-response relationship between circulating androgen levels and BPH has never been demonstrated [15, 16]. In addition, during male senescence, androgens tend to decrease and not to increase [17]. Several recent studies indicate that a low testosterone (T), more than a high T, might have a detrimental effect on prostate biology. In fact, LUTS can even be lessened by androgen supplementation in hypogonadal men [18–25]. Recent data indicate that not only low testosterone but also high estradiol can favor BPH/LUTS progression. It is important to note that circulating T is actively metabolized to estrogens and part of T hormonal activity depends upon its binding to the estrogen receptors (ERs), that are present in both the prostate and bladder [26]. In addition, the enzyme P450 aromatase which converts androgens to estrogens [27] is highly expressed not only in fat tissue but also in the urogenital tract [28]. Evidence of an increased estrogen/androgen ratio was originally provided by Marmorston et al. almost half a century ago [29] reporting that the estrogen/androgen ratio in 24-hour urinary collections was elevated in men with BPH, as compared to normal controls. Several studies have observed a correlation between plasma  $17\beta$ estradiol ( $17\beta E_2$ ) levels and prostate volume or other features of BPH [30–32], while others have not [33].



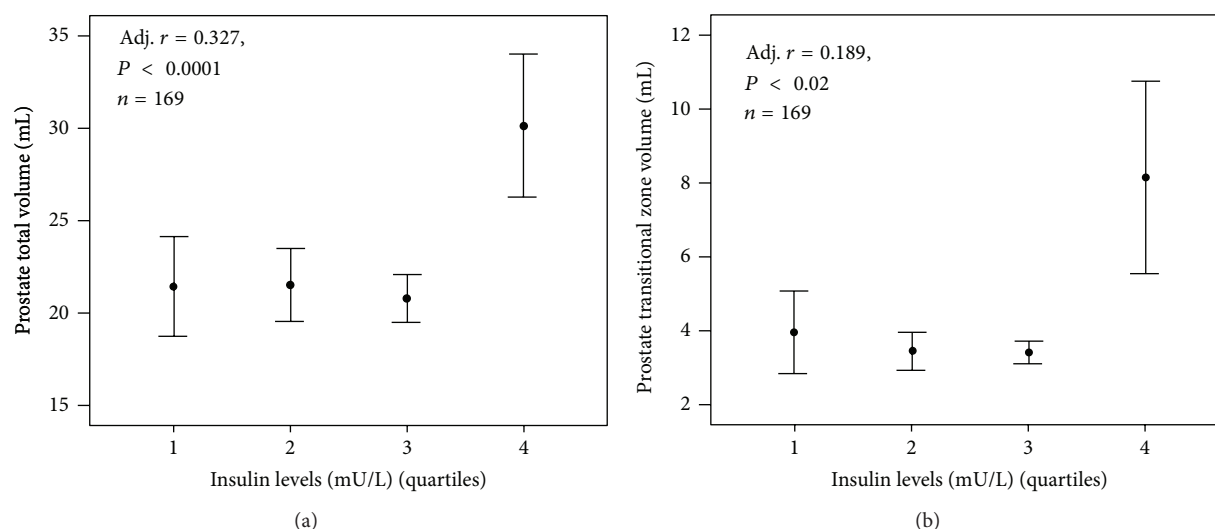


FIGURE 1: Association between insulin levels and prostate total or transitional zone volume. Association between insulin levels and prostate total (a) or transitional zone (b) volume. Insulin levels are reported as quartiles. All data are adjusted for age and total testosterone. Data are derived from a series of subjects seeking medical care for couple infertility at our unit. The number of subjects with available parameters is reported in the inset. Note that the statistical analyses have been performed using insulin levels as a continuous variable, even if grouped in quartiles for graphical purposes.

In two longitudinal, population-based cohort studies it was recently shown that a higher baseline  $17\beta E_2$  was associated with a worse forthcoming maximal flow rate and urinary symptoms [34, 35].

### 3. BPH/LUTS and Metabolic Syndrome

The historical view that BPH-related LUTS are merely generated by the compression of the urethra through the volumetric increased transitional prostate has been heavily challenged in the last few years [36]. In fact, nowadays, BPH/LUTS are not only viewed as a mere hydraulic problem, to be solved by a surgical intervention, but as a metabolic problem, to be solved with a multidisciplinary approach, which includes also the endocrinologist. Several recent studies have provided convincing evidence of a possible role of MetS, and/or its individual components, in the development of BPH, prostate growth, and worsening of LUTS [36].

**3.1. Hyperinsulinemia, Glucose Intolerance/T2DM, and BPH.** Possible links between BPH and T2DM were noted, in a retrospective study, as far back as 1966 [37]. Since that time, hyperinsulinaemia/glucose intolerance (the key component of MetS) and even T2DM have been considered as potential risk factors for BPH/LUTS based on several studies [38, 39]. In a population-based cohort of African-American men aged 40–79 years, BPH patients reporting a diabetes history have a 2-fold increase in the risk of moderate-severe LUTS [40]. In diabetic individuals, a similar odds ratio for having LUTS was reported in the second Nord-Trondelag Health Study [41]. In a stepwise regression analysis, Nandeesh et al. [42] found that insulin levels were an independent predictor of prostate volume in symptomatic BPH patients aged over

sixty. Interestingly, a similar conclusion was drawn by us in a sample of 171 young subjects undergoing transrectal sonography for couple infertility and not complaining of LUTS [43]. We found an association between prostate volume and insulin levels, which was retained after adjusting for total testosterone, other metabolic factors, and blood pressure [43]. All these findings indicate that insulin is an independent risk factor for BPH, most probably stimulating prostate growth acting on IGF receptors [44]. Figure 1 shows the relationship between increasing insulin levels (represented as quartiles) and prostate total and transitional zone volume, as detected by transrectal sonography, in the sample of subjects consulting for couple infertility, collected as previously described [43]. The highest quartile of insulin levels is associated with a clear increase in prostate size.

**3.2. Obesity and BPH.** In worldwide conducted studies, obesity—and in particular visceral obesity—was found to be often comorbid with BPH [45–49]. Although there were also some negative reports [50, 51], a recent meta-analysis, including a total of 19 studies, reported a positive association between BMI and LUTS associated with BPH (odds ratio (OR) = 1.28%) [52]. In population-based case-control studies, a marginal positive association was observed between risk of BPH and increased BMI. [52]. The impact of obesity on prostate size is apparent even in early adulthood, as demonstrated by a sonographic study conducted in 222 young men seeking medical care for couple infertility [53].

**3.3. Dyslipidemia and BPH.** The prostate synthesizes cholesterol at a level similar to the liver and accumulates it in a deposit within the gland in an age-dependent manner [54]. More than 70 years ago, Swyer [55] analyzed the cholesterol

TABLE 1: Characteristics of the studies comparing International Prostatic Symptom score (IPSS) and prostate volume in patients with and without metabolic syndrome (MetS) according to different criteria. NCEP-ATPIII: National Cholesterol Education Program-Third Adult Treatment Panel; IDF: International Diabetes Federation; AHA/NHLBI: American Heart Association/National Heart, Lung, and Blood Institute.

| Study                   | Overall population |             |               | Men with MetS    |                      | Men without MetS |                  |                      |
|-------------------------|--------------------|-------------|---------------|------------------|----------------------|------------------|------------------|----------------------|
|                         | MetS criteria      | Age (years) | Number of pts | IPSS total score | Prostate volume (cc) | Number of pts    | IPSS total score | Prostate volume (cc) |
| Ozden et al., 2007 [67] | NCEP ATP III       | 60          | 38            | 22               | 37.4                 | 40               | 20               | 32                   |
| Park et al., 2008 [68]  | NCEP ATP III       | 74 ± 8.1    | 102           | 11.1             | 41.7                 | 246              | 12.3             | 40.4                 |
| Yim et al., 2011 [69]   | NCEP ATP III       | 41.4 ± 5.2  | 140           | —                | 18.4                 | 708              | —                | 17.8                 |
| Jeong et al., 2011 [70] | NCEP ATP III       | 46.4 ± 8.4  | 354           | 6.8              | 20.6                 | 1003             | 6.5              | 19.7                 |
| Byun et al., 2011 [71]  | NCEP ATP III       | 55.6 ± 9.72 | 209           | 6.85             | 31.4                 | 499              | 7.89             | 29.8                 |
| Yang et al., 2012 [72]  | NCEP ATP III       | 53.8 ± 6.9  | 142           | —                | 30.1                 | 278              | —                | 25.2                 |
| Gacci et al., 2013 [4]  | AHA/NHLBI; IDF     | 68.2 ± 7.4  | 86            | 22.5             | 63                   | 185              | 20.9             | 58                   |
| Park et al., 2013 [73]  | NCEP ATP III       | 50–59       | 355           | 10               | 34                   | 869              | 10               | 28                   |

content in the prostate of BPH subjects and reported that its concentration was twice that in a normal prostate. Later on, Nandeesh et al. [56] reported that circulating total and HDL cholesterol were associated, in a positive and negative manner, respectively, with prostate enlargement in a series of 50 symptomatic BPH cases and 38 controls. However, other studies did not confirm the association [57–59]. In the Rancho Bernardo cohort study, Parsons et al. [60] found a 4-fold increased risk of BPH among diabetic men with elevated low density lipoprotein (LDL) cholesterol, but not in the overall cohort. This observation suggests that dyslipidemia per se is not sufficient enough to concur with BPH determinism, but the presence of other metabolic derangements, like T2DM, favors the process, because of an unfavorable total and LDL cholesterol particle size and density [60].

**3.4. Hypertension and BPH.** An association between BPH, hypertension, and T2DM was originally reported in a retrospective study 50 years ago [61]. Later on, hypertension was associated with increased odds of surgery for BPH in the Physician's Health Study [62] and with a higher prevalence of LUTS in other studies [63–65]. However, because both hypertension and BPH prevalence increase as a function of aging, the relationship between the two conditions was overlooked.

**3.5. Metabolic Syndrome and BPH.** From all the previous considerations (see Sections 3.1–3.4) it can be derived that each individual factor of MetS has been associated in some study with BPH/LUTS prevalence or progression, although several authors noted that their clustering, more than their individual presence, underlies the link. In 1998,

Hammarsten et al. [66] elaborated this concept investigating the relationship between prostate volume and individual MetS components in 158 men with BPH, demonstrating that T2DM, hypertension, obesity, high insulin, and low HDL-cholesterol levels were all risk factors for the development of BPH. Thereafter, only few additional studies, based on the concept of the MetS construct, have investigated the association between MetS and BPH/LUTS; results are summarized in Table 1 [4, 67–73]. All the studies found an association between the presence of MetS, even if defined with different criteria, and prostate volume, whereas the relationship between MetS and LUTS is more controversial (see Table 1). However, changing definition of MetS has little impact on its long-term metabolic and CV consequences [74, 75]. In the study of Gacci et al. [4], reduced HDL-cholesterol and increased triglyceride levels were noted to be the main determinants of MetS-related prostate alterations.

A recently published epidemiological survey of the Boston area (BACH) confirmed an association between MetS and LUTS; however, when subjects were stratified by age, the association was confirmed only in the youngest individuals [76].

In the previously mentioned cohort of relatively young male subjects examined for couple infertility we recently reported a stepwise, component-dependent association between increasing MetS severity and prostate enlargement at color Doppler ultrasound (CDU) [43]. No association between MetS-related prostate CDU abnormalities and semen parameters was detected, even though, in this cohort, MetS was associated with poor sperm morphology [43, 77]. Increased central obesity and reduced HDL cholesterol were the main correlates of prostate enlargement in this young, asymptomatic population. This and previous

evidence suggest that, beginning at a young age, MetS and in particular high waist circumference and reduced HDL cholesterol play an important role in prostate overgrowth. Interestingly, no association between MetS severity and prostate-related symptoms was observed, using either IPSS or the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) [43], which is a brief self-reported questionnaire for screening prostatitis symptoms [78].

#### 4. BPH/LUTS and Inflammation

**4.1. Epidemiological Evidence.** In the last decade, cross-sectional and longitudinal observation of several large cohorts have finally confirmed that chronic inflammation is a crucial component of BPH pathogenesis. An examination of baseline prostate biopsies in a subgroup of 1,197 patients, followed for more than 4 years in the Medical Therapies of Prostate Symptoms (MTOPS) study to assess BPH-disease progression, found that men in the placebo arm with inflammation were significantly more likely to experience BPH worsening and at higher risk of acute urinary retention (AUR) or BPH-related surgery than those without [79]. This was confirmed in the subgroup analysis of 8,224 men in the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial indicating that histologic inflammation was present in more than 78% men and that the severity of LUTS and the intensity of inflammation were related [80]. Another study retrospectively reviewed all histopathological examinations of 3,942 patients with BPH and showed that 43% of patients had histologic inflammation and 69% of them had chronic inflammation. In addition, inflammation in the prostate increased significantly with the increase in prostate volume and age [81]. Finally, the data from the placebo arm (1359 men) of the Prostate Cancer Prevention Trial (PCPT) demonstrated that circulating levels of inflammatory markers, including elevated CRP and interleukin-6 (IL-6), were associated with risk of incident, symptomatic BPH [82].

**4.2. Physiopathology.** Within the prostate, several classes of immunocompetent cells (lymphocytes, macrophages, and granulocytes) are physiologically resident and termed human prostate-associated lymphoid tissue (PALT). Activation of the intraglandular immune system PALT is the usual response to infectious agents. However, we believe that this initial acute inflammation could be succeeded by chronic inflammation that persisted if favored by hormonal and metabolic derangements or by exposure to other environmental and dietary factors [83]. Activated PALT recruits and stimulates the proliferation of other immunocompetent cells leading to an upregulation of several proinflammatory chemokines and cytokines [84]. Prostatic stromal cells—acting as targets of bacterial or viral toll-like receptor (TLR) agonists and, later on, as antigen-presenting cells (APC)—play a crucial role in the induction of inflammatory responses. They in fact activate CD4<sup>+</sup> lymphocytes and favor their differentiation to the effector subsets Th1 and Th17 [85]. In addition, TLR activation leads to the production of proinflammatory cytokines (IL-6)

and chemokines (IL-8 and CXCL10) capable of recruiting CXCR1- and CXCR2-positive leukocytes and CD15<sup>+</sup> neutrophils and further promoting prostate cell hyperplasia, through the direct action of IL-8 or the release of other intraprostatic growth factors, like basic FGF [85–87]. Stromal BPH cells are able to secrete IL-8, CXCL-10, and IL-6 not only in response to specific proinflammatory stimuli (i.e., TNF $\alpha$  or the TLR 4 agonist lipopolysaccharide), but also to metabolic insults and, in particular, to oxidized LDL and insulin. This suggests the hypothesis that lipids can induce and sustain an inflammatory response in human prostatic cells [87, 88].

**4.3. Clinical Evidence.** In line with this preclinical evidence, in a multicentre study on 271 consecutive men treated with simple prostatectomy, we demonstrated that the presence of MetS—and in particular of some of its components, such as dyslipidemia—is associated with a more severe intraprostatic inflammation [87, 88]. In particular, histopathological examination of BPH specimens demonstrated that the inflammatory score (IS), as well as the positivity for the pan leukocyte marker CD45, significantly increased as a function of MetS components [86–88]. Among MetS components, reduced HDL cholesterol and elevated triglycerides were significantly associated with elevated IS and CD45 positivity. Fats could have, therefore, a detrimental effect on prostate cells, boosting prostate inflammation, a key factor in the development and progression of BPH/LUTS. In the previously mentioned cohort of young, infertile subjects [43], we noted a significant, stepwise correlation between the number of MetS components and seminal IL-8, which has been proposed as a surrogate marker of prostate inflammation [89–92]. In addition, in the same population, a higher MetS severity was associated with sonographic features of prostate inflammation, including texture nonhomogeneity, major calcification size, and elevated arterial peak systolic velocity. Abdominal adiposity and dyslipidemia were the main determinants, among MetS factors, of sonographic alterations and increased seminal IL-8 [43].

**4.4. Experimental Models of MetS and Prostate Inflammation.** We recently developed an animal model of MetS by feeding New Zealand male rabbits a high fat diet (HFD) for 12 weeks. MetS in rabbits was characterized by glucose intolerance, dyslipidemia, hypertension, increased visceral fat accumulation, and hypogonadotropic hypogonadism with a concomitant hyperestrogenism [93–95]. In MetS animals we have described a specific prostate [96] and bladder [93] phenotype, which includes features of inflammation, tissue remodeling, and hypoxia. Interestingly, almost all these alterations were positively associated with a low-testosterone and high-estrogen milieu [93, 96, 97]. Accordingly, Figure 2 (upper panel) shows that MetS severity, in rabbit fed HFD or a regular diet (RD), is associated with a stepwise increase in AR and ER $\alpha$ , but not ER $\beta$  (not shown), gene expression within the prostate. In addition, in the same figure, it is shown that also the nonclassical, G protein-coupled estrogen receptor, GPER/GPR30, increases as a function of number of MetS factors. This indicates a potentially increased sensitivity of

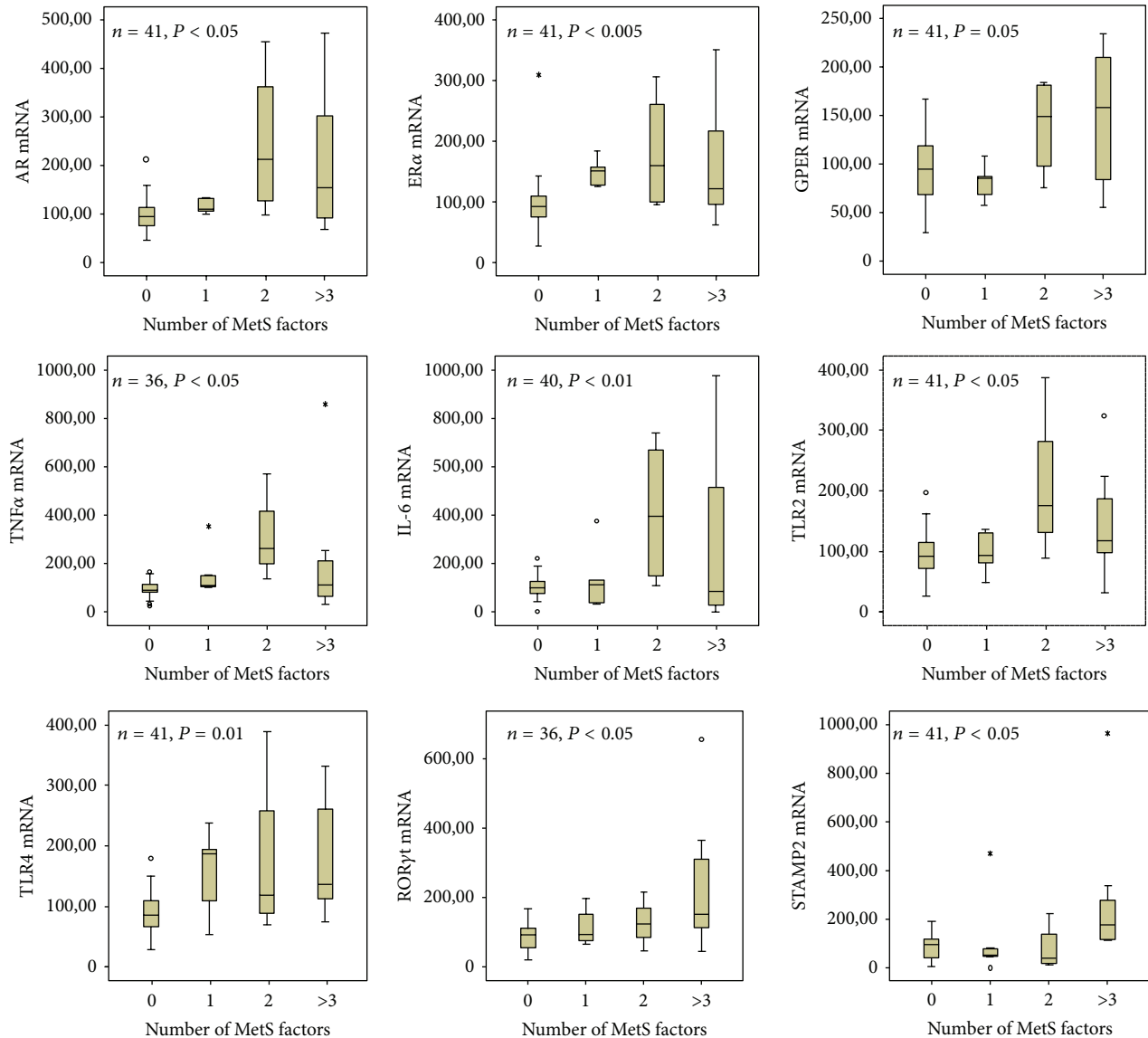


FIGURE 2: Gene expression of sex steroid receptors (upper panel) and inflammatory markers (middle and lower panels) in prostate of rabbits fed a regular diet (RD) or a high fat diet (HFD), according to metabolic syndrome (MetS severity). MetS severity was categorized as previously described [138], according to the number of factors present (abscissa). Ordinate axis indicates level of mRNA expression in arbitrary unit, as derived from quantitative RT-PCR analysis of the indicated prostate samples. Level of significance was derived from Kruskal-Wallis analysis of the data.

the MetS prostate to changing sex steroids. We, in fact, found that T administration to HFD rabbits reverted the majority of MetS-induced prostate alterations [96]. This finding is in line with the observation that, in human BPH stromal cells, the selective AR agonist DHT was able to blunt TNFα, LPS, or CD4(+)T cell-induced secretion of inflammatory/growth factors, including IL-6, IL-8, and bFGF, by blocking NF-κB nuclear translocation [86]. A protective effect of DHT was also found on oxLDL- or insulin-induced IL-8 secretion [87]. Interestingly, DHT was also able to prevent TNFα-induced LOX-1 (the receptor for oxLDL) mRNA expression. This strongly indicates a potential beneficial effect of AR signaling on diet-induced prostate inflammation. In contrast,

tamoxifen dosing to HFD rabbits further exacerbated MetS-induced prostate alterations, most probably by stimulating GPER/GPR30, as demonstrated by experiments with selective ligands for these receptors and by genetic ablation of their expression [26].

We also recently reported that the prostate of HFD-rabbits showed an increased expression of both mRNA and protein for phosphodiesterase type 5 (PDE5), the enzyme that catalyzed cGMP breakdown [97]. PDE5 expression within the prostate was associated with the majority of HFD-induced markers of inflammation, fibrosis, and myofibroblast activation, and, in particular, with COX2 and TNFα among inflammatory genes and with TGFβ, ROCK2, and αSMA



TABLE 2: Characteristics of the studies included in the meta-analysis.

| Study                         | Age (years) | Duration (weeks) | Overall population |                   | Placebo number of pts | PDE5 number of pts |
|-------------------------------|-------------|------------------|--------------------|-------------------|-----------------------|--------------------|
|                               |             |                  | Drugs              | Dosage (mg)       |                       |                    |
| McVary et al., 2007 [113]     | 60          | 12               | Sildenafil         | 50 (2 weeks); 100 | 155                   | 168                |
| McVary et al., 2007 [114]*    | 61.5        | 12               | Tadalafil          | 5 (6 weeks); 20   | 126                   | 125                |
| Stief et al., 2008 [115]      | 55.9        | 8                | Vardenafil         | 10                | 110                   | 105                |
| Roehrborn et al., 2008 [116]* | 62.0        | 12               | Tadalafil          | 2.5; 5; 10; 20    | 185                   | 701                |
| Porst et al., 2009 [117]*     | 61.9        | 12               | Tadalafil          | 2.5; 5; 10; 20    | 105                   | 386                |
| Tamimi et al., 2010 [118]*    | 60.9        | 12               | UK-369003          | 10; 25; 50, 100   | 37                    | 246                |
| Porst et al., 2011 [119]      | 64.8        | 12               | Tadalafil          | 5                 | 152                   | 148                |
| Egerdie et al., 2012 [120]*   | 62.5        | 12               | Tadalafil          | 2.5; 5            | 200                   | 406                |
| Oelke et al., 2012 [121]      | 63.6        | 12               | Tadalafil          | 5                 | 172                   | 171                |
| Brock et al., 2013 [122]      | 63.3        | 12               | Tadalafil          | 5                 | 545                   | 544                |
| Dmochowski et al., 2013 [123] | 58.6        | 12               | Tadalafil          | 20                | 101                   | 99                 |
| Yokoyama et al., 2013 [124]*  | 63.2        | 12               | Tadalafil          | 2.5; 5            | 154                   | 306                |

\*The effect derived from a ponderated mean at end point on International Prostate Symptom Score and maximum urinary flow rate were analyzed.

among those genes specifically involved in fibrosis and myofibroblast activation. Interestingly, HFD-induced PDE5 overexpression was counteracted by T dosing. Consistent with this effect, a negative correlation between prostate PDE5 mRNA expression and plasma testosterone/estradiol ratio was identified. However, a direct role of hypogonadism in HFD-induced PDE5 upregulation was ruled out by the observation that hypogonadotropic hypogonadal rabbits (GnRH analog-treated group), characterized by a reduced plasma testosterone/estradiol ratio, showed prostatic PDE5 mRNA expression similar to that of the RD group, which was not modified by T treatment [97]. Hence, we can hypothesize that HFD-related derangements, rather than hypogonadism per se, may be related to the PDE5 overexpression in the prostate.

## 5. Possible Intervention in MetS-Associated BPH/LUTS

Current therapy for BPH/LUTS is largely based on the use of  $\alpha_1$ -adrenergic receptor blockers, which relax prostatic smooth muscle, and 5- $\alpha$  reductase inhibitors, which reduce prostatic volume. Accordingly, current EAU guidelines attributed level of evidence of 1b and 1a to  $\alpha_1$ -blockers and 5- $\alpha$  reductase inhibitors, respectively, for the treatment of men with moderate-to-severe LUTS [98]. Recently, the possible use of PDE5 inhibitors was also recognized as a valuable treatment of the condition, with a level of evidence of 1b [98]. However, the same guidelines also suggest the usefulness of lifestyle modifications, without better explanation except for avoidance or moderation of caffeine or alcohol intake that may have a diuretic and irritant effect, thereby increasing fluid output and enhancing frequency, urgency, and nocturia [98].

**5.1. Lifestyle Modification.** Current evidence, suggesting a close relationship among BPH/LUTS, MetS, hypogonadism, and inflammation, indicates that the impact of lifestyle modification should be more carefully analyzed. Prospective data of the Health Professionals Follow-up Study (HPFS), on

more than 18,000 men without LUTS at baseline, recently showed that men with higher total and abdominal adiposity or who gained weight at follow-up were more likely to develop LUTS or experience progressive LUTS [99]. Previous meta-analyses have clearly demonstrated that lifestyle modifications, such as weight loss and increased consumption of fruit and vegetables, can reduce the incidence of obesity-related morbidities including hypogonadism [100], type 2 diabetes [101], coronary artery disease [102], and stroke [103]. Quite unexpectedly, studies on efficacy of lifestyle modifications on BPH/LUTS outcome are still lacking.

In 2002, Suzuki et al. [104] first reported that men with high energy intakes and particularly with high consumption of protein and polyunsaturated fatty acid were at a greater risk of developing BPH. Data from the placebo arm in the Prostate Cancer Prevention Trial (PCPT), which enrolled 18,880 men aged over 50 years, confirmed that high consumption of red meat and a high fat diet increased the risk of BPH [105]. In addition, the same authors reported that high consumption of vegetables reduced risk of BPH [105]. Similarly, data from HPFS study have demonstrated that consumption of fruits and vegetables rich in  $\beta$ -carotene lutein or vitamin C was inversely related to BPH [106]. As reported above, oxidative damage and inflammation are thought to be associated with development of BPH. High consumption of unsaturated fatty acids might contribute to lipid peroxidation of the cell membrane exacerbating the inflammation and impairing 5 $\alpha$ -reductase activity [107]. Conversely, high intake of fruits and vegetables was found to be associated with less oxidative stress, as measured by malondialdehyde concentration [108]. The effect of diet on BPH/LUTS is also supported by the lower incidence of prostate related problems in some Asian countries using a predominantly plant-based diet, as compared with Western countries, using a provokingly animal-based diet [109].

Physical activities were also shown to reduce the possibility of prostate enlargement, LUTS, and LUTS-related surgery [110]. In particular, increasing walking by 3 h/week decreases the risk of BPH by 10% [110]. In a meta-analysis that

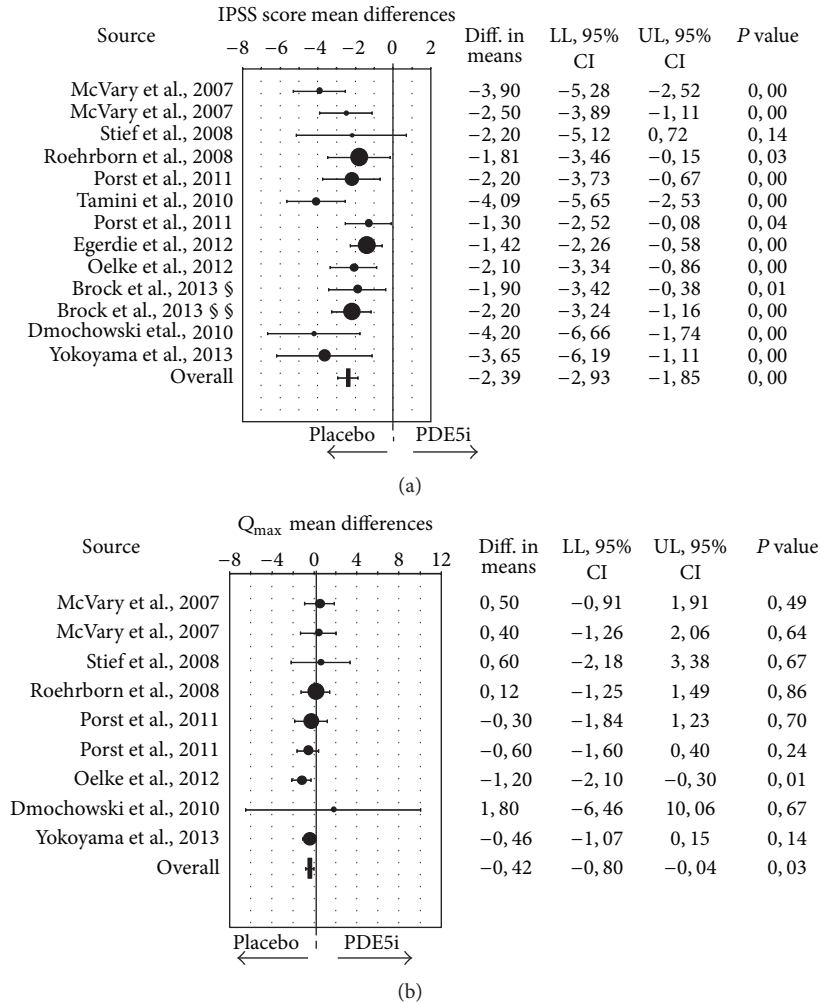


FIGURE 3: Weighted differences (with 95% confidence interval (CI)) of International Prostate Symptom Score (IPSS; (a)) and maximum flow rate ( $Q_{max}$ ; (b)), for the studies on phosphodiesterase type 5 inhibitors (PDE5-Is) versus placebo. § no erectile dysfunction; §§ erectile dysfunction.

enrolled 43,083 male patients, intensity of exercise was related to reduction of risk of prostate enlargement. Compared to the sedentary group, the risk for BPH or LUTS was significantly reduced with OR = 0.70, 0.74, and 0.74 for men engaging in light, moderate, and heavy physical activity, respectively [111].

In conclusion, type of diet and level of physical activity are emerging as other important factors affecting prostate health in the aging male, most probably reducing risk factors such as MetS, hypogonadism, and inflammation. However, whether physical exercise, weight loss, and modifications of dietary habit can really alter the natural history of BPH/LUTS remains to be determined. Further research is advisable to better clarify these points.

**5.2. PDE5 Inhibitors and BPH/LUTS.** Emerging evidence suggests that PDE5i might reduce moderate-to-severe (storage and voiding) LUTS in men with or without ED [98]. Accordingly, tadalafil (5 mg once daily) has been approved by the US Food and Drug Administration (FDA) and by the European Medical Agency (EMA) and licensed for

the treatment of male LUTS in Europe. By meta-analyzing the available evidence we previously reported that PDE5i alone, as compared with placebo, is able to improve LUTS symptoms, as detected by the decrease of IPSS score [112]. In addition, the association of PDE5i and  $\alpha$ 1-adrenergic blockers improved both IPSS score and maximum urinary flow rate ( $Q_{max}$ ) at the end point, as compared with  $\alpha$  blockers alone [112]. Since our last analysis, other five double-blind, placebo-controlled, randomized clinical trials (RCT) comparing the effect of PDE5i versus placebo on BPH/LUTS, have been published (see Table 2). Hence, so far, 12 RCTs [113–124] have specifically evaluated the effect of PDE5i alone in patients with BPH/LUTS. Overall, the studies enrolled 5158 patients, with a mean follow-up of 11.6 weeks (Table 2). Similar to previous analysis [112], we now report that PDE5i treatment was associated with a significant improvement of LUTS, as detected by the reduction of total IPSS score (Figure 3(a)). In addition, present meta-analysis also originally shows that PDE5i users report a small, but significant, improvement in  $Q_{max}$  (Figure 3(b)). Hence, the current analysis, in

a larger cohort of subjects, further indicates a role of PDE5i in improving LUTS in patients with BPH. In addition, it shows for the first time a possible role of PDE5i in improving urinary outflow in the same category of subjects.

Despite the aforementioned clinical evidence, the mechanism of action (MOA) of this class of medication in BPH/LUTS is still a matter of debate. Several dedicated recent reviews are available on this topic [112, 125–127]. Preclinical studies demonstrated that prostate, bladder, and urethra, as well as their relative blood vessels, all represent potential targets of PDE5i [128, 129]. Experimental evidence suggested that chronic blockade of PDE5 could impact several pathways involved in LUTS generation [88, 112, 125–127], including a reduced nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) and an increased RhoA/Rho-kinase signalling [130–132]. In addition, PDE5i can also reduce chronic pelvic hypoxia and its related functional and morphologic changes in the bladder and prostate, by increasing blood perfusion [129, 133]. A possible direct effect for PDE5i in modulating autonomic nervous system overactivity and bladder/prostate afferent nerve activity was also suggested [134]. However, in the last few years, some experimental and clinical data have offered a new MOA for PDE5i in BPH/LUTS, reducing MetS-associated prostate inflammation. In the previously described rabbit model of MetS-associated prostate alterations we found that tadalafil dosing was able to reduce inflammation and leukocyte infiltration (CD 45 scoring), along with fibrosis/myofibroblast activation [97]. In a retrospective pilot study on a BPH population ( $n = 60$ ), previously enrolled in a double-blind, placebo-controlled, clinical study on the efficacy of daily vardenafil (10 mg) added to tamsulosin (0.4 mg) [135], we evaluated prostatic CD 45 score in those undergoing simple prostatectomy for persistent/recurrent severe urinary symptoms. Patient cohort was categorized according to the presence of MetS. In those without MetS, CD45 positivity was low and unaffected by vardenafil dosing. In those with MetS, increased CD45 positivity was significantly blunted by chronic vardenafil treatment [88]. It is interesting to note that even in this small cohort the MetS factor most closely associated with CD45 positivity was dyslipidemia. Interestingly, in isolated human BPH stromal cells both tadalafil and vardenafil decreased TNF $\alpha$ -induced expression of genes related to inflammation (COX-2, IL-8, IL-6, IP-10, and MCP-1) and tissue remodelling ( $\alpha$ SMA, bFGF). Similar results were obtained when TNF $\alpha$ -induced secretion of IL-8 and CXCR-10 was considered. Both vardenafil and tadalafil were able to blunt IL-8 secretion induced also by metabolic stimuli, such as oxLDL, AGE, and IGF-1. The effect was apparently due to the ability of these PDE5i to stimulate PKG activity because it was mimicked by a nonhydrolysable cGMP analog and blocked by a PKG antagonist. Finally, both PDE5i significantly reduced the ability of TNF $\alpha$  to increase the expression of oxLDL receptor, LOX-1 [88].

## 6. Conclusions

People are living longer and, in some parts of the world, healthier lives. In 2006, almost 500 million people worldwide

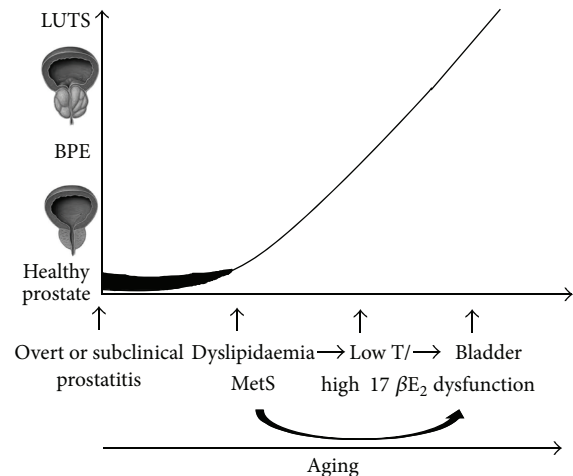


FIGURE 4: Graphical representation of a proposed multifactorial pathogenesis of benign prostatic hyperplasia/low urinary tract symptoms (BPH/LUTS). Symptomatic or asymptomatic prostate inflammation (very common in young individuals), in the presence of permissive factors such as metabolic syndrome (MetS), and in particular dyslipidemia, or an altered sex steroid milieu, can progress through prostate enlargement (BPE). The latter can or cannot be associated with LUTS, in particular in the presence of bladder dysfunction. Recent data indicates that MetS itself can also favour bladder alteration.

were 65 and older. By 2030, that total is projected to increase to 1 billion—1 in every 8 of the earth's inhabitants. Significantly, the most rapid increases in the 65 and older population are occurring in developing countries, which will see a jump of 140 percent by 2030 [136]. Hence, we must proactively face the health issues of the elderly. BPH/LUTS represent significant bother among aging men; they were historically considered as a “normal” consequence of the aging process and, as such, their negative effects on men's well-being only dealt with through medical or surgical intervention. This view has been challenged in the last decade and now BPH/LUTS are seen more as preventable than inexorable ailments of the elderly [137]. Evidence presented in this review indicates that several modifiable metabolic factors play a role in the determinism or progression of LUTS/BPH. MetS and its components, hypogonadism, and prostate inflammation are, in fact, emerging as medical conditions commonly associated with BPH/LUTS. Figure 4 summarizes our view. In our view, BPH/LUTS may be viewed as a complex disorder that also involves a metabolic component that may begin early in the life of the male, and, although asymptomatic, it is likely detectable even in the early stages of the disease. The mechanisms underpinning the relationship between MetS and prostate inflammation are likely to be similar in young and old men but chronic exposure to elevated inflammation, along with low T/high 17βE2, may contribute to BPH in the long term. Preventing the development of the disease even from the asymptomatic phase should be the basis for designing a resilient program of elderly healthcare. Analysis of the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk cohort has clearly demonstrated

that the adverse CV effects of having MetS on coronary heart disease could be substantially reduced or nullified by increasing physical activity. Several epidemiological studies support this view also for BPH/LUTS; intervention studies are urgently needed.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

## Acknowledgment

The authors would like to thank Davide Francomano, Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy, for his helpful clinical collaboration and for his critical reading of the paper.

## References

- [1] S. Salvioli, D. Monti, C. Lanzarini et al., "Immune system, cell senescence, aging and longevity—inflam-aging reappraised," *Current Pharmaceutical Design*, vol. 19, no. 9, pp. 1675–1679, 2013.
- [2] G. Corona, G. Rastrelli, A. Morelli, L. Vignozzi, E. Mannucci, and M. Maggi, "Hypogonadism and metabolic syndrome," *Journal of Endocrinological Investigation*, vol. 34, no. 7, pp. 557–567, 2011.
- [3] G. Corona, G. Rastrelli, and M. Maggi, "Diagnosis and treatment of late-onset hypogonadism: systematic review and meta-analysis of TRT outcomes," *Best Practice & Research Clinical Endocrinology & Metabolism*, vol. 27, no. 7, pp. 557–579, 2013.
- [4] M. Gacci, L. Vignozzi, A. Sebastianelli et al., "Metabolic syndrome and lower urinary tract symptoms: the role of inflammation," *Prostate Cancer and Prostatic Diseases*, vol. 16, no. 1, pp. 101–106, 2013.
- [5] S. W. Hayward and G. R. Cunha, "The prostate: development and physiology," *Radiologic Clinics of North America*, vol. 38, no. 1, pp. 1–14, 2000.
- [6] G. R. Cunha and W. A. Riche, "A historical perspective on the role of stroma in the pathogenesis of benign prostatic hyperplasia," *Differentiation*, vol. 82, no. 4-5, pp. 168–172, 2011.
- [7] J. M. Shannon and G. R. Cunha, "Characterization of androgen binding and deoxyribonucleic acid synthesis in prostate-like structures induced in the urothelium of testicular feminized (Tfm/Y) mice," *Biology of Reproduction*, vol. 31, no. 1, pp. 175–183, 1984.
- [8] G. R. Cunha and L. W. K. Chung, "Stromal-epithelial interactions. I. Induction of prostatic phenotype in urothelium of testicular feminized (Tfm/y) mice," *Journal of Steroid Biochemistry*, vol. 14, no. 12, pp. 1317–1324, 1981.
- [9] P. C. Haughney, S. W. Hayward, R. Dahiya, and G. R. Cunha, "Species-specific detection of growth factor gene expression in developing murine prostatic tissue," *Biology of Reproduction*, vol. 59, no. 1, pp. 93–99, 1998.
- [10] S. O. Lee, J. Tian, C. K. Huang et al., "Suppressor role of androgen receptor in proliferation of prostate basal epithelial and progenitor cells," *Journal of Endocrinology*, vol. 213, no. 2, pp. 173–182, 2012.
- [11] G. Corona, E. Baldi, and M. Maggi, "Androgen regulation of prostate cancer: where are we now?" *Journal of Endocrinological Investigation*, vol. 34, no. 3, pp. 232–243, 2011.
- [12] S. J. Berry, D. S. Coffey, P. C. Walsh, and L. L. Ewing, "The development of human benign prostatic hyperplasia with age," *The Journal of Urology*, vol. 132, no. 3, pp. 474–479, 1984.
- [13] P. C. Walsh and J. D. Wilson, "The induction of prostatic hypertrophy in the dog with androstenediol," *Journal of Clinical Investigation*, vol. 57, no. 4, pp. 1093–1097, 1976.
- [14] P. Abrams, "LUTS, BPH, BPO: a plea for the logical use of correct terms," *Reviews in Urology*, vol. 1, no. 2, p. 65, 1999.
- [15] C.-C. Liu, S.-P. Huang, W.-M. Li et al., "Relationship between serum testosterone and measures of benign prostatic hyperplasia in aging men," *Urology*, vol. 70, no. 4, pp. 677–680, 2007.
- [16] S. Martin, K. Lange, M. T. Haren, A. W. Taylor, and G. Witter, "Risk factors for progression and improvement of lower urinary tract symptoms (LUTS) in a prospective cohort of men," *The Journal of Urology*, vol. 191, no. 1, pp. 130–137, 2013.
- [17] F. C. W. Wu, A. Tajar, S. R. Pye et al., "Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European male aging study," *Journal of Clinical Endocrinology and Metabolism*, vol. 93, no. 7, pp. 2737–2745, 2008.
- [18] J. S. Tenover, "Effects of testosterone supplementation in the aging male," *Journal of Clinical Endocrinology and Metabolism*, vol. 75, no. 4, pp. 1092–1098, 1992.
- [19] S. Holmäng, P. Mårin, G. Lindstedt, and H. Hedelin, "Effect of long-term oral testosterone undecanoate treatment on prostate volume and serum prostate-specific antigen concentration in eugonadal middle-aged men," *Prostate*, vol. 23, no. 2, pp. 99–106, 1993.
- [20] K. Shigehara, K. Sugimoto, H. Konaka et al., "Androgen replacement therapy contributes to improving lower urinary tract symptoms in patients with hypogonadism and benign prostate hypertrophy: a randomised controlled study," *Aging Male*, vol. 14, no. 1, pp. 53–58, 2011.
- [21] A. Haider, L. J. Gooren, P. Padungtod, and F. Saad, "Concurrent improvement of the metabolic syndrome and lower urinary tract symptoms upon normalisation of plasma testosterone levels in hypogonadal elderly men," *Andrologia*, vol. 41, no. 1, pp. 7–13, 2009.
- [22] S. Kalinchenko, E. L. Vishnevskiy, A. N. Koval, G. J. Mskhalaya, and F. Saad, "Beneficial effects of testosterone administration on symptoms of the lower urinary tract in men with late-onset hypogonadism: a pilot study," *Aging Male*, vol. 11, no. 2, pp. 57–61, 2008.
- [23] J. A. Pearl, D. Berhanu, N. François et al., "Testosterone supplementation does not worsen lower urinary tract symptoms," *The Journal of Urology*, vol. 190, no. 5, pp. 1828–1833, 2013.
- [24] Y. H. Ko, G. Moon du, and K. H. Moon, "Testosterone replacement alone for testosterone deficiency syndrome improves moderate lower urinary tract symptoms: one year follow-up," *The World Journal of Men's Health*, vol. 31, no. 1, pp. 47–52, 2013.
- [25] S. Karazindiyanoğlu and S. Çayan, "The effect of testosterone therapy on lower urinary tract symptoms/bladder and sexual functions in men with symptomatic late-onset hypogonadism," *Aging Male*, vol. 11, no. 3, pp. 146–149, 2008.
- [26] P. Comoglio, A. Morelli, I. Cellai et al., "Opposite effects of tamoxifen on metabolic syndrome induced bladder and prostate alterations: a role for GPR30/GPER?" *Prostate*, vol. 74, no. 1, pp. 10–28, 2014.



- [27] T. M. Nicholson and W. A. Ricke, "Androgens and estrogens in benign prostatic hyperplasia: past, present and future," *Differentiation*, vol. 82, no. 4-5, pp. 184-199, 2011.
- [28] A. K. Chavalmane, P. Comeglio, A. Morelli et al., "Sex steroid receptors in male human bladder: expression and biological function," *Journal of Sexual Medicine*, vol. 7, no. 8, pp. 2698-2713, 2010.
- [29] J. Marmorston, L. J. Lombardo Jr., S. M. Myers, H. Giersen, E. Stern, and C. E. Hopkins, "Urinary excretion of estrone, estradiol and estriol by patients with prostatic cancer and benign prostate hypertrophy," *The Journal of Urology*, vol. 93, no. 2, pp. 287-295, 1965.
- [30] A. W. Partin, J. E. Oesterling, J. I. Epstein, R. Horton, and P. C. Walsh, "Influence of age and endocrine factors on the volume of benign prostatic hyperplasia," *The Journal of Urology*, vol. 145, no. 2, pp. 405-409, 1991.
- [31] A. W. Meikle, R. A. Stephenson, W. P. McWhorter, M. H. Skolnick, and R. G. Middleton, "Effects of age, sex steroids, and family relationships on volumes of prostate zones in men with and without prostate cancer," *Prostate*, vol. 26, no. 5, pp. 253-259, 1995.
- [32] J. Hammarsten, J.-E. Damber, M. Karlsson et al., "Insulin and free oestradiol are independent risk factors for benign prostatic hyperplasia," *Prostate Cancer and Prostatic Diseases*, vol. 12, no. 2, pp. 160-165, 2009.
- [33] Y. Miwa, T. Kaneda, and O. Yokoyama, "Association between lower urinary tract symptoms and serum levels of sex hormones in men," *Urology*, vol. 72, no. 3, pp. 552-555, 2008.
- [34] J. L. St. Sauver, D. J. Jacobson, M. E. McGree et al., "Associations between longitudinal changes in serum estrogen, testosterone, and bioavailable testosterone and changes in benign urologic outcomes," *American Journal of Epidemiology*, vol. 173, no. 7, pp. 787-796, 2011.
- [35] P. Abrams, L. Cardozo, M. Fall et al., "The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society," *Urology*, vol. 61, no. 1, pp. 37-49, 2003.
- [36] C. de Nunzio, W. Aronson, S. J. Freedland, E. Giovannucci, and J. K. Parsons, "The correlation between metabolic syndrome and prostatic diseases," *European Urology*, vol. 61, no. 3, pp. 560-570, 2012.
- [37] J. B. Bourke and J. P. Griffin, "Diabetes mellitus in patients with benign prostatic hyperplasia," *British Medical Journal*, vol. 4, no. 629, pp. 492-493, 1968.
- [38] J. Hammarsten and B. Högestedt, "Hyperinsulinaemia as a risk factor for developing benign prostatic hyperplasia," *European Urology*, vol. 39, no. 2, pp. 151-158, 2001.
- [39] M. C. Michel, L. Mehlburger, H. Schumacher, H.-U. Bressel, and M. Goepel, "Effect of diabetes on lower urinary tract symptoms in patients with benign prostatic hyperplasia," *The Journal of Urology*, vol. 163, no. 6, pp. 1725-1729, 2000.
- [40] M. A. Joseph, S. D. Harlow, J. T. Wei et al., "Risk factors for lower urinary tract symptoms in a population-based sample of African-American men," *American Journal of Epidemiology*, vol. 157, no. 10, pp. 906-914, 2003.
- [41] A. Seim, C. Hoyo, T. Østbye, and L. Vatten, "The prevalence and correlates of urinary tract symptoms in Norwegian men: the HUNT Study," *British Journal of Urology International*, vol. 96, no. 1, pp. 88-92, 2005.
- [42] H. Nandeesha, B. C. Koner, L. N. Dorairajan, and S. K. Sen, "Hyperinsulinemia and dyslipidemia in non-diabetic benign prostatic hyperplasia," *Clinica Chimica Acta*, vol. 370, no. 1-2, pp. 89-93, 2006.
- [43] F. Lotti, G. Corona, L. Vignozzi et al., "Metabolic syndrome and prostate abnormalities in male subjects of infertile couples," *Asian Journal of Andrology*, 2014.
- [44] A. Vikram, G. Jena, and P. Ramarao, "Insulin-resistance and benign prostatic hyperplasia: the connection," *European Journal of Pharmacology*, vol. 641, no. 2-3, pp. 75-81, 2010.
- [45] J. C. Kim, J.-Y. Lee, J. H. Kim et al., "Effects of obesity on lower urinary tract symptoms in Korean BPH patients," *Asian Journal of Andrology*, vol. 11, no. 6, pp. 663-668, 2009.
- [46] J. K. Parsons, "Benign prostatic hyperplasia and male lower urinary tract symptoms: epidemiology and risk factors," *Current Bladder Dysfunction Reports*, vol. 5, no. 4, pp. 212-218, 2010.
- [47] J. M. Kim, P. H. Song, H. T. Kim, and K. H. Moon, "Effect of obesity on prostate-specific antigen, prostate volume, and international prostate symptom score in patients with benign prostatic hyperplasia," *Korean Journal of Urology*, vol. 52, no. 6, pp. 401-405, 2011.
- [48] J. B. Bourke and J. P. Griffin, "Hypertension, diabetes mellitus, and blood groups in benign prostatic hypertrophy," *British Journal of Urology*, vol. 38, no. 1, pp. 18-23, 1966.
- [49] S. E. Dahle, A. P. Chokkalingam, Y.-T. Gao, J. Deng, F. Z. Stanczyk, and A. W. Hsing, "Body size and serum levels of insulin and leptin in relation to the risk of benign prostatic hyperplasia," *The Journal of Urology*, vol. 168, no. 2, pp. 599-604, 2002.
- [50] R. J. Glynn, E. W. Campion, G. R. Bouchard, and J. E. Silbert, "The development of benign prostatic hyperplasia among volunteers in the normative aging study," *American Journal of Epidemiology*, vol. 121, no. 1, pp. 78-90, 1985.
- [51] S. Sidney, C. P. Quesenberry Jr., M. C. Sadler, H. A. Guess, E. G. Lydick, and E. V. Cattolica, "Incidence of surgically treated benign prostatic hypertrophy and of prostate cancer among blacks and whites in a prepaid health care plan," *American Journal of Epidemiology*, vol. 134, no. 8, pp. 825-829, 1991.
- [52] S. Wang, Q. Mao, Y. Lin et al., "Body mass index and risk of BPH: a meta-analysis," *Prostate Cancer and Prostatic Diseases*, vol. 15, no. 3, pp. 265-272, 2012.
- [53] F. Lotti, G. Corona, G. M. Colpi et al., "Elevated body mass index correlates with higher seminal plasma interleukin 8 levels and ultrasonographic abnormalities of the prostate in men attending an andrology clinic for infertility," *Journal of Endocrinological Investigation*, vol. 34, no. 10, pp. 336-342, 2011.
- [54] M. R. Freeman and K. R. Solomon, "Cholesterol and prostate cancer," *Journal of Cellular Biochemistry*, vol. 91, no. 1, pp. 54-69, 2004.
- [55] G. Swyer, "Cholesterol content of normal and enlarged prostates," *Cancer Research*, vol. 2, pp. 372-375, 1942.
- [56] H. Nandeesha, B. C. Koner, L. N. Dorairajan, and S. K. Sen, "Hyperinsulinemia and dyslipidemia in non-diabetic benign prostatic hyperplasia," *Clinica Chimica Acta*, vol. 370, no. 1-2, pp. 89-93, 2006.
- [57] A. Gupta, S. Gupta, M. Pavuk, and C. G. Roehrborn, "Anthropometric and metabolic factors and risk of benign prostatic hyperplasia: a prospective cohort study of Air Force veterans," *Urology*, vol. 68, no. 6, pp. 1198-1205, 2006.
- [58] M. Lekili, T. Müezzinoğlu, B. S. Uyanik, and C. Büyüksu, "Serum lipid levels in benign prostatic hyperplasia," *World Journal of Urology*, vol. 24, no. 2, pp. 210-213, 2006.

- [59] A. Zucchetto, A. Tavani, L. Dal Maso et al., "History of weight and obesity through life and risk of benign prostatic hyperplasia," *International Journal of Obesity*, vol. 29, no. 7, pp. 798–803, 2005.
- [60] J. K. Parsons, J. Bergstrom, and E. Barrett-Connor, "Lipids, lipoproteins and the risk of benign prostatic hyperplasia in community-dwelling men," *British Journal of Urology International*, vol. 101, no. 3, pp. 313–318, 2008.
- [61] J. B. Bourke and J. P. Griffin, "Hypertension, diabetes mellitus, and blood groups in benign prostatic hypertrophy," *British Journal of Urology*, vol. 38, no. 1, pp. 18–23, 1966.
- [62] P. H. Gann, C. H. Hennekens, C. Longcope, W. Verhoek-Ofstedahl, F. Grodstein, and M. J. Stampfer, "A prospective study of plasma hormone levels, nonhormonal factors, and development of benign prostatic hyperplasia," *Prostate*, vol. 26, no. 1, pp. 40–49, 1995.
- [63] A. Seim, C. Hoyo, T. Østbye, and L. Vatten, "The prevalence and correlates of urinary tract symptoms in Norwegian men: the HUNT Study," *British Journal of Urology International*, vol. 96, no. 1, pp. 88–92, 2005.
- [64] S. Rohrmann, E. Smit, E. Giovannucci, and E. A. Platz, "Association between markers of the metabolic syndrome and lower urinary tract symptoms in the Third National Health and Nutrition Examination Survey (NHANES III)," *International Journal of Obesity*, vol. 29, no. 3, pp. 310–316, 2005.
- [65] M. A. Joseph, S. D. Harlow, J. T. Wei et al., "Risk factors for lower urinary tract symptoms in a population-based sample of African-American men," *American Journal of Epidemiology*, vol. 157, no. 10, pp. 906–914, 2003.
- [66] J. Hammarsten, B. Högestedt, N. Holthuis, and D. Mellström, "Components of the metabolic syndrome—risk factors for the development of benign prostatic hyperplasia," *Prostate Cancer and Prostatic Diseases*, vol. 1, no. 3, pp. 157–162, 1998.
- [67] C. Ozden, O. L. Ozdal, G. Urgancioglu, H. Koyuncu, S. Gokkaya, and A. Memis, "The correlation between metabolic syndrome and prostatic growth in patients with benign prostatic hyperplasia," *European Urology*, vol. 51, no. 1, pp. 199–206, 2007.
- [68] H. K. Park, H. W. Lee, K. S. Lee et al., "Relationship between lower urinary tract symptoms and metabolic syndrome in a community-based elderly population," *Urology*, vol. 72, no. 3, pp. 556–560, 2008.
- [69] S. J. Yim, Y. S. Cho, and K. J. Joo, "Relationship between metabolic syndrome and prostate volume in Korean men under 50 years of age," *Korean Journal of Urology*, vol. 52, no. 6, pp. 390–395, 2011.
- [70] J. H. Jeong, E. T. Kim, and D. K. Kim, "Association of metabolic syndrome and benign prostate enlargement in young Korean males," *Korean Journal of Urology*, vol. 52, no. 11, pp. 757–762, 2011.
- [71] H. K. Byun, Y. H. Sung, W. Kim, J. H. Jung, J. M. Song, and H. C. Chung, "Relationships between prostate-specific antigen, prostate volume, and components of metabolic syndrome in healthy Korean men," *Korean Journal of Urology*, vol. 53, no. 11, pp. 774–778, 2011.
- [72] T. K. Yang, J. T. Hsieh, S. C. Chen, H. C. Chang, H. J. Yang, and K. H. Huang, "Metabolic syndrome associated with reduced lower urinary tract symptoms in middle-aged men receiving health checkup," *Urology*, vol. 80, no. 5, pp. 1093–1097, 2012.
- [73] Y. W. Park, S. B. Kim, H. Kwon et al., "The relationship between lower urinary tract symptoms/benign prostatic hyperplasia and the number of components of metabolic syndrome," *Urology*, vol. 82, no. 3, pp. 674–679, 2013.
- [74] G. Corona, E. Mannucci, L. Petrone et al., "A comparison of NCEP-ATPIII and IDF metabolic syndrome definitions with relation to metabolic syndrome-associated sexual dysfunction," *Journal of Sexual Medicine*, vol. 4, no. 3, pp. 789–796, 2007.
- [75] G. Corona, G. Rastrelli, L. Vignozzi, E. Mannucci, and M. Maggi, "Testosterone, cardiovascular disease and the metabolic syndrome," *Best Practice and Research*, vol. 25, no. 2, pp. 337–353, 2011.
- [76] V. Kupelian, K. T. McVary, S. A. Hall et al., "Association of lower urinary tract symptoms and the metabolic syndrome: results from the Boston Area Community Health Survey," *The Journal of Urology*, vol. 189, no. 1, pp. S107–S114, 2013.
- [77] F. Lotti, G. Corona, E. Maseroli et al., "Clinical implications of measuring prolactin levels in males of infertile couples," *Andrology*, vol. 1, no. 5, pp. 764–771, 2013.
- [78] M. S. Litwin, M. McNaughton-Collins, F. J. Fowler Jr. et al., "The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure," *The Journal of Urology*, vol. 162, no. 2, pp. 369–375, 1999.
- [79] C. G. Roehrborn, J. G. Nuckolls, J. T. Wei, and W. Steers, "The benign prostatic hyperplasia registry and patient survey: study design, methods and patient baseline characteristics," *British Journal of Urology International*, vol. 100, no. 4, pp. 813–819, 2007.
- [80] J. C. Nickel, C. G. Roehrborn, M. P. O'Leary, D. G. Bostwick, M. C. Somerville, and R. S. Rittmaster, "The relationship between prostate inflammation and lower urinary tract symptoms: examination of baseline data from the REDUCE trial," *European Urology*, vol. 54, no. 6, pp. 1379–1384, 2008.
- [81] F. di Silverio, V. Gentile, A. de Matteis et al., "Distribution of inflammation, pre-malignant lesions, incidental carcinoma in histologically confirmed benign prostatic hyperplasia: a retrospective analysis," *European Urology*, vol. 43, no. 2, pp. 164–175, 2003.
- [82] J. M. Schenk, A. R. Kristal, M. L. Neuhouser et al., "Biomarkers of systemic inflammation and risk of incident, symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial," *American Journal of Epidemiology*, vol. 171, no. 5, pp. 571–582, 2010.
- [83] L. Vignozzi, G. Rastrelli, G. Corona, M. Gacci, G. Forti, and M. Maggi, "Benign prostatic hyperplasia: a new metabolic disease?" *Journal of Endocrinological Investigation*, 2014.
- [84] L. Adorini, G. Penna, B. Fibbi, and M. Maggi, "Vitamin D receptor agonists target static, dynamic, and inflammatory components of benign prostatic hyperplasia: annals of the New York Academy of Sciences," *Annals of the New York Academy of Sciences*, vol. 1193, pp. 146–152, 2010.
- [85] G. Penna, B. Fibbi, S. Amuchastegui et al., "Human benign prostatic hyperplasia stromal cells as inducers and targets of chronic immuno-mediated inflammation," *Journal of Immunology*, vol. 182, no. 7, pp. 4056–4064, 2009.
- [86] L. Vignozzi, I. Cellai, R. Serni et al., "Antiinflammatory effect of androgen receptor activation in human benign prostatic hyperplasia cells," *Journal of Endocrinology*, vol. 214, no. 1, pp. 31–43, 2012.
- [87] L. Vignozzi, M. Gacci, I. Cellai et al., "Fat boosts, while androgen receptor activation counteracts, BPH-associated prostate inflammation," *Prostate*, vol. 73, no. 8, pp. 789–800, 2013.
- [88] L. Vignozzi, M. Gacci, I. Cellai et al., "PDE5 inhibitors blunt inflammation in human BPH: a potential mechanism of action

- for PDE5 inhibitors in LUTS,” *Prostate*, vol. 73, no. 13, pp. 1391–1402, 2013.
- [89] G. Penna, N. Mondaini, S. Amuchastegui et al., “Seminal plasma cytokines and chemokines in prostate inflammation: interleukin 8 as a predictive biomarker in chronic prostatitis/chronic pelvic pain syndrome and benign prostatic hyperplasia,” *European Urology*, vol. 51, no. 2, pp. 524–533, 2007.
- [90] G. Penna, B. Fibbi, S. Amuchastegui et al., “The vitamin D receptor agonist elocalcitol inhibits IL-8-dependent benign prostatic hyperplasia stromal cell proliferation and inflammatory response by targeting the RhoA/Rho kinase and NF- $\kappa$ B pathways,” *Prostate*, vol. 69, no. 5, pp. 480–493, 2009.
- [91] B. Fibbi, G. Penna, A. Morelli, L. Adorini, and M. Maggi, “Chronic inflammation in the pathogenesis of benign prostatic hyperplasia,” *International Journal of Andrology*, vol. 33, no. 3, pp. 475–488, 2010.
- [92] F. Lotti and M. Maggi, “Interleukin 8 and the male genital tract,” *Journal of Reproductive Immunology*, vol. 100, no. 1, pp. 54–65, 2013.
- [93] A. Morelli, P. Comeglio, S. Filippi et al., “Testosterone and farnesoid X receptor agonist INT-747 counteract high fat diet-induced bladder alterations in a rabbit model of metabolic syndrome,” *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 132, no. 1–2, pp. 80–92, 2012.
- [94] S. Filippi, L. Vignozzi, A. Morelli et al., “Testosterone partially ameliorates metabolic profile and erectile responsiveness to PDE5 inhibitors in an animal model of male metabolic syndrome,” *Journal of Sexual Medicine*, vol. 6, no. 12, pp. 3274–3288, 2009.
- [95] L. Vignozzi, A. Morelli, S. Filippi et al., “Farnesoid X receptor activation improves erectile function in animal models of metabolic syndrome and diabetes,” *Journal of Sexual Medicine*, vol. 8, no. 1, pp. 57–77, 2011.
- [96] L. Vignozzi, A. Morelli, E. Sarchielli et al., “Testosterone protects from metabolic syndrome-associated prostate inflammation: an experimental study in rabbit,” *Journal of Endocrinology*, vol. 212, no. 1, pp. 71–84, 2012.
- [97] A. Morelli, P. Comeglio, S. Filippi et al., “Mechanism of action of phosphodiesterase type 5 inhibition in metabolic syndrome-associated prostate alterations: an experimental study in the rabbit,” *Prostate*, vol. 73, no. 4, pp. 428–441, 2013.
- [98] M. Oelke, A. Bachmann, A. Descazeaud et al., “EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction,” *European Urology*, vol. 64, no. 1, pp. 118–140, 2013.
- [99] A. M. Mondul, E. Giovannucci, and E. A. Platz, “A prospective study of obesity and incidence and progression of lower urinary tract symptoms,” *The Journal of Urology*, pp. 05477–05479, 2013.
- [100] G. Corona, G. Rastrelli, M. Monami et al., “Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis,” *European Journal of Endocrinology*, vol. 168, no. 6, pp. 829–843, 2013.
- [101] M. Hamer and Y. Chida, “Intake of fruit, vegetables, and antioxidants and risk of type 2 diabetes: systematic review and meta-analysis,” *Journal of Hypertension*, vol. 25, no. 12, pp. 2361–2369, 2007.
- [102] L. Dauchet, P. Amouyel, S. Hercberg, and J. Dallongeville, “Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies,” *Journal of Nutrition*, vol. 136, no. 10, pp. 2588–2593, 2006.
- [103] F. J. He, C. A. Nowson, and G. A. MacGregor, “Fruit and vegetable consumption and stroke: meta-analysis of cohort studies,” *The Lancet*, vol. 367, no. 9507, pp. 320–326, 2006.
- [104] S. Suzuki, E. A. Platz, I. Kawachi, W. C. Willett, and E. Giovannucci, “Intakes of energy and macronutrients and the risk of benign prostatic hyperplasia,” *American Journal of Clinical Nutrition*, vol. 75, no. 4, pp. 689–697, 2002.
- [105] A. R. Kristal, K. B. Arnold, J. M. Schenk et al., “Dietary patterns, supplement use, and the risk of symptomatic benign prostatic hyperplasia: results from the Prostate Cancer Prevention Trial,” *American Journal of Epidemiology*, vol. 167, no. 8, pp. 925–934, 2008.
- [106] S. Rohrmann, E. Giovannucci, W. C. Willett, and E. A. Platz, “Fruit and vegetable consumption, intake of micronutrients, and benign prostatic hyperplasia in US men,” *American Journal of Clinical Nutrition*, vol. 85, no. 2, pp. 523–529, 2007.
- [107] T. Liang and S. Liao, “Inhibition of steroid 5 $\alpha$ -reductase by specific aliphatic unsaturated fatty acids,” *Biochemical Journal*, vol. 285, no. 2, pp. 557–562, 1992.
- [108] G. Block, M. Dietrich, E. P. Norkus et al., “Factors associated with oxidative stress in human populations,” *American Journal of Epidemiology*, vol. 156, no. 3, pp. 274–285, 2002.
- [109] R. Tewari, S. Rajender, S. M. Natu et al., “Diet, obesity, and prostate health: are we missing the link?” *Journal of Andrology*, vol. 33, no. 5, pp. 763–776, 2012.
- [110] E. A. Platz, I. Kawachi, E. B. Rimm et al., “Physical activity and benign prostatic hyperplasia,” *Archives of Internal Medicine*, vol. 158, no. 21, pp. 2349–2356, 1998.
- [111] J. K. Parsons and C. Kashefi, “Physical activity, benign prostatic hyperplasia, and lower urinary tract symptoms,” *European Urology*, vol. 53, no. 6, pp. 1228–1235, 2008.
- [112] M. Gacci, G. Corona, M. Salvi et al., “A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with  $\alpha$ -blockers for lower urinary tract symptoms due to benign prostatic hyperplasia,” *European Urology*, vol. 61, no. 5, pp. 994–1003, 2012.
- [113] K. T. McVary, W. Monnig, J. L. Camps Jr., J. M. Young, L.-J. Tseng, and G. van den Ende, “Sildenafil citrate improves erectile function and urinary symptoms in men with erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia: a randomized, double-blind trial,” *The Journal of Urology*, vol. 177, no. 3, pp. 1071–1077, 2007.
- [114] K. T. McVary, C. G. Roehrborn, J. C. Kaminetsky et al., “Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia,” *The Journal of Urology*, vol. 177, no. 4, pp. 1401–1407, 2007.
- [115] C. G. Stief, H. Porst, D. Neuser, M. Beneke, and E. Ulbrich, “A randomised, placebo-controlled study to assess the efficacy of twice-daily vardenafil in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia,” *European Urology*, vol. 53, no. 6, pp. 1236–1244, 2008.
- [116] C. G. Roehrborn, K. T. McVary, A. Elion-Mboussa, and L. Viktrup, “Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study,” *The Journal of Urology*, vol. 180, no. 4, pp. 1228–1234, 2008.
- [117] H. Porst, K. T. McVary, F. Montorsi et al., “Effects of once-daily tadalafil on erectile function in men with erectile dysfunction and signs and symptoms of benign prostatic hyperplasia,” *European Urology*, vol. 56, no. 4, pp. 727–736, 2009, Corrigendum. *European Urology*. Vol. 59, no. 6, pp. 2082, 2011.



- [118] N. A. M. Tamimi, I. Mincik, S. Haughie, J. Lamb, A. Crossland, and P. Ellis, "A placebo-controlled study investigating the efficacy and safety of the phosphodiesterase type 5 inhibitor UK-369,003 for the treatment of men with lower urinary tract symptoms associated with clinical benign prostatic hyperplasia," *British Journal of Urology International*, vol. 106, no. 5, pp. 674–680, 2010.
- [119] H. Porst, E. D. Kim, A. R. Casabé et al., "Efficacy and safety of tadalafil once daily in the treatment of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results of an international randomized, double-blind, placebo-controlled trial," *European Urology*, vol. 60, no. 5, pp. 1105–1113, 2011.
- [120] R. B. Egerdie, S. Auerbach, C. G. Roehrborn et al., "Tadalafil 2.5 or 5mg administered once daily for 12 weeks in men with both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia: results of a randomized, placebo-controlled, double-blind study," *Journal of Sexual Medicine*, vol. 9, no. 1, pp. 271–281, 2012.
- [121] M. Oelke, F. Giuliano, V. Mirone, L. Xu, D. Cox, and L. Viktrup, "Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo-controlled clinical trial," *European Urology*, vol. 61, no. 5, pp. 917–925, 2012.
- [122] G. Brock, G. Broderick, C. G. Roehrborn, L. Xu, D. Wong, and L. Viktrup, "Tadalafil once daily in the treatment of lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) in men without erectile dysfunction," *British Journal of Urology International*, vol. 112, no. 7, pp. 990–997, 2013.
- [123] R. Dmochowski, C. Roehrborn, S. Klise, L. Xu, J. Kaminetsky, and S. Kraus, "Urodynamic effects of once daily tadalafil in men with lower urinary tract symptoms secondary to clinical benign prostatic hyperplasia: a randomized, placebo controlled 12-Week clinical trial," *The Journal of Urology*, vol. 183, no. 3, pp. 1092–1097, 2010.
- [124] O. Yokoyama, M. Yoshida, S. C. Kim et al., "Tadalafil once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a randomized placebo- and tamsulosin-controlled 12-week study in Asian men," *International Journal of Urology*, vol. 20, no. 2, pp. 193–201, 2013.
- [125] F. Giuliano, S. Ückert, M. Maggi, L. Birder, J. Kissel, and L. Viktrup, "The mechanism of action of phosphodiesterase type 5 inhibitors in the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia," *European Urology*, vol. 63, no. 3, pp. 506–516, 2013.
- [126] M. Gacci, I. Eardley, F. Giuliano et al., "Critical analysis of the relationship between sexual dysfunctions and lower urinary tract symptoms due to benign prostatic hyperplasia," *European Urology*, vol. 60, no. 4, pp. 809–825, 2011.
- [127] K.-E. Andersson, W. C. de Groat, K. T. McVary et al., "Tadalafil for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia: pathophysiology and mechanism(s) of action," *Neurourology and Urodynamics*, vol. 30, no. 3, pp. 292–301, 2011.
- [128] B. Fibbi, A. Morelli, L. Vignozzi et al., "Characterization of phosphodiesterase Type 5 expression and functional activity in the human male lower urinary tract," *Journal of Sexual Medicine*, vol. 7, no. 1, pp. 59–69, 2010.
- [129] A. Morelli, E. Sarchielli, P. Comeglio et al., "Phosphodiesterase type 5 expression in human and rat lower urinary tract tissues and the effect of tadalafil on prostate gland oxygenation in spontaneously hypertensive rats," *Journal of Sexual Medicine*, vol. 8, no. 10, pp. 2746–2760, 2011.
- [130] A. Morelli, S. Filippi, P. Sandner et al., "Vardenafil modulates bladder contractility through cGMP-mediated inhibition of RhoA/Rho kinase signaling pathway in spontaneously hypertensive rats," *Journal of Sexual Medicine*, vol. 6, no. 6, pp. 1594–1608, 2009.
- [131] S. Filippi, A. Morelli, P. Sandner et al., "Characterization and functional role of androgen-dependent PDE5 activity in the bladder," *Endocrinology*, vol. 148, no. 3, pp. 1019–1029, 2007.
- [132] L. Vignozzi, S. Filippi, P. Comeglio et al., "Tadalafil effect on metabolic syndrome-associated bladder alterations: an experimental study in a rabbit model," *Journal of Sexual Medicine*, vol. 73, no. 4, pp. 428–441, 2013.
- [133] A. Morelli, S. Filippi, P. Comeglio et al., "Acute vardenafil administration improves bladder oxygenation in spontaneously hypertensive rats," *Journal of Sexual Medicine*, vol. 7, no. 1, pp. 107–120, 2010.
- [134] D. Behr-Roussel, S. Oger, S. Caisey et al., "Vardenafil decreases bladder afferent nerve activity in unanesthetized, decerebrate, spinal cord-injured rats," *European Urology*, vol. 59, no. 2, pp. 272–277, 2011.
- [135] M. Gacci, G. Vittori, N. Tosi et al., "A randomized, placebo-controlled study to assess safety and efficacy of Vardenafil 10mg and Tamsulosin 0.4mg vs. Tamsulosin 0.4mg alone in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia," *Journal of Sexual Medicine*, vol. 9, no. 6, pp. 1624–1633, 2012.
- [136] K. Kinsella and Y. Gist, *Older Workers, Retirement, and Pensions. A Comparative International Chartbook*. Washington, DC: U.S. Census Bureau and U.S. National Institute on Aging, and U.S. Census Bureau. International Data Base, 1995, <http://www.census.gov/ipc/www/idbnew.html>.
- [137] J. K. Parsons, "Modifiable risk factors for benign prostatic hyperplasia and lower urinary tract symptoms: new approaches to old problems," *The Journal of Urology*, vol. 178, no. 2, pp. 395–401, 2007.
- [138] A. Morelli, E. Sarchielli, P. Comeglio et al., "Metabolic syndrome induces inflammation and impairs gonadotropin-releasing hormone neurons in the preoptic area of the hypothalamus in rabbits," *Molecular and Cellular Endocrinology*, vol. 382, no. 1, pp. 107–119, 2013.



## Research Article

# Progressive Improvement of *T*-Scores in Men with Osteoporosis and Subnormal Serum Testosterone Levels upon Treatment with Testosterone over Six Years

Ahmad Haider,<sup>1</sup> Ulrich Meergans,<sup>2</sup> Abdulmaged Traish,<sup>3</sup> Farid Saad,<sup>4,5</sup> Gheorghe Doros,<sup>6</sup> Paul Lips,<sup>7</sup> and Louis Gooren<sup>7,8</sup>

<sup>1</sup> Private Urology Practice, 27570 Bremerhaven, Germany

<sup>2</sup> Department of Orthopedics, Wesermuende Hospital, 27607 Langen, Germany

<sup>3</sup> Departments of Biochemistry and of Urology, Boston University School of Medicine, Boston, MA 02118, USA

<sup>4</sup> Bayer Pharma, Global Medical Affairs Andrology, 13353 Berlin, Germany

<sup>5</sup> Gulf Medical University School of Medicine, Ajman, UAE

<sup>6</sup> Department of Biostatistics, Boston University School of Public Health, Boston, MA 02118, USA

<sup>7</sup> Endocrine Section, Department of Internal Medicine, VU University Medical Center, 1081 HV Amsterdam, The Netherlands

<sup>8</sup> Chiang Mai 50220, Thailand

Correspondence should be addressed to Farid Saad; [farid.saad@bayer.com](mailto:farid.saad@bayer.com)

Received 27 November 2013; Accepted 31 December 2013; Published 13 February 2014

Academic Editor: Antonio Aversa

Copyright © 2014 Ahmad Haider et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Testosterone deficiency leads to bone loss and testosterone treatment has a beneficial effect. This study investigated the effects of normalizing serum testosterone on bone mineral density in 45 men with osteoporosis, diagnosed with testosterone deficiency (serum testosterone levels < 12.1 nmol/L, *T*-scores: (mean ± SD)  $-3.12 \pm 0.45$ , minimum:  $-4.10$ , and maximum:  $-2.60$ ). In a cumulative, prospective, registry study of hypogonadal men (mean age:  $53 \pm 7$  years) they received parenteral testosterone undecanoate of 1000 mg/12 weeks for up to six years. After one year 44 men were included in the registry, after two years 36 men, after three years 32 men, after four years 25 men, after five years 10 men and after six years 4 men. The declining numbers do not reflect drop-out rates but are a result of the registry design. Over the 6 year period there was a significant and progressive improvement of the *T*-scores in these men. Normalizing of serum testosterone leads to an improvement of bone mineral density and this improvement was progressive with the time period of testosterone administration. In this study of 6-years many men with testosterone deficiency suffered from classical diagnoses (Klinefelter's syndrome and testicular pathology) hitherto undiagnosed.

## 1. Introduction

Osteoporosis remains underrecognized and undertreated, more so in men than in women, adding considerably to fracture burden and costs [1].

Though men suffer fewer fractures than women, fracture-related morbidity and mortality are higher in men than in women [2], partly due to greater frailty. Age-related changes in blood androgens and estrogens may contribute to the development or progression of frailty in men [3]. Men usually have higher bone mineral density which contributes to lower fracture incidence in men. Bioavailable androgens and

oestrogens regulate these aspects of musculoskeletal sexual dimorphism [4]. Numerous studies point to the significance of normal serum testosterone to maintain bone mineral density (BMD) at various stages of life [5]. Testosterone deficiency leads to loss of BMD and testosterone treatment has a beneficial effect [6]. This study investigated the effects of normalizing serum testosterone on BMD in 45 men with osteoporosis who had consulted an orthopedic surgeon and who were diagnosed as testosterone deficient.

Testosterone deficiency may not be an entity in itself but it may be part of another condition and other constituents of the disease might contribute to bone loss as well. Our

patients were suffering from a number of diseases, which, apart from the associated testosterone deficiency, could account for the loss of bone mineral density as well. These conditions included Klinefelter's syndrome, Crohn's disease, alcohol abuse, Hodgkin's lymphoma, kidney transplant, and undescended testis.

## 2. Subjects and Methods

The study was carried out in a Private Urology Practice, Bremerhaven, Germany, between the years 2004 and 2012. Patients had been referred to the Orthopedic Clinic for complaints of the locomotor system. This clinic routinely measures serum testosterone levels in patients with osteoporosis (defined by a *T*-score more than 2.5 standard deviations below the mean value for young adult reference data), especially when patients are young. If, indeed, subnormal serum testosterone levels are encountered, the patient is referred to the Urology Practice for assessment of the etiology of subnormal testosterone levels and possible administration of testosterone, provided there are no contraindications.

The cut-off level for below-normal serum testosterone was determined on the basis of the following considerations: although there is no international consensus as to the normal range of testosterone, clinical data suggest that the normal range of testosterone in adult men is between 12 and 40 nmol/L. A threshold of 12.1 nmol/L was confirmed by an international group of authors based on analyses of several well-known studies in which liquid chromatography tandem mass spectrometry had been used [7].

Men with Klinefelter's syndrome often have reduced bone mass [8, 9]. Remarkably, in one study the loss of bone mineral density in this group did not correlate with serum testosterone or with CAG repeats of the androgen receptor [10]. Muscle strength, previous history of testosterone treatment, age at diagnosis and bone markers were predictors of BMD, but testosterone was not [11]. So, positive effects of testosterone on BMD may be indirect by its well-known effects on muscle.

Men with Crohn's disease show reduced bone mass and bone formation [12]. T cell-mediated increased osteoclast formation from peripheral blood may be a factor [13]. Bone cells from patients with quiescent Crohn's disease show a reduced growth potential and an impeded maturation [14]. In a pilot study we have found a beneficial effect of testosterone on the clinical course of Crohn's disease. The mechanism of this improvement may be immunosuppressive effects of testosterone, reducing chronic inflammation of the intestinal wall in men with Crohn's disease [15].

Men with alcohol abuse may have a bone remodeling imbalance, with a predominant decrease in bone formation. In addition, recent studies have reported new mechanisms by which alcohol may act on bone remodeling, including osteocyte apoptosis, oxidative stress, and Wnt signaling pathway modulation [16].

A single patient had been treated for Hodgkin's lymphoma. Men who have been successfully treated for malignancies earlier in life may develop hypogonadism when they age (>50 year) [17].

Three patients had had a kidney transplant. Impaired renal function maybe associated with loss of BMD and lowered testosterone [18].

Seven patients had a history of undescended testis, most of them bilateral and some with unilateral orchiectomy or testicular atrophy. If not appropriately treated [19], this often leads to a loss of exocrine and endocrine testicular function.

The study was a cumulative, prospective, registry study of men (mean age:  $53.07 \pm 6.89$  years; minimum: 40; maximum: 68 years) with testosterone levels below 12.1 nmol/L. Their *T*-scores were (mean  $\pm$  SD)  $-3.12 \pm 0.45$  (minimum  $-4.10$  and maximum  $-2.60$ ). They received parenteral testosterone undecanoate of 1000 mg/12 weeks following an initial 6-week interval for up to six years. After six years, 44 men were included in the registry, after five years 36 men, after four years 32 men, after three years 25 men, after two years 10 men, and after one year 4 men. The declining numbers do not reflect drop-out rates but are a result of the registry design. New patients are consecutively entered once they have completed one year of treatment.

Exclusion criteria for testosterone administration included a previous diagnosis of primary or secondary hypogonadism, previous treatment with androgens, bone metastases, prostate cancer, prostate specific antigen (PSA) levels  $> 4$  ng/mL, International Prostate Symptom Score (IPSS)  $> 19$  points, a history of congestive heart failure or recent angina, history of cerebral vascular accident or untreated sleep apnoea.

All initial serum testosterone samples had been obtained between 7.00 and 11.00 h a.m. Serum testosterone levels were measured before testosterone administration, and then before the second injection at 6 weeks, subsequently before the next injection of testosterone undecanoate was due, as a rule; 12 weeks later. Serum testosterone was measured by commercially available chemiluminescent immunoassays.

BMD was measured by using a whole body dual-energy X-ray densitometer (Norland XR-800). All calculations were performed according to the instructions of the manufacturer and standardized procedures. The daily system quality assurance calibration procedures were strictly performed according to the instructions of the manufacturer using a QA Calibration Standard and a QC Spine Phantom. The accuracy of AP Spine Scans and Hip Scans was within 1.0% of industry standard. The *In vivo* Precision of AP Spine Scan is 0.84% (BMD L 2–4 CV). The *In vivo* Precision of Hip Scan is 1.4% (BMD Femoral Neck CV).

Bone mineral density is expressed in  $\text{g}/\text{cm}^2$ . The individual bone mineral density (BMD) variation was expressed as a *T*-score of measurements of the spine (L2–4) and femoral neck.

Not only was BMD assessed in this study but also the metabolic conditions were followed up. At each visit, body weight, waist circumference, body mass index, serum levels of total cholesterol, HDL, LDL, triglycerides, glucose, and hemoglobin A1c were measured after an overnight fast. Systolic and diastolic blood pressure were measured. C-reactive protein as an indicator of chronic inflammation was determined. The Aging Male Symptoms scale was measured

TABLE 1: Patient characteristics and gains in *T*-score upon testosterone treatment.

| No | Year of birth | Diagnosis                              | Initial testosterone nmol/L | Initial <i>T</i> -score | Months of testosterone | <i>T</i> -score |
|----|---------------|--|-----------------------------|-------------------------|------------------------|-----------------|
| 1  | 1950          | Alcohol abuse                          | 11.1                        | -3.1                    | 39                     | -2.1            |
| 2  | 1949          | Alcohol abuse                          | 12.1                        | -3.1                    | 57                     | -2.1            |
| 3  | 1951          | Alcohol abuse                          | 11.8                        | -3.9                    | 48                     | -3.1            |
| 4  | 1964          | Alcohol abuse                          | 7.6                         | -3.9                    | 39                     | -1.9            |
| 5  | 1955          | Alcohol abuse                          | 8.7                         | -2.9                    | 27                     | -2.1            |
| 6  | 1948          | Alcohol abuse                          | 8.3                         | -2.7                    | 48                     | -1.5            |
| 7  | 1962          | Klinefelter's syndrome                 | 9.7                         | -2.9                    | 75                     | -1.3            |
| 8  | 1952          | Klinefelter's syndrome                 | 7.6                         | -3.7                    | 75                     | -1.5            |
| 9  | 1969          | Klinefelter's syndrome                 | 8.3                         | -3.7                    | 15                     | -1.9            |
| 10 | 1967          | Klinefelter's syndrome                 | 10.1                        | -3.8                    | 12                     | -2.1            |
| 11 | 1961          | Klinefelter's syndrome                 | 10.1                        | -3.4                    | 12                     | -2.9            |
| 12 | 1959          | Klinefelter's syndrome                 | 10.7                        | -3.6                    | 15                     | -2.1            |
| 13 | 1963          | Klinefelter's syndrome                 | 9.4                         | -3.8                    | 15                     | -1.9            |
| 14 | 1963          | Klinefelter's syndrome                 | 9.0                         | -4.1                    | 15                     | -2.1            |
| 15 | 1959          | Klinefelter's syndrome                 | 7.3                         | -3.6                    | 12                     | -2.9            |
| 16 | 1967          | Klinefelter's syndrome                 | 8.3                         | -3.7                    | 12                     | -2.5            |
| 17 | 1971          | Klinefelter's syndrome                 | 10.7                        | -3.1                    | 9                      | -2.7            |
| 18 | 1952          | Klinefelter's syndrome                 | 10.1                        | -2.8                    | 57                     | -1.8            |
| 19 | 1955          | Klinefelter's syndrome                 | 11.1                        | -2.6                    | 54                     | -1.6            |
| 20 | 1959          | Klinefelter's syndrome                 | 8.0                         | -2.9                    | 54                     | -1.7            |
| 21 | 1955          | Klinefelter's syndrome                 | 10.7                        | -2.9                    | 51                     | -1.7            |
| 22 | 1961          | Klinefelter's syndrome                 | 11.1                        | -3.1                    | 45                     | -1.8            |
| 23 | 1957          | Klinefelter's syndrome                 | 8.3                         | -2.8                    | 57                     | -1.7            |
| 24 | 1965          | Klinefelter's syndrome                 | 11.1                        | -2.8                    | 36                     | -1.7            |
| 25 | 1950          | Klinefelter's syndrome                 | 8.7                         | -2.7                    | 63                     | -1.5            |
| 26 | 1965          | Klinefelter's syndrome                 | 10.7                        | -2.9                    | 39                     | -1.9            |
| 27 | 1965          | Klinefelter's syndrome                 | 11.4                        | -2.8                    | 39                     | -1.8            |
| 28 | 1951          | Klinefelter's syndrome                 | 10.1                        | -2.8                    | 51                     | -1.5            |
| 29 | 1949          | Crohn's disease                        | 7.3                         | -2.9                    | 54                     | -1.8            |
| 30 | 1949          | Crohn's disease                        | 7.3                         | -2.9                    | 51                     | -1.8            |
| 31 | 1947          | Crohn's disease                        | 6.6                         | -2.7                    | 63                     | -1.9            |
| 32 | 1950          | Crohn's disease                        | 10.7                        | -2.9                    | 57                     | -1.4            |
| 33 | 1959          | Crohn's disease/Klinefelter's syndrome | 7.3                         | -2.9                    | 33                     | -1.8            |
| 34 | 1946          | Primary hypogonadism                   | 8.3                         | -2.6                    | 60                     | -1.6            |
| 35 | 1962          | Primary hypogonadism                   | 9.7                         | -2.7                    | 30                     | -1.7            |
| 36 | 1951          | Primary hypogonadism                   | 10.1                        | -2.8                    | 54                     | -1.7            |
| 37 | 1949          | Primary hypogonadism                   | 7.6                         | -2.6                    | 60                     | -1.5            |
| 38 | 1950          | Primary hypogonadism                   | 7.3                         | -2.8                    | 57                     | -1.7            |
| 39 | 1960          | Primary hypogonadism                   | 7.3                         | -3.7                    | 36                     | -1.8            |
| 40 | 1938          | Primary hypogonadism                   | 8.7                         | -3.7                    | 75                     | -1.5            |
| 41 | 1952          | Primary hypogonadism                   | 11.1                        | -2.9                    | 24                     | -1.8            |
| 42 | 1950          | Primary hypogonadism                   | 12.1                        | -2.7                    | 60                     | -1.3            |
| 43 | 1939          | Primary hypogonadism                   | 11.8                        | -2.7                    | 57                     | -1.5            |
| 44 | 1941          | Renal insufficiency                    | 7.6                         | -2.9                    | 69                     | -1.2            |
| 45 | 1949          | Renal insufficiency                    | 8.7                         | -3.8                    | 72                     | -1.5            |

[20] and also the International Index of Erectile Function (erectile function domain) was assessed [21].

A number of safety parameters in relation to testosterone treatment were assessed: prostate volume, serum prostate specific antigen (PSA), residual bladder volume after voiding, the International Prostate Symptoms Score

(IPSS), hemoglobin and hematocrit values, and serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Ethical guidelines as formulated by the German "Ärztekammer" (the German Medical Association) for observational studies in patients receiving standard treatment

TABLE 2: Serum levels of testosterone over 72 months of testosterone treatment.

| Visit month testosterone | N  | Mean $\pm$ SD (nmol/L) | Minimum | Maximum |
|--------------------------|----|------------------------|---------|---------|
| 0 months                 | 45 | 9.35 $\pm$ 1.5         | 6.59    | 12.13   |
| 12 months                | 44 | 17.3 $\pm$ 2.66        | 13.52   | 23.92   |
| 24 months                | 36 | 17.23 $\pm$ 2.22       | 14.21   | 23.58   |
| 36 months                | 32 | 16.83 $\pm$ 1.91       | 13.52   | 20.46   |
| 48 months                | 25 | 17.28 $\pm$ 2.09       | 14.56   | 21.84   |
| 60 months                | 9  | 16.95 $\pm$ 1.87       | 14.21   | 19.76   |
| 72 months                | 4  | 14.91 $\pm$ 0.63       | 14.21   | 15.60   |

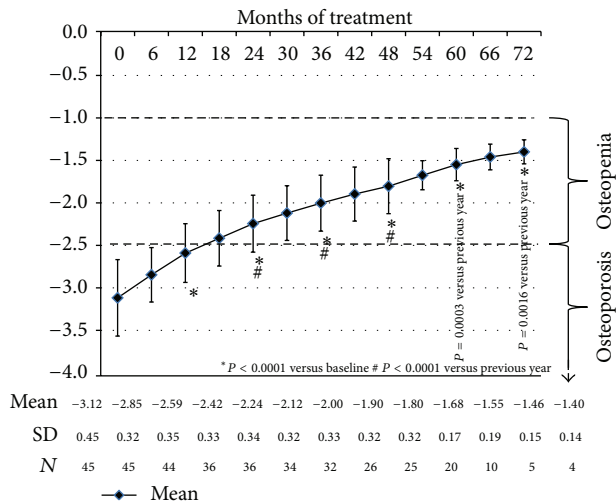


FIGURE 1: T-scores during testosterone administration.

were followed. All subjects consented to be included in the research of their treatment protocol which is in accordance with the Declaration of Helsinki <http://www.wma.net>. All procedures were carried out with the adequate understanding and written consent of the subjects.

**2.1. Statistical Analysis.** For continuous variables, the mean, median, standard deviation, range, minimum, maximum, and sample size for the overall sample and various groups were reported at each time point. For categorical variables the frequency distribution was reported. We tested the hypotheses regarding change in outcome scores across the study period by fitting a linear mixed effects model to the data. Time (to indicate follow-up interviews) was included as fixed effect in the model. A random effect was included in the model for the intercept. Estimation and test of change in scores were determined by computing the differences in least square means at baseline versus the score at each follow-up interview. Statistical significance was set at  $P < 0.05$ .

### 3. Results

Particulars of the 45 patients are presented in Table 1.

Serum testosterone levels rose significantly upon testosterone administration. Trough levels after 1 to 6 years were well above the cutoff for hypogonadal values (12.1 nmol/L), so the values were steady in a eugonadal range (Table 2).

TABLE 3: T-scores over 72 months of testosterone treatment.

| Visit month—T-Scores | N  | Mean $\pm$ SD    | Minimum | Maximum |
|----------------------|----|------------------|---------|---------|
| 0 month              | 45 | -3.12 $\pm$ 0.45 | -4.10   | -2.60   |
| 12 months            | 44 | -2.59 $\pm$ 0.35 | -3.80   | -2.10   |
| 24 months            | 36 | -2.24 $\pm$ 0.34 | -3.70   | -1.80   |
| 36 months            | 32 | -2 $\pm$ 0.32    | -3.50   | -1.70   |
| 48 months            | 25 | -1.8 $\pm$ 0.32  | -3.10   | -1.50   |
| 60 months            | 10 | -1.55 $\pm$ 0.19 | -1.90   | -1.30   |
| 72 months            | 4  | -1.4 $\pm$ 0.14  | -1.50   | -1.20   |

TABLE 4: Comparison of T-scores over periods of testosterone treatment.

| Comparison          | Difference $\pm$ SE | P-Value |
|---------------------|---------------------|---------|
| 12 Months—Baseline  | 0.53 $\pm$ 0.04     | <0.0001 |
| 24 Months—Baseline  | 0.85 $\pm$ 0.04     | <0.0001 |
| 36 Months—Baseline  | 1.13 $\pm$ 0.04     | <0.0001 |
| 48 Months—Baseline  | 1.34 $\pm$ 0.04     | <0.0001 |
| 60 Months—Baseline  | 1.58 $\pm$ 0.06     | <0.0001 |
| 24 Months—12 Months | 0.32 $\pm$ 0.04     | <0.0001 |
| 36 Months—24 Months | 0.28 $\pm$ 0.04     | <0.0001 |
| 48 Months—36 Months | 0.21 $\pm$ 0.05     | <0.0001 |
| 60 Months—48 Months | 0.24 $\pm$ 0.07     | 0.0003  |
| 72 Months—60 Months | 0.33 $\pm$ 0.1      | 0.0016  |

Over the 6-year period there was a significant improvement of the T-score in these men (Table 3).

The improvement was progressive: each year of testosterone treatment led to a significant further improvement of the T-scores (Table 4) to a state defined as osteopenia ( $-1$  to  $-2.49$  below the mean value for young adult reference data).

Figure 1 shows that over the 6 year period the T-scores of men improved and were no longer classified as osteoporosis but as osteopenia.

Table 4 compares T-scores over periods of testosterone treatment from 12 months to 72 months.

Metabolic parameters, blood pressure, and serum CRP showed an improvement over the study period, so did the AMS and IIEF-EF (Table 5).

Safety parameters were assessed (Table 6).

Prostate volume increased slightly but significantly while serum PSA did not change. Values of the IPSS and the residual bladder volume showed a decrease. Hemoglobin and



TABLE 5: Effects of testosterone on metabolic variables (means  $\pm$  SD).

|                           | Visit month     |                 |                 |                 |                 |                 |                 | Difference 60 months-baseline |
|---------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-------------------------------|
|                           | 0 month         | 12 months       | 24 months       | 36 months       | 48 months       | 60 months       | 72 months       |                               |
| N                         | 45              | 44              | 36              | 32              | 25              | 10              | 4               |                               |
| WC (cm)                   | 101.6 $\pm$ 6.4 | 100.1 $\pm$ 5.5 | 99.2 $\pm$ 4.9  | 98.4 $\pm$ 4.2  | 97.7 $\pm$ 4.3  | 97.7 $\pm$ 5.2  | 95.8 $\pm$ 4.4  | -6.3 $\pm$ 0.5 <sup>1</sup>   |
| Weight (kg)               | 97.1 $\pm$ 14.4 | 94.1 $\pm$ 13.3 | 92.2 $\pm$ 11.9 | 91.0 $\pm$ 10.7 | 86.6 $\pm$ 9.8  | 87.0 $\pm$ 10.2 | 86.8 $\pm$ 7.9  | -14.1 $\pm$ 1.1 <sup>1</sup>  |
| BMI                       | 29.9 $\pm$ 5.0  | 29.0 $\pm$ 4.7  | 28.7 $\pm$ 4.2  | 28.3 $\pm$ 3.8  | 27.0 $\pm$ 3.4  | 27.5 $\pm$ 4.1  | 27.7 $\pm$ 2.5  | -4.4 $\pm$ 0.3 <sup>1</sup>   |
| Fasting glucose (mg/dL)   | 5.47 $\pm$ 0.36 | 5.32 $\pm$ 0.36 | 5.35 $\pm$ 0.51 | 5.33 $\pm$ 0.32 | 5.34 $\pm$ 0.18 | 5.39 $\pm$ 0.13 | 5.36 $\pm$ 0.06 | -0.15 $\pm$ 0.11 <sup>2</sup> |
| Total cholesterol (mg/dL) | 248 $\pm$ 29    | 195 $\pm$ 21    | 185 $\pm$ 17    | 185 $\pm$ 14    | 183 $\pm$ 14    | 187 $\pm$ 12    | 193 $\pm$ 10    | -63 $\pm$ 5 <sup>1</sup>      |
| HDL (mg/dL)               | 50 $\pm$ 15     | 55 $\pm$ 15     | 58 $\pm$ 14     | 59 $\pm$ 15     | 57 $\pm$ 14     | 57 $\pm$ 17     | 60 $\pm$ 19     | 8 $\pm$ 1 <sup>1</sup>        |
| LDL (mg/dL)               | 159 $\pm$ 32    | 143 $\pm$ 29    | 131 $\pm$ 25    | 133 $\pm$ 24    | 132 $\pm$ 20    | 125 $\pm$ 28    | 122 $\pm$ 33    | -30 $\pm$ 3 <sup>1</sup>      |
| Triglycerides (mg/dL)     | 241 $\pm$ 32    | 195 $\pm$ 25    | 186 $\pm$ 18    | 184 $\pm$ 13    | 190 $\pm$ 14    | 188 $\pm$ 14    | 190 $\pm$ 10    | -55 $\pm$ 5 <sup>1</sup>      |
| Systolic BP (mm Hg)       | 136 $\pm$ 10    | 128 $\pm$ 9     | 126 $\pm$ 7     | 127 $\pm$ 7     | 128 $\pm$ 5     | 127 $\pm$ 3     | 126 $\pm$ 5     | -12 $\pm$ 2 <sup>1</sup>      |
| Diastolic BP (mm Hg)      | 83 $\pm$ 7      | 76 $\pm$ 5      | 74 $\pm$ 4      | 75 $\pm$ 4      | 74 $\pm$ 4      | 75 $\pm$ 3      | 71 $\pm$ 4      | -9 $\pm$ 1 <sup>1</sup>       |
| AMS                       | 47 $\pm$ 10     | 21 $\pm$ 3      | 18 $\pm$ 1      | 17 $\pm$ 1      | 17 $\pm$ 1      | 17 $\pm$ 1      | 18 $\pm$ 1      | -30 $\pm$ 1 <sup>1</sup>      |
| IIIEF-EF                  | 19.5 $\pm$ 5.1  | 23.0 $\pm$ 4.6  | 23.8 $\pm$ 5.1  | 23.8 $\pm$ 4.7  | 24.2 $\pm$ 4.5  | 26.6 $\pm$ 1.8  | 28.5 $\pm$ 0.6  | 4.8 $\pm$ 0.6 <sup>1</sup>    |
| N                         | 19              | 7               | 7               | 6               | 3               | 3               | 2               |                               |
| HbA1c (%)                 | 5.9 $\pm$ 1.3   | 6.5 $\pm$ 1.4   | 6.2 $\pm$ 1.0   | 5.8 $\pm$ 1.0   | 6.4 $\pm$ 0.5   | 6.1 $\pm$ 0.6   | 6.4 $\pm$ 0.8   | 1.4 $\pm$ 0.2 <sup>1</sup>    |
| N                         | 45              | 19              | 15              | 17              | 12              | 5               | 1               |                               |
| CRP (mg/L)                | 6.2 $\pm$ 7.6   | 3.7 $\pm$ 5.4   | 2.8 $\pm$ 3.7   | 4.2 $\pm$ 4.4   | 2.8 $\pm$ 2.9   | 1.7 $\pm$ 1.5   | 2.2             | -7.7 $\pm$ 1 <sup>1</sup>     |

<sup>1</sup>  $P < 0.0001$ .<sup>2</sup> Non significant.

WC: Waist Circumference.

BMI: Body Mass Index.

HDL: High Density Lipoprotein.

LDL: Low Density Lipoprotein.

BP: Blood Pressure.

AMS: Aging Male Symptoms Scale.

IIIEF-EF: International Index of Erectile Function.

HbA1c: Hemoglobin A1c.

CRP: C-reactive protein.

hematocrit rose but remained within normal limits. Serum ALT and AST decreased significantly.

#### 4. Discussion

In this study men with osteoporosis and lower-than-normal serum testosterone were treated with testosterone undecanoate whereupon serum testosterone levels normalized. Their copathologies varied strongly but testosterone deficiency was a common denominator. Other elements of their disease may have contributed to their bone loss as well. But in all men, an improvement of *T*-scores was found upon testosterone treatment with a significant progression over duration of the testosterone treatment. In fact, while all men had been in the category of osteoporosis at baseline, the mean *T*-scores improved to a level which is classified as osteopenia. Part of the positive effects may have been due to the positive effects of testosterone on muscle [22–24]. The increase of *T*-scores was impressive, amounting to 1.5 points. The calculated fracture risk reduction would be at least 50%. Several studies have documented the beneficial effects of testosterone administration on BMD in hypogonadal men [9, 25–31]. One study demonstrated that adequacy of testosterone is pivotal for the restoration of BMD in men [32]. Serum testosterone after administration of testosterone

undecanoate was well in the eugonadal range. It is now well documented in the literature that a chronic state of testosterone deficiency leads to a host of pathologies in (aging) men [33, 34]. These pathologies (metabolic syndrome, inflammatory factors, lower urinary tract symptoms, erectile dysfunction, and psychological functions) were also assessed in this study and showed improvements over the duration of the study (Table 5).

A significant part of the group studied were relatively young men, particularly the men with Klinefelter's syndrome. In a recent study it was reported that over one-third of men less than 50 years with testosterone deficiency and infertility or sexual dysfunction were found to have reduced BMD. These were no men with a classical condition of testosterone deficiency (Klinefelter's or Kallmann's syndrome etc.). Over a mean follow-up of 2.5 years testosterone therapy in this population increased BMD [35]. These findings argue for measurement of BMD in relatively young hypogonadal men.

We noted not only an improvement of *T*-scores in the men studied but also a progressive improvement of the metabolic status of the study subjects: body weight, BMI and waist circumference improved progressively which was also the case for lipids, blood pressure, hemoglobin A1c, and a parameter of inflammation. These improvements upon testosterone treatment have been reported from our clinic [36–38]. There was a progressive improvement of serum ALT

TABLE 6: Safety parameters of men receiving testosterone treatment (means  $\pm$  SD).

| Visit month                   | N  | Prostate volume (mL)       | N  | PSA (ng/dL)                  | N  | Residual volume (mL)           | N  | IPSS score                  | N  | Hemoglobin (g/L)            | N  | Hematocrit (%)             | N  | ALT (U/L)                    | N  | AST (U/L)                    |
|-------------------------------|----|----------------------------|----|------------------------------|----|--------------------------------|----|-----------------------------|----|-----------------------------|----|----------------------------|----|------------------------------|----|------------------------------|
| 0 month                       | 45 | 19.8 $\pm$ 7.4             | 45 | 0.96 $\pm$ 1.05              | 41 | 26.0 $\pm$ 17.0                | 45 | 3.1 $\pm$ 3.0               | 45 | 14.6 $\pm$ 0.6              | 45 | 44.4 $\pm$ 2.0             | 45 | 44.8 $\pm$ 21.7              | 45 | 43.7 $\pm$ 20.9              |
| 12 months                     | 16 | 21.9 $\pm$ 9.8             | 20 | 1.26 $\pm$ 1.00              | 39 | 18.7 $\pm$ 14.2                | 44 | 2.1 $\pm$ 2.1               | 44 | 14.9 $\pm$ 0.5              | 44 | 46.4 $\pm$ 2.2             | 44 | 29.6 $\pm$ 14.2              | 44 | 27.7 $\pm$ 12.6              |
| 24 months                     | 10 | 26.8 $\pm$ 10.6            | 17 | 1.45 $\pm$ 1.05              | 33 | 15.5 $\pm$ 10.6                | 35 | 1.9 $\pm$ 1.8               | 36 | 15.0 $\pm$ 0.4              | 36 | 47.7 $\pm$ 1.7             | 36 | 26.6 $\pm$ 11.9              | 36 | 26.8 $\pm$ 9.6               |
| 36 months                     | 12 | 26.9 $\pm$ 9.2             | 15 | 1.40 $\pm$ 1.12              | 29 | 14.7 $\pm$ 9.0                 | 32 | 1.8 $\pm$ 1.4               | 32 | 15.1 $\pm$ 0.4              | 32 | 48.4 $\pm$ 1.8             | 32 | 24.6 $\pm$ 8.4               | 32 | 25.6 $\pm$ 7.9               |
| 48 months                     | 8  | 29.3 $\pm$ 10.6            | 9  | 1.37 $\pm$ 1.19              | 22 | 13.0 $\pm$ 5.5                 | 25 | 1.4 $\pm$ 0.9               | 25 | 15.1 $\pm$ 0.4              | 25 | 48.4 $\pm$ 1.4             | 25 | 25.2 $\pm$ 5.6               | 25 | 25.4 $\pm$ 5.9               |
| 60 months                     | 3  | 27.7 $\pm$ 16.2            | 4  | 1.59 $\pm$ 1.20              | 10 | 13.5 $\pm$ 6.7                 | 10 | 1.8 $\pm$ 1.1               | 10 | 15.1 $\pm$ 0.4              | 10 | 48.0 $\pm$ 1.8             | 10 | 22.8 $\pm$ 5.2               | 10 | 22.4 $\pm$ 4.8               |
| 72 months                     | 3  | 24.3 $\pm$ 16.7            | 3  | 1.04 $\pm$ 1.21              | 4  | 12.5 $\pm$ 5.0                 | 4  | 1.8 $\pm$ 1.0               | 4  | 15.2 $\pm$ 0.3              | 4  | 49.0 $\pm$ 1.8             | 4  | 22.0 $\pm$ 3.5               | 4  | 21.0 $\pm$ 2.9               |
| Difference 60 months-baseline |    | 3.1 $\pm$ 0.5 <sup>1</sup> |    | 0.15 $\pm$ 0.09 <sup>2</sup> |    | -19.12 $\pm$ 2.23 <sup>1</sup> |    | -2.5 $\pm$ 0.4 <sup>1</sup> |    | 0.54 $\pm$ 0.1 <sup>1</sup> |    | 3.8 $\pm$ 0.4 <sup>1</sup> |    | -28.4 $\pm$ 2.5 <sup>1</sup> |    | -25.5 $\pm$ 2.3 <sup>1</sup> |

<sup>1</sup>P < 0.0001.<sup>2</sup>Non significant.

PSA: Prostate specific antigen.

IPSS: International prostate symptom score.

ALT: Alanine aminotransferase.

AST: Aspartate aminotransferase.

and AST probably indicating improvement of liver steatosis, as we have reported earlier [39]. Sexual function, as measured by International Index of Erectile Function, improved significantly over time as reported earlier [40, 41]. We noted also an improvement of the Aging Male Symptoms scale, also reported in other studies [31]. Earlier we have reported that there is a relation with parameters of inflammation such C-reactive protein [37].

Serious attention was paid to safety aspects of testosterone administration to men, for a part elderly, in this study. No malignancies occurred in the study population. We noted a slight increase in prostate volume over the study period, which also occurs in men not treated with testosterone, simply because they age [42, 43]. Serum PSA did not change significantly over the study period. Remarkably, residual volume in the bladder and scores of International Prostate Symptom Score improved considerably upon testosterone treatment, a positive effect earlier reported from this clinic [44]. As expected, hemoglobin levels and the hematocrit rose upon testosterone treatment but remained within safe limits as reported earlier [45]. There was no indication of a disturbance of liver function. The safety of testosterone administration to elderly men is now well documented in the literature [46].

One of the limitations of this study is the nature of the registry design. This single-center, open-label study is not a randomized controlled study and therefore limits the scope of interpretation of the presented findings. Simply, subjects were treated in a urology clinical setting. It is an observational study, not blinded, and not placebo-controlled. The study was not primarily designed to monitor the effects of normalizing serum testosterone in hypogonadal men on bone mineral density and was performed in a urology setting. We never expected to have such a large number of patients with osteoporosis, and, therefore, biomarkers of bone remodeling were not measured.

## 5. Conclusions

This study analyzed testosterone deficiency in a population of middle-aged to elderly men who were referred to an orthopedic clinic with complaints of the locomotor system and were diagnosed with osteoporosis. Their copathologies varied widely but a state of testosterone deficiency was a common denominator. In spite of the varieties of etiologies of their testosterone deficiency, they all benefited from testosterone treatment restoring their serum testosterone to the mid normal range of reference values. Osteoporosis improved to osteopenia. It would appear from our study that men attending an orthopedic clinic should be assessed for testosterone deficiency, first on clinical grounds whether they have copathology associated with testosterone deficiency, and second by confirmation of measurement of testosterone. In case of lower-than-normal serum testosterone, treatment with testosterone not only improved their bone mineral density but benefited also their metabolic state, mood and sexual functioning. Risks of testosterone administration to elderly men are acceptable and manageable.

## Conflict of Interests

A. Haider has received compensation for data entry for the present study from Bayer Pharma. G. Doros has received compensation for statistical analyses for the present study from Bayer Pharma. F. Saad is a full-time employee of Bayer Pharma.

## References

- [1] M. Laurent, E. Gielen, F. Claessens, S. Boonen, and D. Vanderschueren, "Osteoporosis in older men: recent advances in pathophysiology and treatment," *Best Practice & Research Clinical Endocrinology & Metabolism*, vol. 27, no. 4, pp. 527–539, 2013.
- [2] P. N. Kannegaard, S. van der Mark, P. Eiken, and B. Abrahamsen, "Excess mortality in men compared with women following a hip fracture. National analysis of comedications, comorbidity and survival," *Age and Ageing*, vol. 39, no. 2, pp. 203–209, 2010.
- [3] T. G. Travison, A.-H. Nguyen, V. Naganathan et al., "Changes in reproductive hormone concentrations predict the prevalence and progression of the frailty syndrome in older men: the concord health and ageing in men project," *The Journal of Clinical Endocrinology & Metabolism*, vol. 96, no. 8, pp. 2464–2474, 2011.
- [4] F. Callewaert, M. Sinnesael, E. Gielen, S. Boonen, and D. Vanderschueren, "Skeletal sexual dimorphism: relative contribution of sex steroids, GH-IGF1, and mechanical loading," *Journal of Endocrinology*, vol. 207, no. 2, pp. 127–134, 2010.
- [5] H. A. Fink, S. K. Ewing, K. E. Ensrud et al., "Association of testosterone and estradiol deficiency with osteoporosis and rapid bone loss in older men," *The Journal of Clinical Endocrinology & Metabolism*, vol. 91, no. 10, pp. 3908–3915, 2006.
- [6] S. P. Tuck and R. M. Francis, "Testosterone, bone and osteoporosis," *Frontiers of Hormone Research*, vol. 37, pp. 123–132, 2009.
- [7] S. Bhasin, M. Pencina, G. K. Jasuja et al., "Reference ranges for testosterone in men generated using liquid chromatography tandem mass spectrometry in a community-based sample of healthy nonobese young men in the framingham heart study and applied to three geographically distinct cohorts," *The Journal of Clinical Endocrinology & Metabolism*, vol. 96, no. 8, pp. 2430–2439, 2011.
- [8] E. Nieschlag, "Klinefelter syndrome: the commonest form of hypogonadism, but often overlooked or untreated," *Deutsches Ärzteblatt International*, vol. 110, no. 20, pp. 347–353, 2013.
- [9] D. G. Jo, H. S. Lee, Y. M. Joo, and J. T. Seo, "Effect of testosterone replacement therapy on bone mineral density in patients with Klinefelter syndrome," *Yonsei Medical Journal*, vol. 54, no. 6, pp. 1331–1335, 2013.
- [10] A. Ferlin, M. Schipilliti, C. Vinanzi et al., "Bone mass in subjects with Klinefelter syndrome: role of testosterone levels and androgen receptor gene CAG polymorphism," *The Journal of Clinical Endocrinology & Metabolism*, vol. 96, no. 4, pp. E739–E745, 2011.
- [11] A. Bojesen, N. Birkebæk, K. Kristensen et al., "Bone mineral density in Klinefelter syndrome is reduced and primarily determined by muscle strength and resorptive markers, but not directly by testosterone," *Osteoporosis International*, vol. 22, no. 5, pp. 1441–1450, 2011.
- [12] A. E. Oostlander, N. Bravenboer, E. Sohl et al., "Histomorphometric analysis reveals reduced bone mass and bone formation

- in patients with quiescent Crohn's disease," *Gastroenterology*, vol. 140, no. 1, pp. 116–123, 2011.
- [13] A. E. Oostlander, V. Everts, T. Schoenmaker et al., "T cell-mediated increased osteoclast formation from peripheral blood as a mechanism for Crohn's disease-associated bone loss," *Journal of Cellular Biochemistry*, vol. 113, no. 1, pp. 260–268, 2012.
  - [14] A. E. Oostlander, N. Bravenboer, H. W. van Essen et al., "Bone cells from patients with quiescent Crohn's disease show a reduced growth potential and an impeded maturation," *Journal of Cellular Biochemistry*, vol. 113, no. 7, pp. 2424–2431, 2012.
  - [15] A. Haider, W. Kurtz, E. J. Giltay, L. J. Gooren, and F. Saad, "Administration of testosterone to elderly hypogonadal men with Crohn's disease improves their Crohn's disease activity index: a pilot study," *Hormone Molecular Biology and Clinical Investigation*, vol. 2, no. 3, pp. 287–292, 2010.
  - [16] D. B. Maurel, N. Boisseau, C. L. Benhamou, and C. Jaffre, "Alcohol and bone: review of dose effects and mechanisms," *Osteoporosis International*, vol. 23, no. 1, pp. 1–16, 2012.
  - [17] C. E. Kiserud, A. Fosså, T. Bjørø, H. Holte, M. Cvancarova, and S. D. Fosså, "Gonadal function in male patients after treatment for malignant lymphomas, with emphasis on chemotherapy," *British Journal of Cancer*, vol. 100, no. 3, pp. 455–463, 2009.
  - [18] J. J. Carrero and P. Stenvinkel, "The vulnerable man: impact of testosterone deficiency on the uraemic phenotype," *Nephrology Dialysis Transplantation*, vol. 27, no. 11, pp. 4030–4041, 2012.
  - [19] E. Martin Ritzén, A. Bergh, R. Bjerknes et al., "Nordic consensus on treatment of undescended testes," *Acta Paediatrica*, vol. 96, no. 5, pp. 638–643, 2007.
  - [20] L. A. Heinemann, "Aging Males' Symptoms scale: a standardized instrument for the practice," *Journal of Endocrinological Investigation*, vol. 28, no. 11, pp. 34–38, 2005.
  - [21] R. C. Rosen, J. C. Cappelleri, and N. Gendrano III, "The International Index of Erectile Function (IIEF): a state-of-the-science review," *International Journal of Impotence Research*, vol. 14, no. 4, pp. 226–244, 2002.
  - [22] P. J. Snyder, H. Peachey, P. Hannoush et al., "Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age," *The Journal of Clinical Endocrinology & Metabolism*, vol. 84, no. 8, pp. 2647–2653, 1999.
  - [23] G. Caminiti, M. Volterrani, F. Iellamo et al., "Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure: a double-blind, placebo-controlled, randomized study," *Journal of the American College of Cardiology*, vol. 54, no. 10, pp. 919–927, 2009.
  - [24] A. A. Ferrando, M. Sheffield-Moore, C. W. Yeckel et al., "Testosterone administration to older men improves muscle function: molecular and physiological mechanisms," *American Journal of Physiology*, vol. 282, no. 3, pp. E601–E607, 2002.
  - [25] J. K. Amory, N. B. Watts, K. A. Easley et al., "Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone," *The Journal of Clinical Endocrinology & Metabolism*, vol. 89, no. 2, pp. 503–510, 2004.
  - [26] C. Wang, R. S. Swerdloff, A. Iranmanesh et al., "Effects of transdermal testosterone gel on bone turnover markers and bone mineral density in hypogonadal men," *Clinical Endocrinology*, vol. 54, no. 6, pp. 739–750, 2001.
  - [27] L. Katznelson, J. S. Finkelstein, D. A. Schoenfeld, D. I. Rosenthal, E. J. Anderson, and A. Klubanski, "Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism," *The Journal of Clinical Endocrinology & Metabolism*, vol. 81, no. 12, pp. 4358–4365, 1996.
  - [28] H. M. Behre, S. Kliesch, E. Leifke, T. M. Link, and E. Nieschlag, "Long-term effect of testosterone therapy on bone mineral density in hypogonadal men," *The Journal of Clinical Endocrinology & Metabolism*, vol. 82, no. 8, pp. 2386–2390, 1997.
  - [29] P. J. Snyder, H. Peachey, P. Hannoush et al., "Effect of testosterone treatment on bone mineral density in men over 65 years of age," *The Journal of Clinical Endocrinology & Metabolism*, vol. 84, no. 6, pp. 1966–1972, 1999.
  - [30] A. Aversa, R. Bruzziches, D. Francomano et al., "Effects of long-acting testosterone undecanoate on bone mineral density in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 36 months controlled study," *The Aging Male*, vol. 15, no. 2, pp. 96–102, 2012.
  - [31] J. Rodriguez-Tolra, J. Torremade, S. di Gregorio, L. del Rio, and E. Franco, "Effects of testosterone treatment on bone mineral density in men with testosterone deficiency syndrome," *Andrology*, vol. 1, no. 4, pp. 570–575, 2013.
  - [32] A. Aminorroaya, S. Kelleher, A. J. Conway, L. P. Ly, and D. J. Handelsman, "Adequacy of androgen replacement influences bone density response to testosterone in androgen-deficient men," *European Journal of Endocrinology*, vol. 152, no. 6, pp. 881–886, 2005.
  - [33] G. Corona, L. Vignozzi, A. Sforza, and M. Maggi, "Risks and benefits of late onset hypogonadism treatment: an expert opinion," *The World Journal of Men's Health*, vol. 31, no. 2, pp. 103–125, 2013.
  - [34] G. Corona, G. Rastrelli, and M. Maggi, "Diagnosis and treatment of late-onset hypogonadism: systematic review and meta-analysis of TRT outcomes," *Best Practice & Research Clinical Endocrinology & Metabolism*, vol. 27, no. 4, pp. 557–579, 2013.
  - [35] R. Kacker, W. Conners, J. Zade, and A. Morgentaler, "Bone mineral density and response to treatment in men less than fifty years with testosterone deficiency and sexual dysfunction or infertility," *The Journal of Urology*, 2013.
  - [36] F. Saad, L. J. Gooren, A. Haider, and A. Yassin, "A dose-response study of testosterone on sexual dysfunction and features of the metabolic syndrome using testosterone gel and parenteral testosterone undecanoate," *Journal of Andrology*, vol. 29, no. 1, pp. 102–105, 2008.
  - [37] E. J. Giltay, A. Haider, F. Saad, and L. J. Gooren, "C-reactive protein levels and ageing male symptoms in hypogonadal men treated with testosterone supplementation," *Andrologia*, vol. 40, no. 6, pp. 398–400, 2008.
  - [38] F. Saad, A. Haider, G. Doros, and A. Traish, "Long-term treatment of hypogonadal men with testosterone produces substantial and sustained weight loss," *Obesity*, vol. 21, no. 10, pp. 1975–1981, 2013.
  - [39] A. Haider, L. J. G. Gooren, P. Padungtod, and F. Saad, "Improvement of the metabolic syndrome and of non-alcoholic liver steatosis upon treatment of hypogonadal elderly men with parenteral testosterone undecanoate," *Experimental and Clinical Endocrinology & Diabetes*, vol. 118, no. 3, pp. 167–171, 2010.
  - [40] F. Saad, L. Gooren, A. Haider, and A. Yassin, "An exploratory study of the effects of 12 month administration of the novel long-acting testosterone undecanoate on measures of sexual function and the metabolic syndrome," *Archives of Andrology*, vol. 53, no. 6, pp. 353–357, 2007.



- [41] F. Saad, L. Gooren, A. Haider, and A. Yassin, "Effects of testosterone gel followed by parenteral testosterone undecanoate on sexual dysfunction and on features of the metabolic syndrome," *Andrologia*, vol. 40, no. 1, pp. 44–48, 2008.
- [42] S. J. Jacobsen, C. J. Girman, H. A. Guess, T. Rhodes, J. E. Oesterling, and M. M. Lieber, "Natural history of prostatism: longitudinal changes in voiding symptoms in community dwelling men," *The Journal of Urology*, vol. 155, no. 2, pp. 595–600, 1996.
- [43] J. B. Anderson, C. G. Roehrborn, J. A. Schalken, and M. Emberton, "The progression of benign prostatic hyperplasia: examining the evidence and determining the risk," *European Urology*, vol. 39, no. 4, pp. 390–399, 2001.
- [44] A. Haider, L. J. Gooren, P. Padungtod, and F. Saad, "Concurrent improvement of the metabolic syndrome and lower urinary tract symptoms upon normalisation of plasma testosterone levels in hypogonadal elderly men," *Andrologia*, vol. 41, no. 1, pp. 7–13, 2009.
- [45] A. Haider, L. J. G. Gooren, P. Padungtod, and F. Saad, "A safety study of administration of parenteral testosterone undecanoate to elderly men over minimally 24 months," *Andrologia*, vol. 42, no. 6, pp. 349–355, 2010.
- [46] A. Morgentaler, "Testosterone and prostate cancer: what are the risks for middle-aged men?" *Urologic Clinics of North America*, vol. 38, no. 2, pp. 119–124, 2011.

## Clinical Study

# Effects of Five-Year Treatment with Testosterone Undecanoate on Metabolic and Hormonal Parameters in Ageing Men with Metabolic Syndrome

**Davide Francomano, Andrea Lenzi, and Antonio Aversa**

*Department of Experimental Medicine, Medical Pathophysiology, Food Science and Endocrinology Section, Sapienza University of Rome, Viale Regina Elena 324, 00161 Rome, Italy*

Correspondence should be addressed to Antonio Aversa; [antonio.aversa@uniroma1.it](mailto:antonio.aversa@uniroma1.it)

Received 17 October 2013; Accepted 5 December 2013; Published 12 February 2014

Academic Editor: Roberto Bruzziches

Copyright © 2014 Davide Francomano et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Metabolic and hormonal modifications after long-term testosterone (T) treatment have never been investigated. 20 hypogonadal men (mean T = 241 ng/dL–8.3 nmol/L) with metabolic syndrome (MS, mean age 58) were treated with T-undecanoate injections every 12 weeks for 60 months. 20 matched subjects in whom T was unaccepted or contraindicated served as controls. Primary endpoints were variations from baseline of metabolic and hormonal parameters. In T-group, significant reductions in waist circumference ( $-9.6 \pm 3.8$  cm,  $P < 0.0001$ ), body weight ( $-15 \pm 2.8$  Kg,  $P < 0.0001$ ), and glycosylated hemoglobin ( $-1.6 \pm 0.5\%$ ,  $P < 0.0001$ ) occurred, along with improvements in insulin sensitivity (HOMA-I;  $-2.8 \pm 0.6$ ,  $P < 0.0001$ ), lipid profile (total/HDL-cholesterol ratio  $-2.9 \pm 1.5$ ,  $P < 0.0001$ ), systolic and diastolic blood pressure ( $-23 \pm 10$  and  $-16 \pm 8$  mm Hg,  $P < 0.0001$ , resp.), and neck and lumbar T-scores ( $+0.5 \pm 0.15$  gr/cm<sup>2</sup>,  $P < 0.0001$ ;  $+0.7 \pm 0.8$ ,  $P < 0.0001$ , resp.). Also, serum vitamin D ( $+14.0 \pm 1.3$  ng/mL,  $P < 0.01$ ), TSH ( $-0.9 \pm 0.3$  mUI/mL,  $P < 0.01$ ), GH ( $0.74 \pm 0.2$  ng/mL,  $P < 0.0001$ ), and IGF1 ( $105 \pm 11$  ng/mL,  $P < 0.01$ ) levels changed in T-group but not in controls. Normalization of T levels in men with MS improved obesity, glycemic control, blood pressure, lipid profile, and bone mineral density compared with controls. Amelioration in hormonal parameters, that is, vitamin D, growth hormone, and thyrotropin plasma levels, were reported.

## 1. Introduction

Obesity, and particularly visceral fat excess, is associated with insulin resistance, hyperglycemia, atherogenic dyslipidemia, and hypertension as well as prothrombotic and proinflammatory states and with vitamin D deficiency [1]. Several papers have suggested that a significant relationship between low levels of testosterone (T) and the metabolic syndrome (MS) exists [2]. Also, epidemiological studies have found that low T levels are a predictor of mortality in elderly men [3]. In addition, increasing evidence is accumulating regarding inverse associations between the severity of features of the MS and plasma T [4]. An inverse relationship between waist circumference (WC), a surrogate of visceral obesity, and T levels exists [5], thus leading to hyperinsulinism and reduced levels of sex hormone binding globulin (SHBG) and luteinizing hormone (LH), and all these factors along

with increased leptin contribute to the suppression testicular steroidogenesis [6]. Also, in centrally obese individuals, there is an overactivity of the corticotropin-releasing-hormone (CRH)—corticotropin (ACTH)—cortisol axis as speculated by pioneer work of Björntorp and coauthors who demonstrated that this increased activity may result in a suppression of the production of T and growth hormone (GH) [7].

The European male ageing (EMAS) study is the first epidemiological study suggesting an upper limit of 11 nmol/L (FT 220 pmol/L) as the one correct for treating testosterone deficiency syndrome (TDS) [8]. Despite the fact that in this study the reported prevalence of hypogonadism was low (17%), Corona et al. reported an incidence as high as 29.3% in obese men [9]. This can be explained by the fact that EMAS investigated a relatively healthy sample of the general population, whereas Corona assessed T levels in outpatients presenting with erectile dysfunction (ED). In fact,

T substitution in men with such values determines significant improvement in body composition, as reported in several studies [10, 11]. If this may be considered the threshold T level for the appearance of major symptoms like erectile dysfunction or decreased sexual desire, this may not be true for reverting body composition and mineral density changes induced by TDS. As previously demonstrated by other authors, the improvement in metabolic parameters may require achievement of higher and sustained therapeutic levels of testosterone over the time [12]. Moreover, evidence exists suggesting that T regulates adipogenesis and therefore increases lean body mass and reduces fat mass thus regulating body composition [13]. Long-term hormonal and anthropometric variations during T replacement therapy (TRT) in men with metabolic syndrome have not been investigated in controlled studies.

Aim of this study was to evaluate the effects of TRT on metabolic and hormonal parameters in hypogonadal men with MS.

## 2. Patients and Methods

**2.1. Inclusion, and Exclusion Criteria.** Forty patients, aged from 45 to 65 years, were enrolled into this prospective study. Patients were included in the study if they were between 45 and 65 years of age, had MS and/or type 2 diabetes mellitus (T2DM) defined by the International Diabetes Federation [14] and total serum T level below 320 ng/dL (11 nmol/L) or calculated free-T levels below 255 pmol/L (74 pg/mL) on two early morning separate days (between 8:00 and 11:00 a.m.) at least 1 week apart, and had at least two symptoms of hypogonadism. Patients were not included in the study in case of the following: use of TRT or anabolic steroids or any other hormone replacement therapy in the previous 12 months; history of prostate or breast cancer or other tumours; drug or alcohol abuse; blood coagulation alterations; symptomatic obstructive sleep-apnoea syndrome; haematocrit level  $\geq 52\%$  at baseline; age-adjusted elevated prostate-specific antigen (PSA) level or abnormal digital rectal examination (DRE) of prostate suspicious for cancer or severe symptomatic benign prostatic hyperplasia; an International Prostate Symptom Scale (IPSS)  $>13$  at baseline; use of 5- $\alpha$ -reductase inhibitors; presence of any uncontrolled endocrine disorder including diabetes (HbA1c  $\geq 9$ ); presence of New York Heart Association III or IV heart failure; hepatic insufficiency; severe neurological and psychiatric disease; and patients requiring or undergoing fertility treatment. We also excluded men who had diseases potentially affecting the skeleton, such as chronic renal disease or malabsorption, or were taking medications or drugs affecting bone turnover including any vitamin supplementation or nutraceuticals or more than three alcoholic drinks a day. All concomitant oral hypoglycemic, anti-hypertensive, and lipid-lowering medications were permitted if started within the previous 12 months and continued throughout the study without dose adjustments. Subjects were asked to maintain their usual physical exercise and lifestyle for the duration of the study. Written informed consent was obtained before commencement of the study

according to Protocol and Good Clinical Practice on the conducting and monitoring of clinical studies and approved by our University Ethical Committee.

**2.2. Primary Outcome Measures.** The primary outcomes were variation from baseline of the metabolic, bone, and hormonal parameters. At baseline, every three (within the first year) and six (in the following 4 years) months, the following evaluations were assessed: general physical examination and anthropometric parameters (i.e., body weight (BW), height, BMI, and waist circumference (WC)), systolic and diastolic blood pressure, heart rate, blood samples for biochemical and hormonal analyses, and digital rectal examination (DRE). Every twelve months, BMD was calculated by using a whole-body dual-energy X-ray absorptiometry (DEXA-HOLOGIC QDR-1000) according to the instructions of the manufacturer and standardized procedures, and the individual bone mineral density (BMD) variation has been measured with a T-score [15]. Calibration with the manufacturer's spine phantom and quality control analysis were performed daily. The long-term precision error *in vitro* was 0.54% (phantom); short-term precision error *in vivo* was 1.2% for the lumbar spine and 2% for the femoral neck [16]. BMD was expressed in grams per square centimeter ( $\text{g}/\text{cm}^2$ ) and result expressed as T-score.

Fasting blood samples were tested for glucose, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) at the hospital's clinical laboratories. Hormonal assessment included serum total T (TT) and LH, as measured by chemiluminescent microparticle immunoassay (CMIA, Architect System) (Abbott Laboratories, Abbott Park, IL, USA), with detection limit of 0.28 M, calculated free T (according to <http://www.issam.ch/>), sex hormone binding globulin (SHBG), estradiol, prolactin, thyroid stimulating hormone (TSH), growth hormone (GH), somatomedin-C (IGF1), insulin, and PSA were analyzed by immunometric assay based on chemiluminescence using an automated clinical chemistry analyzer (Immulite 2000, Diagnostic Product Corp., Los Angeles, CA, USA). To overcome seasonal variability, 25-hydroxy vitamin D (25OHD; ng/mL) was measured by chemiluminescent immunoassay always during the same season and each subject served as an internal control (ARUP Laboratory, Salt Lake City, UT; coefficient of variation (CV) 8.6–10.0%). HbA1c was measured by high performance liquid chromatography (Bio-Rad Laboratories, Hercules, CA, USA). To assess insulin sensitivity, we calculated the HOMA-I using the formula [fasting insulin in mU/L  $\times$  fasting glucose in mmol/L]/22.5.

**2.3. Modality of Treatment.** After screening any patient for the presence of hypogonadism, twenty of 72 patients met the inclusion/exclusion criteria and entered into the study. Patients received TU (TRT group) administered intramuscularly at a dose of 1000 mg every 6 weeks for the first two injections and then every 12 weeks, according to recommendations, for a period of 60 months. Twenty patients not

fulfilling inclusion/exclusion criteria or refusing TRT for personal reasons and preferring lifestyle changes as the primary treatment were observed throughout the time and served as controls. Due to severe overweight, most patients adhered to comply with a standard hypocaloric diet and slight changes in lifestyle that is, low/moderate walking at least three times per week. Each patient was assigned to a personalized nutritional program, consisting in a hypocaloric diet with a protein of 0.8–1 g/Kg of lean body weight, along with a personalized movement program, with recommendation of at least 60 minutes/week of aerobic exercise of low/moderate intensity (40% of maximum heart rate). Physical activity should have been distributed in at least 3 days/week, and there must be no more than 2 consecutive days without activity [17]. The patients were monitored for compliance with a personal diary indicating “yes” or “no” regarding the lifestyle changes prescriptions.

**2.4. Safety.** Safety parameters included DRE, PSA total and free, hemoglobin, hematocrit, liver, and kidney functions were monitored every three (within the first year) and six (in the following 4 years) months, respectively, according to previously published procedures [18].

Patients with the following clinical laboratory parameters were withdrawn either at the baseline or during the course of study: if hematocrits levels were >52%; PSA level increased >1.0 ng/mL above the baseline PSA if baseline PSA was <2.0 ng/mL; PSA levels increase >50% of the baseline PSA if baseline PSA was >2.0 ng/mL.

**2.5. Statistical Analyses.** Data were analyzed using *t*-tests (for single between-group comparisons), analysis of covariance (for between-group comparisons at specific time points, using baseline score as a covariate), and a mixed linear regression model on repeated measures data (for between-group comparisons across all time points) to analyze data for an Intent-to-Treat Group (including all subjects enrolled and treated in this trial with values imputed for their Last Observation Carried Forward (LOCF) for any subjects who did not complete the trial) and a Completer's Group (including only data from subjects who completed the trial per protocol). Data were expressed as means  $\pm$  standard deviation when normally distributed, and as median (quartiles) when non-parametric. A *P* value < 0.05 was taken as statistically significant. Statistical analysis was performed using the computer statistical package SPSS 11.0 (SPSS Inc., Chicago, IL, USA).

### 3. Results

**3.1. Metabolic and Hormonal Parameters.** Demographic characteristics of the patients at baseline are shown in Table 1.

All patients included were hypogonadal because of metabolic disturbances, that is, metabolic syndrome and/or diabetes, and none had primary/secondary hypogonadism with alteration of gonadotropins (data not shown). As expected, at the end of the study, the values of TT were higher in the TRT compared to the control group ( $+9.1 \pm 1.7$  nmol/L,

TABLE 1: Demographic characteristics of patients at baseline.

|  | Control ( <i>n</i> = 20) | Treatment ( <i>n</i> = 20) |
|--|--------------------------|----------------------------|
| Age (years)                            | 57 $\pm$ 8               | 58 $\pm$ 10                |
| BMI (kg/m <sup>2</sup> )               | 31 $\pm$ 6               | 31 $\pm$ 5                 |
| Only metabolic syndrome ( <i>n</i> /%) | 14 (70%)                 | 14 (70%)                   |
| MetS + type 2 diabetes ( <i>n</i> /%)  | 6 (30%)                  | 6 (30%)                    |
| Smokers ( <i>n</i> /%)                 | 4 (20%)                  | 4 (20%)                    |
| Treatments                             |                          |                            |
| None ( <i>n</i> /%)                    | 8 (40%)                  | 6 (30%)                    |
| Metformin ( <i>n</i> /%)               | 8 (40%)                  | 8 (40%)                    |
| Antihypertensives ( <i>n</i> /%)       | 12 (60%)                 | 8 (40%)                    |
| Statins ( <i>n</i> /%)                 | 4 (20%)                  | 5 (25%)                    |
| Fibrates ( <i>n</i> /%)                | 0 (0%)                   | 2 (10%)                    |
| Other ( <i>n</i> /%)                   | 4 (20%)                  | 5 (25%)                    |

*P* < 0.0001) while estradiol levels showed a trend to increase (Table 2).

At LOCF, only TRT group showed a significant reduction of BMI ( $-2.9 \pm 1.4$ , *P* < 0.0001); also, WC ( $-9.6 \pm 3.8$  cm, *P* < 0.0001; Figure 1(a)) and body weight ( $-15 \pm 2.8$  Kg, *P* < 0.0001; Figure 1(b)) significantly decreased in all men (100%) treated with TU compared with controls, who displayed a trend to increase both parameters over the time. This was mainly due to major compliance of TRT group towards diet and physical exercise compared with controls (90% versus 10% of overall patients, *P* < 0.0001, data not shown). There was a significant reduction of blood glucose as evaluated by mean HbA1c levels during the 60 months study follow-up period ( $-1.6 \pm 0.5\%$ , *P* < 0.001; Figure 1(c)) for the TRT group only.

In this latter group, significant reduction in insulin sensitivity as evaluated by HOMA-i ( $-2.8 \pm 0.6$ , *P* < 0.0001) and lipid profile (total/HDL-cholesterol:  $-2.9 \pm 1.5$ , *P* < 0.0001; and Triglycerides:  $-41 \pm 25$ , *P* < 0.0001) was found. Also only TRT group showed a significant reduction in both systolic ( $-23 \pm 10$  mm Hg, *P* < 0.0001; Figure 2(a)) and diastolic ( $-16 \pm 8$  mm Hg, *P* < 0.001; Figure 2(b)) blood pressure, heart rate ( $-15 \pm 5$  bpm, *P* < 0.001; Table 2) and a significant increment in neck and lumbar *T*-scores ( $+0.5 \pm 0.15$  gr/cm<sup>3</sup>, *P* < 0.0001;  $+0.7 \pm 0.8$  gr/cm<sup>3</sup>, *P* < 0.0001, resp.).

Interestingly, serum vitamin D ( $+14.0 \pm 1.3$  ng/mL, *P* < 0.01), TSH ( $-0.9 \pm 0.3$  mUI/mL, *P* < 0.01), GH ( $+0.74 \pm 0.2$ , *P* < 0.0001), and IGF1 ( $+105 \pm 11$ , *P* < 0.01) levels changed in TRT group only (Table 2).

**3.2. Safety.** A significant increase in hematocrit ( $+2.8 \pm 0.9\%$ , *P* < 0.001) and PSA levels ( $+0.37 \pm 0.29$  ng/mL, *P* < 0.01) within the normal reference range values was found in TRT group only without any clinical symptom or worsening in voiding function [19]. This increase occurred within the first 12 months of treatment and remained stable throughout the remaining period of study (Table 2).



TABLE 2: Effects of five-year testosterone undecanoate treatment on anthropometric and hormonal parameters in 40 hypogonadal men with metabolic syndrome. *P* variations were evaluated yearly in the testosterone treatment (TRT) versus controls (CTRL).

|                          | Baseline    |            |          | 12 months   |             |          | 24 months  |            |          | 36 months  |            |          | 48 months  |            |          | 60 months  |            |          |
|--------------------------|-------------|------------|----------|-------------|-------------|----------|------------|------------|----------|------------|------------|----------|------------|------------|----------|------------|------------|----------|
|                          | CTRL        | TRT        | <i>P</i> | CTRL        | TRT         | <i>P</i> | CTRL       | TRT        | <i>P</i> | CTRL       | TRT        | <i>P</i> | CTRL       | TRT        | <i>P</i> | CTRL       | TRT        | <i>P</i> |
| Tot-Chol./HDL-Chol.      | 4.9 ± 3.8   | 5 ± 3.5    | ns       | 5.6 ± 2.7   | 2.7 ± 2.3   | 0.001    | 5.2 ± 2.8  | 2.3 ± 2.1  | 0.0001   | 5.1 ± 2.4  | 2.4 ± 2.2  | 0.0001   | 5.5 ± 2.0  | 2.17 ± 2.0 | 0.0001   | 4.8 ± 2.3  | 2.1 ± 1.5  | 0.0001   |
| Trigl. (mg/dL)           | 187 ± 28    | 196 ± 31   | ns       | 193 ± 21    | 167 ± 21    | 0.001    | 197 ± 24   | 172 ± 22   | 0.0001   | 181 ± 25   | 151 ± 21   | 0.0001   | 189 ± 23   | 147 ± 19   | 0.0001   | 182 ± 23   | 155 ± 19   | 0.0001   |
| Heart rate (bpm)         | 89 ± 10     | 87 ± 10    | ns       | 87 ± 9      | 82 ± 8      | 0.001    | 88 ± 9     | 78 ± 7     | 0.001    | 88 ± 7     | 76 ± 5     | 0.0001   | 87 ± 2     | 75 ± 5     | 0.001    | 88 ± 9     | 72 ± 5     | 0.001    |
| BMI (Kg/m <sup>2</sup> ) | 31 ± 6      | 30.5 ± 5.5 | ns       | 29.9 ± 6    | 28.2 ± 3.1  | ns       | 30 ± 5.5   | 27.5 ± 3.3 | ns       | 30 ± 4.4   | 27.3 ± 3.9 | ns       | 29.2 ± 4.4 | 27.9 ± 4.2 | ns       | 30 ± 4.4   | 27.6 ± 4.1 | ns       |
| HOMA-1                   | 4.25 ± 0.3  | 4.2 ± 0.3  | ns       | 4.05 ± 0.3  | 2.1 ± 0.3   | 0.0001   | 3.65 ± 0.5 | 2.13 ± 0.4 | 0.0001   | 3.35 ± 0.4 | 1.7 ± 0.6  | 0.0001   | 3.35 ± 0.7 | 1.6 ± 0.6  | 0.0001   | 3.15 ± 0.6 | 1.4 ± 0.6  | 0.0001   |
| VIT D (ng/mL)            | 18.4 ± 9.9  | 15.1 ± 8.6 | ns       | 17.8 ± 9.7  | 25.3 ± 6.4  | 0.01     | 20.7 ± 8.1 | 26 ± 5.2   | 0.01     | 17 ± 7.8   | 28.5 ± 6.5 | 0.01     | 18 ± 6.7   | 30.3 ± 7.4 | 0.01     | 16.8 ± 8.1 | 29.1 ± 7.3 | 0.01     |
| Total T (nmol/L)         | 9 ± 1.7     | 8.3 ± 2.4  | ns       | 9.35 ± 1.4  | 15.9 ± 1.4  | 0.0001   | 8.6 ± 1.2  | 16.8 ± 1.7 | 0.0001   | 7.9 ± 0.8  | 17.6 ± 1.5 | 0.0001   | 8.1 ± 1.6  | 16.9 ± 1.7 | 0.0001   | 8.7 ± 1.4  | 17.4 ± 1.7 | 0.0001   |
| SHBG (nmol/L)            | 34 ± 10     | 30 ± 13    | ns       | 35 ± 13     | 31 ± 11     | ns       | 31 ± 12    | 29 ± 9     | ns       | 36 ± 11    | 28 ± 10    | ns       | 34 ± 14    | 28 ± 9     | ns       | 35 ± 12    | 28 ± 8     | ns       |
| Estradiol (pg/mL)        | 30 ± 9      | 26.5 ± 11  | ns       | 29 ± 6      | 32 ± 11.5   | ns       | 26 ± 7     | 31.5 ± 10  | ns       | 28 ± 8     | 29.5 ± 9   | ns       | 29 ± 7     | 32.5 ± 10  | ns       | 34 ± 7     | 32.5 ± 10  | ns       |
| TSH (mIU/mL)             | 1.7 ± 0.3   | 2 ± 0.8    | ns       | 1.9 ± 0.4   | 1.1 ± 0.5   | 0.01     | 2 ± 0.3    | 1.1 ± 0.4  | 0.01     | 2.2 ± 0.2  | 1.3 ± 0.3  | 0.01     | 1.9 ± 0.2  | 1.0 ± 0.4  | 0.01     | 2.5 ± 0.5  | 1.1 ± 0.3  | 0.01     |
| GH (ng/mL)               | 0.20 ± 0.1  | 0.31 ± 0.3 | ns       | 0.25 ± 0.1  | 0.95 ± 0.2  | 0.0001   | 0.25 ± 0.1 | 0.98 ± 0.1 | 0.0001   | 0.32 ± 0.1 | 1.0 ± 0.1  | 0.0001   | 0.4 ± 0.2  | 1.12 ± 0.2 | 0.0001   | 0.22 ± 0.1 | 1.05 ± 0.2 | 0.0001   |
| IGF1 (ng/mL)             | 180 ± 43    | 157 ± 31   | ns       | 188 ± 23    | 215 ± 22    | 0.01     | 189 ± 35   | 252 ± 23   | 0.01     | 195 ± 35   | 241 ± 27   | 0.01     | 140 ± 6    | 251 ± 18   | 0.01     | 177.5 ± 7  | 262 ± 20   | 0.01     |
| Tot. PSA (ng/mL)         | 0.98 ± 0.25 | 1.05 ± 0.2 | ns       | 1.05 ± 0.27 | 1.36 ± 0.31 | 0.01     | 1.03 ± 0.2 | 1.35 ± 0.2 | 0.01     | 1.0 ± 0.2  | 1.34 ± 0.3 | 0.01     | 1.02 ± 0.2 | 1.37 ± 0.2 | 0.01     | 1.04 ± 0.2 | 1.42 ± 0.3 | 0.01     |
| HCT (%)                  | 42.5 ± 0.3  | 43.8 ± 0.2 | ns       | 41.9 ± 0.2  | 46.1 ± 0.8  | 0.001    | 41.8 ± 0.3 | 46.1 ± 0.7 | 0.001    | 43 ± 0.3   | 46.4 ± 0.6 | 0.001    | 41.1 ± 0.7 | 46.5 ± 0.6 | 0.001    | 43.5 ± 0.3 | 46.6 ± 0.9 | 0.001    |
| Lumbar T-score (SD)      | -1.6 ± 0.8  | -1.6 ± 0.9 | ns       | -1.6 ± 0.7  | -1.4 ± 0.8  | 0.05     | -1.7 ± 0.6 | -1.2 ± 0.8 | 0.005    | -1.7 ± 0.8 | -1.0 ± 0.8 | 0.0001   | -1.9 ± 0.6 | -1.1 ± 0.9 | 0.0001   | -1.8 ± 0.7 | -0.9 ± 0.8 | 0.0001   |
| Neck T-score (SD)        | -0.9 ± 0.8  | -0.9 ± 0.8 | ns       | -0.9 ± 0.7  | -0.7 ± 0.7  | 0.05     | -0.9 ± 0.7 | -0.6 ± 0.7 | 0.005    | -1 ± 0.8   | -0.5 ± 0.7 | 0.0001   | -1.1 ± 0.7 | -0.4 ± 0.7 | 0.0001   | -1.3 ± 0.7 | -0.4 ± 0.6 | 0.0001   |

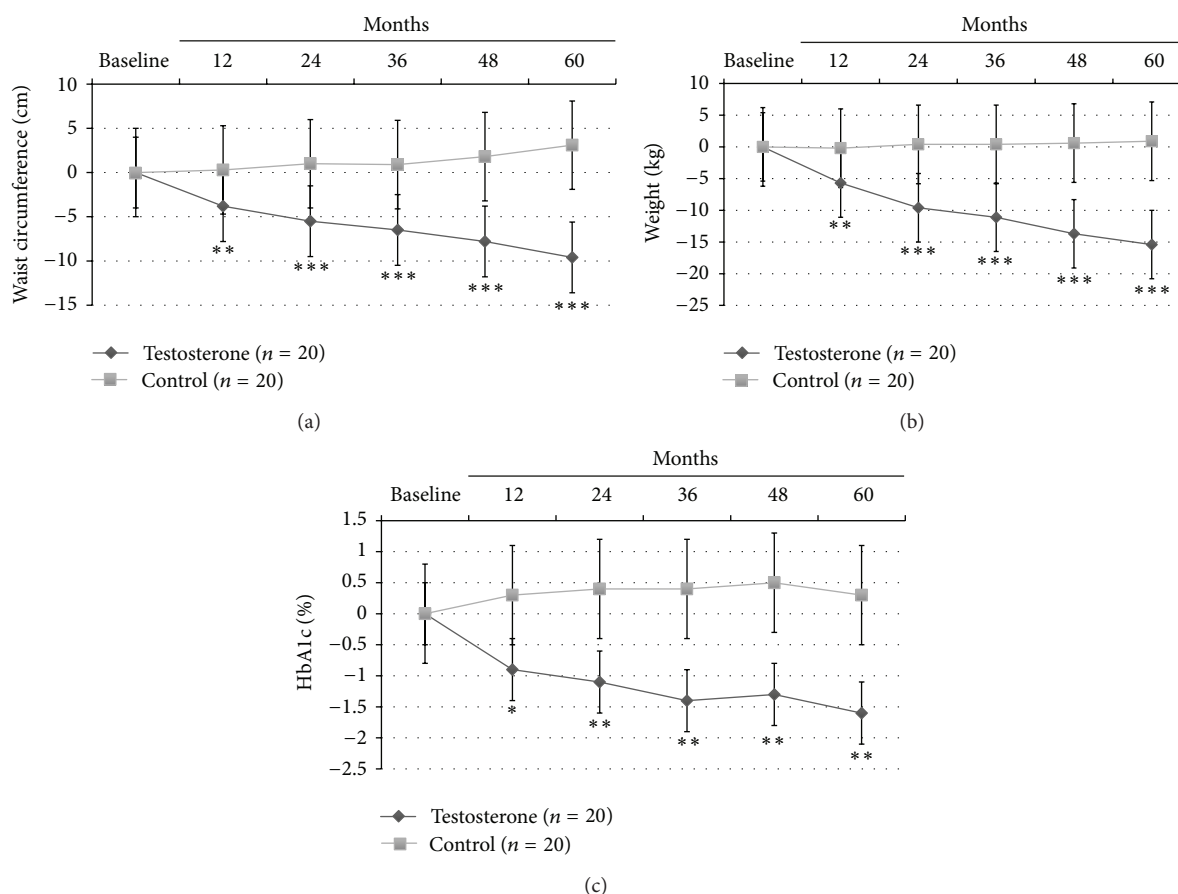


FIGURE 1: Effects of 5-year treatment with long-acting TU on (a) waist circumference (cm), (b) body weight (Kg), and (c) glucose homeostasis (HbA1c) in 40 hypogonadal men ( $T < 11$  nmol/L) with metabolic syndrome (IDF). *P* variations were evaluated yearly in the testosterone treatment (TRT) versus controls (CTRL).

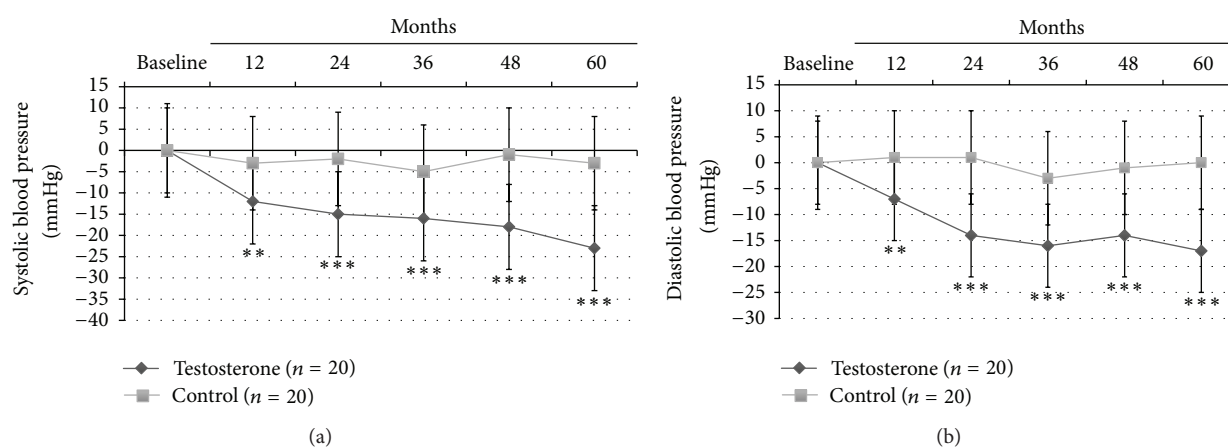


FIGURE 2: Effects of 5-year treatment with long-acting TU on (a) systolic blood pressure (mm Hg) and (b) diastolic blood pressure (mm Hg) in 40 hypogonadal men ( $T < 11$  nmol/L) with metabolic syndrome (IDF). *P* variations were evaluated yearly in the testosterone treatment (TRT) versus controls (CTRL).

#### 4. Discussion

This is the first long-term controlled, nonsponsored study with T-undecanoate (TU) for a 60-month period in hypogonadal men with MS. Anthropometric, hormonal,

and body composition parameters were investigated. Our results clearly demonstrate that TU is able to improve anthropometric measurements in a stepwise yearly manner, that is, WC and total BW; not surprisingly, a significant reduction in blood pressure and heart rate was reported

compared to controls. Also, hormonal panel including vitamin D, TSH, GH, and IGF1 circulating levels all improved and these hormonal changes were not described elsewhere in such a population. No serious adverse event related to TU treatment was reported over the time.

Several recent studies have focused on normalizing T levels by using TU injections in obese hypogonadal men with TDS. Saad et al. investigated the effects of TU injection in 110 elderly men with obesity and MS and demonstrated that age, BMI, and C-reactive protein (CRP) levels, in addition to hypogonadism, can be used clinically to predict which men mostly benefit from T supplementation with regard to components of the MS [20]. Aversa et al. demonstrated that three-years TU in middle-aged men with TDS and MS determined a significant increase in both vertebral and femoral BMD that was correlated with the increments in serum T levels, probably independently from estradiol modifications and this was mainly related to CRP reduction [21]. In another study, Saad et al. demonstrated that TU treatment of 255 hypogonadal men determined a weight loss in approximately 95% of all patients, with marked changes in body composition, that is, an increase in lean body mass and a decrease in fat mass [22]. Yassin and Doros confirmed same results in a registry study of 261 hypogonadal men [23]. In all reported studies to date, T treatment consistently showed decreased fat and increased lean body masses. Similarly, Traish et al. reported significant changes in MS components during TRT at physiological levels [24]. Even if obtained in uncontrolled studies, these findings suggest that T may be a physiological modulator of body composition due to its role in promoting myogenesis and inhibiting adipogenesis and its role in carbohydrate, lipid, and protein metabolism. Data obtained in the present controlled study are confirmative of the evidence previously reported in uncontrolled studies that features of the MS present in elderly men must not be a limiting factor in prescribing TU in view of its advantages on metabolic, bone, and hormonal ameliorations as well as on overall improvements in estimated cardiovascular disease (CVD) risk.

T is a well-known regulator of many metabolic functions in liver, adipose tissue, muscles, coronary arteries, and the heart. The TC/HDL-C ratio is another important marker of CVD risk and its modification during treatment may indicate major changes in metabolic function that is, improvement in insulin resistance and decreased ischemic heart disease risk [25]. It is thought that it may represent a better marker than the apoB/apoA1 ratio for identifying insulin resistance and MS in some populations [26]. A recent study demonstrated that patients with peripheral artery disease treated with atorvastatin showed improvement in endothelial function and this was associated with decreased TC/HDL-C ratio, suggesting that this ratio may be related to endothelial damage [27]. The improvement of endothelial function may be the basis for the reduction of blood pressure and heart rate found in the present study. In fact, in previous report from our group we demonstrated that one-year TU is able to improve arterial stiffness and endothelial function in morbidly obese men (unpublished data), thus confirming that a sustained and advantageous effect of TRT on cardiovascular function

is present in men with MS, thus leading to reduced CV risk throughout the time. The present data confirm, in a controlled study, that long-term TU reduces the risk of CVD in men with MS as previously described in observational studies [28].

Morbidly obese patients have been reported to often present with vitamin D insufficiency and secondary hyperparathyroidism. In obese women who undergo weight loss therapy, an abnormal vitamin D metabolism is still reported after 5-year follow-up [29]; similarly, bariatric surgery does not completely revert preexisting vitamin D deficient states and secondary hyperparathyroidism [30]. The reduction in WC and BW during weight loss program appear to be a common finding in the obese population following controlled weight loss programs; however, in our obese hypogonadal male patients (with MS), the finding of persistent and sustained yearly weight loss over the time was very surprising when compared with control group in whom no modification occurred despite the fact that slight lifestyle changes were recommended to both groups. Hagenfeldt et al. firstly described the improvement in vitamin D plasma levels after TRT in a small group of men with Klinefelter's syndrome through a possible, indirect action of increased estradiol circulating levels due to aromatization [31]. Other authors have speculated that, in normal conditions, Leydig cell may contribute to the 25-hydroxylation of vitamin D through the CYP2R1 enzyme that catalyzes the hydroxylation of cholecalciferol to 25-hydroxyvitamin D [32]. This enzyme is in turn regulated by insulin-like 3 (INSL3), which has also a role in osteoblast function, through an LH-T related mechanism. Testicular dysfunction determines reduced T levels, along with low INSL3 and 25-hydroxyvitamin D levels, and consequently may lead to an increased risk of osteopenia and osteoporosis. In our patients a mild osteopenia was present, and improvements in bone mineral density were reported despite no modification in estradiol levels. We speculate that the increase in vitamin D obtained by our patients may be partly due to T-induced overall trunk fat mass reduction, since in cross-sectional studies we had previously demonstrated a close relationship between trunk fat mass, vitamin D, osteocalcin, and testosterone levels in obese men [1]. Also, a direct effect of testosterone on renal expression of the 1- $\alpha$ -hydroxylase gene might be possible, as androgen receptors have been demonstrated in kidney tissue [33].

On the other hand, other hormones or regulatory factors could mediate the effect on vitamin D indirectly. GH and IGF-I have been reported to influence vitamin D metabolism both in animals and in humans [34]. Previous studies demonstrated that increasing serum T concentrations to the mid-normal range with low-dose T administration for 26 weeks increases nocturnal, spontaneous, pulsatile GH secretion, and morning IGF-I concentrations in healthy older men, supporting the hypothesis that age-related reductions in T may contribute to the concurrent "somatopause" [35]. Accordingly, in the present study, the stimulatory effects obtained after TRT on GH secretion may be interpreted as an indirect effect due to the activation of lipolytic cascade of adipocytes leading to a better insulin sensitization, reduction of abdominal fat, and amelioration of pituitary

function. Several reports in the literature consider obesity as a sort of “panhypopituitarism” condition determining a multiendocrine dysfunction. It is well established that caloric restriction applied for a relatively short term usually is able to increase GH release significantly in normal weight subjects [36]; however, this release results significantly reduced in obese subjects, who exhibit large diet-induced weight losses [37]. The recovery of the GH/IGF-I axis after weight loss suggests an acquired defect, rather than a preexisting pituitary disorder. Noteworthy, in our control group, we hypothesize that the persistent impairment of endocrine axes, that is, GH/IGF-I might have acted toward expansion and maintenance of fat mass and have contributed to perpetuation of the obese state.

Few studies have investigated the effects of controlled weight loss on thyroid hormone axis in male obese subjects. Cross-sectional studies have demonstrated that T3 and TSH correlate positively with adiposity [38]. In a recent study, moderate weight loss intervention resulted in a significant decrease in circulating T3 and only a marginal decrease in TSH and in fT4 [39]. Altogether, these observations indicate that even a moderate weight loss intervention may generate some perturbation in this axis. Our data obtained in TRT group clearly show that the stepwise decrease in fat mass, anthropometric and blood pressure parameters throughout the time may be considered an important factor also impacting on thyroid homeostasis. The fact that these changes were not observed in the control group is in keeping with the failure in achieving a correct weight (and abdominal fat) loss.

A limitation of the study represented by the low number of subjects investigated. We understand that it is difficult to rely on overall changes occurring in a small cohort of patients, but we are aware of the fact that this is a spontaneous, unsponsored study not designed to specifically investigate the effects of T on metabolic and hormonal pattern; thus patients were followed up for their specific comorbidities. Another limitation of this study was that a limited number of plasma hormones was investigated; thus PTH, gonadotropins, osteocalcin, and free fraction of thyroid hormones were not measured in all patients, in part because of financial constraints.

The marked weight loss observed in hypogonadal men with MS replaced with TU is an important finding of the present study and is in agreement with previous *in vitro* studies where T regulates lineage of mesenchymal pluripotent cells by promoting the myogenic lineage and inhibiting the adipogenic lineage [40]. T also inhibits triglyceride uptake and lipoprotein lipase activity resulting in rapid turnover of triglycerides in the subcutaneous abdominal adipose tissue and mobilizes lipids from the visceral fat depot [41]. Thus, T-induced changes on metabolism and body composition might have been determined by increased motivation, enhancement of mood, and promotion of more energy expenditure; this in turn might be responsible of the multiple endocrine modifications occurred on pituitary function. The changes in vitamin D levels and hormonal status (GH, IGF1, and TSH) are likely to be explained by the reduction of trunk fat mass content. By contrast, in control

groups all these changes were not present despite the fact that lifestyle changes were applied.

In conclusion, this study demonstrates that TU in hypogonadal men with MS has favorable effect on body composition and metabolic parameters, after five-years replacement. The present study also provides first evidence that remarkable reduction of blood pressure and heart rate, as well as amelioration of vitamin D, GH/IGF1, and TSH plasma levels, are also attained. This may in turn yield to different overall CVD estimated risk and overall survival rates as well as to different pharmacological management of T2DM, hypertension, and dyslipidemia in men with MS and obesity.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

## References

- [1] S. Migliaccio, D. Francomano, R. Bruzziches et al., “Trunk fat negatively influences skeletal and testicular functions in obese men: clinical implications for the aging male,” *International Journal of Endocrinology*, vol. 2013, Article ID 182753, 6 pages, 2013.
- [2] G. Corona, G. Forti, and M. Maggi, “Why can patients with erectile dysfunction be considered lucky? the association with testosterone deficiency and metabolic syndrome,” *Aging Male*, vol. 11, no. 4, pp. 193–199, 2008.
- [3] M. Maggio, F. Lauretani, G. P. Ceda et al., “Relationship between low levels of anabolic hormones and 6-year mortality in older men: the aging in the chianti area (InCHIANTI) study,” *Archives of Internal Medicine*, vol. 167, no. 20, pp. 2249–2254, 2007.
- [4] B. A. Mohr, S. Bhasin, C. L. Link, A. B. O'Donnell, and J. B. McKinlay, “The Effect of changes in adiposity on testosterone levels in older men: longitudinal results from the Massachusetts male aging study,” *European Journal of Endocrinology*, vol. 155, no. 3, pp. 443–452, 2006.
- [5] J. Svartberg, D. Von Mühlen, J. Sundsfjord, and R. Jorde, “Waist circumference and testosterone levels in community dwelling men. The Tromsø study,” *European Journal of Epidemiology*, vol. 19, no. 7, pp. 657–663, 2004.
- [6] A. M. Isidori, M. Caprio, F. Strollo et al., “Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels,” *Journal of Clinical Endocrinology and Metabolism*, vol. 84, no. 10, pp. 3673–3680, 1999.
- [7] P. Björntorp, “Visceral obesity: a ‘civilization syndrome,’” *Obesity Research*, vol. 3, pp. 206–222, 1993.
- [8] F. C. W. Wu, A. Tajar, J. M. Beynon et al., “Identification of late-onset hypogonadism in middle-aged and elderly men,” *The New England Journal of Medicine*, vol. 363, no. 2, pp. 123–135, 2010.
- [9] G. Corona, G. Rastrelli, M. Monami et al., “Body mass index regulates hypogonadism-associated CV risk: results from a cohort of subjects with erectile dysfunction,” *Journal of Sexual Medicine*, vol. 8, no. 7, pp. 2098–2105, 2011.
- [10] F. Saad, A. Aversa, A. M. Isidori, and L. J. Gooren, “Testosterone as potential effective therapy in treatment of obesity in men with testosterone deficiency: a review,” *Current Diabetes Reviews*, vol. 8, no. 2, pp. 131–143, 2012.
- [11] S. Y. Kalinchenko, Y. A. Tishova, G. J. Mskhalaya, L. J. G. Gooren, E. J. Giltay, and F. Saad, “Effects of testosterone



- supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study," *Clinical Endocrinology*, vol. 73, no. 5, pp. 602–612, 2010.
- [12] G. Hackett, N. Cole, M. Bhartia et al., "The response to testosterone undecanoate in men with type 2 diabetes is dependent on achieving threshold serum levels (the BLAST study)," *International Journal of Clinical Practice*, 2013.
  - [13] S. Bhasin, T. G. Travison, T. W. Storer et al., "Effect of testosterone supplementation with and without a dual 5 $\alpha$ -reductase inhibitor on fat-free mass in men with suppressed testosterone production: a randomized controlled trial," *Journal of the American Medical Association*, vol. 307, no. 9, pp. 931–939, 2012.
  - [14] K. G. M. M. Alberti and P. Zimmet, "The metabolic syndrome—a new worldwide definition," *The Lancet*, vol. 366, no. 9491, pp. 1059–1062, 2005.
  - [15] B. M. Prior, K. J. Cureton, C. M. Modlesky et al., "In vivo validation of whole body composition estimates from dual-energy X-ray absorptiometry," *Journal of Applied Physiology*, vol. 83, no. 2, pp. 623–630, 1997.
  - [16] C.-C. Glüer, "Monitoring skeletal changes by radiological techniques," *Journal of Bone and Mineral Research*, vol. 14, no. 11, pp. 1952–1962, 1999.
  - [17] American Diabetes Association, "Standards of medical care in diabetes," *Diabetes Care*, vol. 34, no. 1, pp. S11–S61, 2011/2011.
  - [18] A. Aversa, R. Bruzziches, D. Francomano, G. Spera, and A. Lenzi, "Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome," *Journal of Endocrinological Investigation*, vol. 33, no. 11, pp. 776–783, 2010.
  - [19] D. Francomano, A. Ilacqua, R. Bruzziches, A. Lenzi, and A. Aversa, "Effects of 5-year treatment with testosterone undecanoate on lower urinary tract symptoms in obese men with hypogonadism and metabolic syndrome," *Urology*, vol. 83, no. 1, pp. 167–174, 2014.
  - [20] F. Saad, H. Haider, E. J. Giltay, and L. J. G. Gooren, "Age, obesity and inflammation at baseline predict the effects of testosterone administration on the metabolic syndrome," *Hormone Molecular Biology and Clinical Investigation*, vol. 6, no. 1, pp. 193–199, 2011.
  - [21] A. Aversa, R. Bruzziches, D. Francomano et al., "Effects of long-acting testosterone undecanoate on bone mineral density in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 36 months controlled study," *Aging Male*, vol. 15, no. 2, pp. 96–102, 2011.
  - [22] F. Saad, A. Haider, G. Doros, and A. Traish, "Long-term treatment of hypogonadal men with testosterone produces substantial and sustained weight loss," *Obesity*, vol. 21, no. 10, pp. 1975–1981, 2013.
  - [23] A. A. Yassin and G. Doros, "Testosterone therapy in hypogonadal men results in sustained and clinically meaningful weight loss," *Clinical Obesity*, vol. 3, no. 3-4, pp. 73–83, 2013.
  - [24] A. M. Traish, A. Haider, G. Doros, and F. Saad, "Long-term testosterone therapy in hypogonadal men ameliorates elements of the metabolic syndrome: an observational, long-term registry study," *International Journal of Clinical Practice*, 2013.
  - [25] I. Lemieux, B. Lamarche, C. Couillard et al., "Total cholesterol/HDL cholesterol ratio vs LDL cholesterol/HDL cholesterol ratio as indices of ischemic heart disease risk in men," *Archives of Internal Medicine*, vol. 161, no. 22, pp. 2685–2692, 2001.
  - [26] S. W. Kim, J. H. Jee, H. J. Kim et al., "Non-HDL-cholesterol / HDL-cholesterol is a better predictor of metabolic syndrome and insulin-resistance than apolipoproteinB/apolipoprotein A1," *International Journal of Cardiology*, vol. 168, no. 3, pp. 2678–2683, 2013.
  - [27] S. Bleda, J. de Haro, C. Varela, L. Esparza, J. Rodriguez, and F. Acin, "Improving total-cholesterol/HDL-cholesterol ratio results in an endothelial dysfunction recovery in peripheral artery disease patients," *Cholesterol*, vol. 2012, Article ID 895326, 6 pages, 2012.
  - [28] A. Haider, F. Saad, G. Doros, and L. J. G. Gooren, "Hypogonadal obese men with and without diabetes mellitus type 2 lose weight and show improvement in cardiovascular risk factors when treated with testosterone: an observational study," *Obesity Research and Clinical Practice*. In press.
  - [29] M. Holecki, B. Zahorska-Markiewicz, J. Chudek, and A. Więcek, "Changes in bone mineral density and bone turnover markers in obese women after short-term weight loss therapy during a 5-year follow-up," *Polskie Archiwum Medycyny Wewnętrznej*, vol. 120, no. 7-8, pp. 248–254, 2010.
  - [30] J. Sánchez-Hernández, J. Ybarra, I. Gich et al., "Effects of bariatric surgery on vitamin D status and secondary hyperparathyroidism: a prospective study," *Obesity Surgery*, vol. 15, no. 10, pp. 1389–1395, 2005.
  - [31] Y. Hagenfeldt, K. Linde, H.-E. Sjöberg, W. Zumkeller, and S. Arver, "Testosterone increases serum 1,25-dihydroxyvitamin D and insulin-like growth factor-I in hypogonadal men," *International Journal of Andrology*, vol. 15, no. 2, pp. 93–102, 1992.
  - [32] A. Ferlin, R. Selice, U. Carraro, and C. Foresta, "Testicular function and bone metabolism-beyond testosterone," *Nature Reviews Endocrinology*, vol. 9, no. 9, pp. 548–554, 2013.
  - [33] C. R. Shyr, C. C. Chen, T. F. Hsieh et al., "The expression and actions of androgen receptor in upper urinary tract urothelial carcinoma (UUTUC) tissues and the primary cultured cells," *Endocrine*, vol. 43, no. 1, pp. 191–199, 2013.
  - [34] P. Mårin, R. Rosmond, B. A. Bengtsson, C. Gustafsson, G. Holm, and P. Björntorp, "Growth hormone secretion after testosterone administration to men with visceral obesity," *Obesity research*, vol. 2, no. 3, pp. 263–270, 1994.
  - [35] R. Muniyappa, J. D. Sorkin, J. D. Veldhuis et al., "Long-term testosterone supplementation augments overnight growth hormone secretion in healthy older men," *American Journal of Physiology*, vol. 293, no. 3, pp. E769–E775, 2007.
  - [36] M. L. Hartman, J. D. Veldhuis, M. L. Johnson et al., "Augmented growth hormone (GH) secretory burst frequency and amplitude mediate enhanced GH secretion during a two-day fast in normal men," *Journal of Clinical Endocrinology and Metabolism*, vol. 74, no. 4, pp. 757–765, 1992.
  - [37] M. H. Rasmussen, A. Juul, L. L. Kjems, and J. Hilsted, "Effects of short-term caloric restriction on circulating free IGF-I, acid-labile subunit, IGF-binding proteins (IGFBPs)-1-4, and IGFBPs-1-3 protease activity in obese subjects," *European Journal of Endocrinology*, vol. 155, no. 4, pp. 575–581, 2006.
  - [38] M. A. Michalaki, A. G. Vagenakis, A. S. Leonardou et al., "Thyroid function in humans with morbid obesity," *Thyroid*, vol. 16, no. 1, pp. 73–78, 2006.
  - [39] R. V. Agnihothri, A. B. Courville, J. D. Linderman et al., "Moderate weight loss is sufficient to affect thyroid hormone homeostasis and inhibit its peripheral conversion," *Thyroid*, vol. 24, no. 1, pp. 19–26, 2014.
  - [40] R. Singh, J. N. Artaza, W. E. Taylor, N. F. Gonzalez-Cadavid, and S. Bhasin, "Androgens stimulate myogenic differentiation and

inhibit adipogenesis in C3H 10T1/2 pluripotent cells through an androgen receptor-mediated pathway," *Endocrinology*, vol. 144, no. 11, pp. 5081–5088, 2003.

- [41] P. Mårin, B. Odén, and P. Björntorp, "Assimilation and mobilization of triglycerides in subcutaneous abdominal and femoral adipose tissue *in vivo* in men: effects of androgens," *Journal of Clinical Endocrinology and Metabolism*, vol. 80, no. 1, pp. 239–243, 1995.

## Research Article

# Hormonal Modulation in Aging Patients with Erectile Dysfunction and Metabolic Syndrome

**Inês Campos Costa,<sup>1</sup> Hugo Nogueira Carvalho,<sup>1</sup> Luís Pacheco-Figueiredo,<sup>2,3</sup>  
Inês Tomada,<sup>4,5,6</sup> and Nuno Tomada<sup>1,2,5</sup>**

<sup>1</sup> Faculty of Medicine, Universidade do Porto, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal

<sup>2</sup> Department of Urology, São João Central Hospital, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal

<sup>3</sup> School of Health Sciences, Life and Health Sciences Research Institute (ICVS), University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal

<sup>4</sup> Department of Experimental Biology, Faculty of Medicine, Universidade do Porto, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal

<sup>5</sup> Institute for Molecular Cell Biology, Universidade do Porto (IBMC), Rua do Campo Alegre 823, 4150-180 Porto, Portugal

<sup>6</sup> Faculty of Biotechnology, Catholic University of Porto, Rua Dr. António Bernardino de Almeida 400, 4200-072 Porto, Portugal

Correspondence should be addressed to Inês Campos Costa; [inescamposcostamd@gmail.com](mailto:inescamposcostamd@gmail.com)

Received 5 July 2013; Revised 20 August 2013; Accepted 5 September 2013

Academic Editor: Antonio Aversa

Copyright © 2013 Inês Campos Costa et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Erectile dysfunction (ED), metabolic syndrome (MetS), and hypogonadism are closely related, often coexisting in the aging male. Obesity was shown to raise the risk of ED and hypogonadism, as well as other endocrinological disturbances with impact on erectile function. We selected 179 patients referred for ED to our andrology unit, aiming to evaluate gonadotropins and estradiol interplay in context of ED, MetS, and hypogonadism. Patients were stratified into groups in accordance with the presence (or not) of MetS and/or hypogonadism. Noticeable differences in total testosterone (TT) and free testosterone (FT) levels were found between patients with and without MetS. Men with MetS evidenced lower TT circulating levels with an increasing number of MetS parameters, for which hypertriglyceridemia and waist circumference strongly contributed. Regarding the hypothalamic-pituitary-gonadal axis, patients with hypogonadism did not exhibit raised LH levels. Interestingly, among those with higher LH levels, estradiol values were also increased. Possible explanations for this unexpected profile of estradiol may be the age-related adiposity, other estrogen-raising pathways, or even unknown mechanisms. Estradiol is possibly a molecule with further interactions beyond the currently described. Our results further enlighten this still unclear multidisciplinary and complex subject, raising new investigational opportunities.

## 1. Introduction

Erectile dysfunction (ED) is the persistent inability to attain and/or maintain an erection of sufficient rigidity for sexual intercourse. Its prevalence has a tendency to increase over time [1], being expected a worldwide increase of 12.0% from 1995 to 2025 [2]. An observational study revealed that 12.9% of Portuguese men suffer from ED, with 5.8% describing it as moderate/severe, and that ED was most prevalent amongst men over the age of 60 [3]. ED has been linked to metabolic syndrome (MetS) [4], which is an assembly of cardiovascular (CV) and metabolic risk factors, such as visceral adi-

posity, insulin resistance/diabetes, high blood pressure, and dyslipidemia. Although several definitions of MetS have been devised, the one proposed by the National Cholesterol Education Program-Adult Treatment Panel III [5] emerged as the most widely used definition, due to its simplicity and superiority as a predictor of secondary outcomes. Its prevalence in Portuguese male population is 18.7% [6], which is superior to other European countries [7].

Aging and age-related comorbidities are strongly associated with the increased prevalence of ED [1, 8], MetS [6], and hypogonadism [7]. All these conditions often coexist in the same patient [9, 10], whilst hypogonadism and ED

have been demonstrated to increase the risk of MetS [9, 11–15], supporting the idea of a multifactorial/directional endocrinological imbalance that occurs in specific subsets of ED patients. Elderly men are prone to develop late onset hypogonadism (LOH), a condition characterized by a progressive testicular impairment associated with specific sexual symptoms (amongst them, ED) and a deficiency of serum T levels [16, 17]. Several studies support LOH, unveiling that T levels decrease along aging [14, 16, 18, 19].

Obesity by itself contributes to a wide range of endocrine disturbances, such as reduced T levels. Indeed, among ED patients, obese men present lower T levels compared to those observed in the elder [15]. One of the most plausible mechanisms by which obesity contributes to T levels decline is the adipose tissue dependent aromatization of T to estradiol [15]. In line with these remarks, hormonal ED etiology might not be confined to androgen deficiency, as isolated high estradiol levels have been reported in some ED patients [8, 20].

In addition to sexual hormones disturbances, several other endocrinological imbalances might be found in ED patients. ED has been related with glandular anomalies, such as hyper- and hypothyroidism [21, 22]. However, the relationship between the latter and ED is still controversial [21–23]. Nonetheless, it is unlikely that ED associated with hyperthyroidism is owed to hypogonadism, as no thyroid hormone-dependent alteration in calculated free testosterone (FT) levels has been described [21]. Severe hyperprolactinemia has been also reported as a cause of ED, since it may compromise sexual desire and inhibit T secretion [22, 24], an outcome that is potentially reversible by treating the underlying disorder [24].

Hypogonadism and MetS strongly increase the risk of ED at any age and both are risk factors for CV disease [9, 25–27]. From several studies in this area, the importance of understanding the complex interactions between those entities became clear, as well as the underlying modulating factors. In this study, we describe the hormonal milieu of a Portuguese population with ED, comparing MetS to non-MetS groups and correlating T levels with the number of MetS parameters. Moreover, we analyze the hypothalamic-pituitary-gonadal (HPG) axis in ED patients with and without hypogonadism, aiming to describe and evaluate nonexpected hormonal alterations in this axis and further uncover the relation between these three increasingly prevalent conditions.

## 2. Materials and Methods

We selected 179 Caucasian patients referred to our andrology unit for ED between January 2008 and March 2012. All of them gave their written informed consent and had a complete hormone assessment available. A known history of neurological disease, pelvic trauma, major psychiatric disorder, hepatic failure, end-stage renal disease, or drug abuse was an exclusion criterion. A standardized health questionnaire covering medical anamnesis (including sexual history), CV risk factors, smoking and alcohol intake

history and current medication was obtained. All patients underwent a standardized physical examination protocol. Anthropometric evaluation, including weight, height, and waist circumference (WC), was acquired by the same technician with the subjects in light clothing and barefoot. Blood pressure was measured in the right arm using an automatic manometer (DINAMAP Procare 300, GE, UK) in the sitting position after a 10-minute rest period. Blood analysis was performed using samples of venous blood collected between 8:00 and 10:00 a.m., after a 12-hour overnight fasting period.

The following measurements were made by routine laboratory methods: triglycerides (Trig), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), total cholesterol, serum glucose, and albumin. Total testosterone (TT), sex hormone-binding globulin (SHBG), estradiol, prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and insulin were determined by chemiluminescence with a commercially available kit (Cobas; Roche Diagnosis GmbH, Mannheim, Germany). Triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH) were determined by chemiluminescence with a commercially available kit (Abbott Diagnostics Division, Princeton, NJ, USA). Free testosterone was calculated using the *Free and Bioavailable Testosterone calculator*, developed at the Hormonology Department, University Hospital of Ghent, Belgium (<http://www.issam.ch/freetesto.htm>). The electronic process of each patient and available digitalized records were also consulted. Body mass index (BMI) was calculated based on weight in kilograms and height in meters ( $\text{kg}/\text{m}^2$ ). Participants were considered obese if BMI was  $\geq 30 \text{ kg}/\text{m}^2$ . The presence of three or more of the following criteria defined MetS, according to NCEP-ATPIII (2002): central obesity (WC  $>102 \text{ cm}$ ), hypertriglyceridemia (Trig  $\geq 150 \text{ mg}/\text{dL}$  or treatment), low HDL cholesterol ( $<40 \text{ mg}/\text{dL}$  or treatment), hypertension (HT, blood pressure  $\geq 130/85 \text{ mmHg}$  or treatment), and fasting serum glucose  $\geq 110 \text{ mg}/\text{dL}$  [5]. Hypogonadism was defined as TT below  $3.50 \text{ ng}/\text{mL}$  ( $11.10 \text{ nmol}/\text{L}$ ) or calculated FT below  $0.072 \text{ ng}/\text{mL}$  [28]. We considered normal LH levels between the normal range of  $1.70$  to  $8.60 \text{ mIU}/\text{mL}$ . Hypothyroidism was defined as TSH levels  $>4.94 \text{ } \mu\text{U}/\text{mL}$  and T4 levels in the normal range or  $<0.70 \text{ ng}/\text{dL}$ . Hyperthyroidism was defined as TSH levels  $<0.35 \text{ } \mu\text{U}/\text{mL}$ , T3 levels  $>3.71 \text{ pg}/\text{mL}$ , and T4 levels  $>1.48 \text{ ng}/\text{dL}$ . Hypo- and hyperinsulinemia were considered at insulin levels inferior to  $2.60 \text{ } \mu\text{U}/\text{mL}$  and superior to  $24.90 \text{ } \mu\text{U}/\text{mL}$ , respectively.

**2.1. Statistical Analysis.** Absolute and relative frequencies were used to describe categorical variables as well as median and percentiles 25 and 75 were applied in the description of continuous variables.

Chi-square and Kruskal-Wallis tests were used to evaluate the differences between the subgroups with and without MetS, respectively, for categorical and continuous variables. We considered the differences statistically significant when  $P < 0.050$ .

All data analyses were performed using STATA software, version 9.2.



TABLE 1: Population characteristics.

|  | All participants<br>( <i>n</i> = 151) | Participants according to MetS status         |  | <i>P</i> * |
|--|---------------------------------------|---|--|------------|
|  |                                       | Participants<br>with MetS<br>( <i>n</i> = 74) | Participants<br>without MetS<br>( <i>n</i> = 77) |            |
| Age (years), median (P25–P75)                          | 56.0 (50.0–62.0)                      | 56.0 (52.0–62.0)                              | 58.0 (48.0–62.0)                                 | 0.790      |
| Weight (kg), median (P25–P75)                          | 80.0 (72.0–86.0)                      | 82.0 (77.0–94.0)                              | 75.0 (68.9–83.5)                                 | <0.001     |
| Height (cm), median (P25–P75)                          | 179.0 (164.0–173.0)                   | 170.0 (163.0–173.0)                           | 169.0 (164.0–173.0)                              | 0.799      |
| BMI (kg/m <sup>2</sup> ), median (P25–P75)             | 27.9 (25.2–30.5)                      | 29.7 (27.7–31.4)                              | 26.3 (24.4–28.3)                                 | <0.001     |
| Waist circumference (cm), median (P25–P75)             | 104.0 (97.0–111.0)                    | 107.7 (103.0–113.5)                           | 99.5 (95.0–106.0)                                | <0.001     |
| <i>Hormonal panel</i>                                  |                                       |   |  |            |
| Total testosterone (ng/mL), median (P25–P75)           | 4.5 (3.5–5.6)                         | 4.0 (3.2–5.0)                                 | 5.1 (4.1–5.9)                                    | 0.001      |
| Free calculated testosterone (ng/mL), median (P25–P75) | 0.102 (0.074–0.156)                   | 0.122 (0.074–0.653)                           | 0.093 (0.075–0.113)                              | <0.001     |
| SHBG (nmol/L), median (P25–P75)                        | 35.8 (27.3–48.6)                      | 33.6 (23.8–41.6)                              | 40.2 (31.4–55.0)                                 | 0.003      |
| LH (mUI/mL), median (P25–P75)                          | 4.0 (2.7–5.9)                         | 4.1 (3.1–7.6)                                 | 3.7 (2.6–5.4)                                    | 0.062      |
| Estradiol (pg/mL), median (P25–P75)                    | 28.5 (22.0–37.8)                      | 26.0 (21.0–35.4)                              | 31.0 (23.2–40.0)                                 | 0.164      |
| FSH (mUI/mL), median (P25–P75)                         | 5.0 (3.7–7.3)                         | 5.1 (3.7–8.1)                                 | 4.6 (3.5–6.1)                                    | 0.164      |
| TSH (μU/mL), median (P25–P75)                          | 1.3 (1.0–1.8)                         | 1.3 (0.9–1.8)                                 | 1.3 (1.0–1.7)                                    | 0.634      |
| T3 (pg/mL), median (P25–P75)                           | 3.0 (2.8–3.3)                         | 3.0 (2.8–3.3)                                 | 3.0 (2.7–3.3)                                    | 0.404      |
| T4 (ng/dL), median (P25–P75)                           | 1.0 (0.9–1.1)                         | 1.1 (1.0–1.2)                                 | 1.0 (0.9–1.1)                                    | 0.040      |
| <i>Comorbidities</i>                                   |                                       |   |  |            |
| Hypogonadism, <i>n</i> (%)                             | 35.0 (23.2)                           | 17 (23.0)                                     | 18.0 (23.4)                                      | 0.953      |
| Hypothyroidism, <i>n</i> (%)                           | 0.0 (0.0)                             | 0.0 (0.0)                                     | 0.0 (0.0)  | —          |
| Hyperthyroidism, <i>n</i> (%)                          | 1.0 (0.6)                             | 0.0 (0.0)                                     | 0.0 (0.0)  | —          |
| Hyperprolactinemia, <i>n</i> (%)                       | 183 (8.2)                             | —   | —  | —          |
| Alcohol intake, <i>n</i> (%)                           |                                       |   |  |            |
| Absent   | 70.0 (61.9)                           | 25.0 (67.6)                                   | 45.0 (59.2)                                      | 0.541      |
| Frequent   | 41.0 (36.3)                           | 12.0 (32.4)                                   | 29.0 (38.2)                                      |            |
| Former intake  | 2.0 (1.8)                             | —   | 2.0 (2.6)  |            |
| Smoking status, <i>n</i> (%)                           |                                       |   |  |            |
| Never smoked   | 55.0 (36.7)                           | 25.0 (33.8)                                   | 30.0 (39.5)                                      | 0.001      |
| Smoker   | 32.0 (21.3)                           | 9.0 (12.2)                                    | 23.0 (30.3)                                      |            |
| Former intake  | 63.0 (42.0)                           | 40.0 (54.0)                                   | 23 (30.3)  |            |

\* Participants with MetS versus participants without MetS.

Data are expressed as the 25th percentile–the 75th percentile (P25–P75).

Metabolic syndrome (MetS), body mass index (BMI), Sex-hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), free triiodothyronine (T3), and free thyroxine (T4).

### 3. Results

From the 179 patients who were engaged in this study, 28 subjects were excluded due to insufficient data. The remaining 151 subjects had a median age, BMI, and WC, respectively, 56 years (P25–P75: 50–62), 27.9 kg/m<sup>2</sup> (25.2–30.5), and 104.0 cm (97.0–111.0). Current or past alcohol consumption was absent in the majority of patients (61.9%), having only 36.8% reported a current frequent intake (until 37 gr of alcohol per day) and 1.8% history of past intake. Smoking habits were majorly absent (36.7%) or in the past (42.0%),

having only 21.3% reported being active smokers. Further population characteristics are contemplated in Table 1.

Concerning the hormonal profile, the median TT, FT, SHBG, LH, and estradiol levels were 4.5 ng/mL (P25–P75: 3.5–5.6), 0.102 ng/mL (0.074–0.156), 35.8 nmol/L (27.3–48.6), 4.0 ng/mL (2.7–5.9), and 28.5 ng/mL (22.0–37.8), respectively. Levels of FSH, TSH, T3, and T4 were also measured and are described in Table 1. Hypothyroidism was not present in any of the patients, whereas hyperthyroidism was present in one. Hyperprolactinemia was present in 15 patients (8.2%) and hyperinsulinemia in 5 (7.4%).

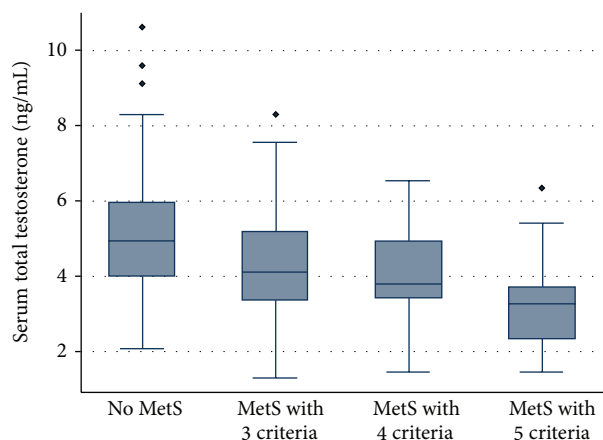


FIGURE 1: Box-plot representation showing a statistical significant decrease of the total testosterone levels (vertical axis) with the increase of the metabolic syndrome (MetS) parameters (horizontal axis) ( $P < 0.001$ ).

MetS, according to NCEP-ATPIII criteria, was present in 49% of our patients. These patients evidenced significantly higher calculated FT levels of 0.1225 ng/mL (0.0738–0.6530), when compared to patients without MetS ( $P < 0.001$ ). Conversely, patients without MetS evidenced median TT of 5.1 ng/mL (4.1–5.9) and median SHBG of 40.2 nmol/L (31.4–55.0), which were significantly higher in comparison to those with MetS ( $P = 0.001$  and  $P = 0.003$ , resp.). Comparison measurements are further described in Table 1.

Age, TSH, FSH, and estradiol levels presented no significant differences between patients with or without MetS ( $P = 0.790$ ,  $P = 0.634$ ,  $P = 0.164$ ,  $P = 0.164$ , resp.). No differences were observed in median LH levels between patients with or without MetS ( $P = 0.062$ ).

The relationship between hypogonadism and MetS was also evaluated. Hypogonadism was present in 23.2% of the patients, and no differences in its frequency were found between patients with and without MetS ( $P = 0.953$ ). However, TT levels were decreased consistently with the increase of the number of parameters of MetS ( $P < 0.001$ ) (Figure 1). Moreover, multivariate regression analysis demonstrated that within MetS, WC ( $P = 0.017$ ) and hypertriglyceridemia ( $P = 0.050$ ) were independently associated with a decrease in serum T levels. In spite of such observations, the presence of MetS did seem not to influence TT and FT levels amongst patients with hypogonadism. Multivariate regression analysis also demonstrated that the MetS is a determinant independent of lower TT levels independent of the other model variables such as age, alcohol consumption, and smoking habits (beta coefficient:  $-0.70$ ; 95% confidence interval:  $-1.29$ ,  $-0.10$ ).

The relationship between MetS with LH levels was evaluated and is presented in Table 2. LH levels were within normal range or decreased in 136 patients, regardless of the presence of MetS. Moreover, amongst patients with hypogonadism, LH levels did not vary with the MetS presence ( $P = 0.844$ ).

On the other hand, as shown in Figure 2, estradiol levels varied in patients with hypogonadism, which was related

TABLE 2: Hypothalamic-pituitary-gonadal axis response to metabolic syndrome (MetS).

|                                | Participants<br>with MetS | <i>P</i> * | Participants<br>without MetS | <i>P</i> * |
|--------------------------------|---------------------------|------------|------------------------------|------------|
| <i>Without hypogonadism</i>    |                           |            |                              |            |
| Raised LH levels, <i>n</i> (%) |                           |            |                              |            |
| Yes                            | 6.0 (10.7)                | 0.903      | 3.0 (5.2)                    | 0.909      |
| No                             | 50.0 (89.3)               |            | 55 (94.8)                    |            |
| <i>With hypogonadism</i>       |                           |            |                              |            |
| Raised LH levels, <i>n</i> (%) |                           |            |                              |            |
| Yes                            | 2.0 (11.8)                | 0.903      | 1.0 (5.9)                    | 0.909      |
| No                             | 15.0 (88.2)               |            | 16.0 (94.1)                  |            |

\* Participants with raised LH levels versus participants without raised LH levels.

LH levels were considered normal from 1.7 to 8.6 mUI/mL. Hypothalamic-pituitary-gonadal (HPG) axis was considered to be disrupted when the LH levels were not raised in individuals with hypogonadism.

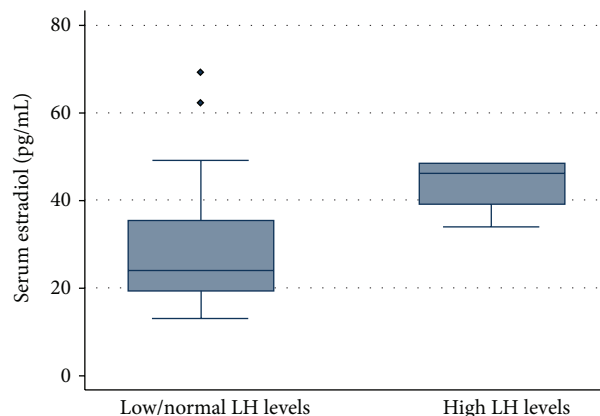


FIGURE 2: Box-plot representation showing a statistical significant increase of the estradiol levels (vertical axis) with the increase of the luteinizing hormone levels (LH) (horizontal axis) ( $P = 0.033$ ).

to dissimilarities in LH levels ( $P = 0.033$ ). In these patients with hypogonadism, we characterized the estrogen levels according to the axis response (low or normal LH levels versus raised LH levels). Indeed, while estradiol levels increased, LH levels were raised (normally functioning axis) and dropped while the LH levels were normal or low.

## 4. Discussion

Hypogonadism and MetS are strongly associated [12, 13, 16], having even been demonstrated that with the increasing number of MetS parameters there is a proportional raise in the incidence of hypogonadism [29]. Although hypogonadism was present in 23.2% of our patients, no noticeable differences were observed among those with or without MetS.

In the recent years, several studies unveiled that the increasing number of MetS components is inversely associated with T levels [12, 13, 27, 30]. Accordingly, our population with hypogonadism and MetS showed a decrease in T

levels with the increase in the number of MetS parameters. Thus, although the presence of MetS did not prove to be a significant determinant of hypogonadism, as it did not lead to a decline in T levels, in MetS patients with already established hypogonadism, the increasing number of MetS features was associated with further decline in T.

In the setting of MetS, hypertriglyceridemia and increased WC have been reported as the most important determinants of hypogonadism [10, 16]. Accordingly, in patients with MetS, these two features revealed the major influence on decreasing T levels, with the former being the strongest independent conditioning factor. In fact, recent literature consistently associates obesity not only with higher risk of hypogonadism [4, 6, 27] but also with lower T levels [8]. Visceral adiposity has been particularly related with reduction of T and SHBG levels (independent of other metabolic disorders) [15, 27]. In this study, WC was one of the MetS parameters with the greatest influence in T levels decrease, presenting itself as a strong risk factor for hypogonadism development. Furthermore, the metabolic and hormonal profile of our population is not only consistent with ED presence but also reinforces the usefulness of MetS screening for ED and CV disease prevention [9, 25–27].

Aiming to establish further relations amongst the conditions described above, several authors observed that the MetS-related T decline was not accompanied by an increase in pituitary LH levels, suggesting impairment in gonadotropin secretion [27]. The term *mixed hypoandrogenism* (primary and secondary) was proposed for this phenomenon [9, 31]. The molecules behind this smoothing compensatory effect of GnRH/LH are still unknown, but estrogens and insulin, as well as leptin, TNF- $\alpha$ , and other adipokines, were proposed candidates [15, 27]. An alternative etiopathogenic explanation for this phenomenon proposes that fat stores undertake an increase aromatization of androgens, therefore raising estrogen levels [9, 15], which in turn decrease LH secretion [9]. Hence, aging being associated with an increase in adipose tissue accretion, a link between age and hypogonadism was established [32]. However, in opposition to *mixed hypoandrogenism* definition, our MetS patients did not evidence changes in the median LH levels compared to non-MetS ones. This was also true when only the patients with hypogonadism were considered, suggesting that other factors than MetS and obesity, such as age or any of the molecules described above, might have a stronger influence on the HPG axis. It is likely that the underlying ED, a common feature of all of our patients, might play a multi-factorial masking role. Although possible unforeseen confounders might also be influencing this relation, the greatest efforts were made in order to exclude patients with known underlying pathologies or comorbidities that could influence the hormonal results.

Theoretically, our data contradicts the concept that estradiol exerts a negative feedback on hypothalamic GnRH secretion [28], as it would not be expected to find raised estradiol levels concomitant with raised LH levels. We hypothesize that, in our group of patients with MetS that did not present estrogenic HPG axis-attenuation effect, obesity is playing an important role in the estradiol levels increase. Nevertheless, we have just a few patients without an estrogenic HPG

axis-attenuation effect and, amongst them, there were not enough MetS cases to accurately test this hypothesis in a MetS setting. On the other hand, when considering data from patients with an estrogenic HPG axis-attenuation effect but without MetS, possible explanations may imply additional molecules, age-related fat deposits, or other estrogen-raising mechanisms. However, even in this setting, the absence of estradiol effect on LH secretion is still puzzling. Thus, taking into account that high estradiol levels have already been described as the only abnormality in a subset of patients with ED, the hypothesis that the later might not only be caused by androgen deficiency is becoming increasingly evident [8, 20]. Furthermore, it has been reported that the chronic exposure to phosphodiesterase type 5 inhibitors (PDE5i), widely used for the treatment of ED, may influence serum estradiol levels [33, 34]. Even though we did not evaluate the influence of PDE5i on the hormonal axis, we cannot exclude the role these drugs might have in the serum T : estradiol ratio of our patients.

When expanding this analysis for a broader endocrinological spectrum, one must consider that even though a very limited number of cases of dysthyroidism were found in our population, thyroid disorders (specially hyperthyroidism) have been related to ED and hypogonadism, and so must be considered in a sexual-dysfunction setting [21, 22]. It is clear from the current literature that collecting a more thorough hormonal panel might be a wise approach to further uncover hormonal relations.

Our study has several limitations, one being its retrospective design. It is possible that some confounders have not been traced, therefore influencing the results. Nevertheless, a thorough analysis of the patients was made in order to exclude underlying pathologies or comorbidities that could alter the results. Moreover, the sample size was sometimes a limiting factor to test some hypothesis.

We concluded that in ED patients with hypogonadism and MetS, the attenuated response of HPG axis (normal or low LH levels) might not always be due to an underlying adiposity-dependent estrogen-raising effect. The lower estradiol levels observed in this peculiar group of patients suggest that they may be influenced by mechanisms that are not yet unveiled. Similarly, the increased estradiol levels in patients with hypogonadism and a normally responsive HPG axis (raised LH levels), mainly when MetS is not present, remain to be elucidated. In addition, the basis for estradiol negative feedback mechanism on the hypothalamic GnRH secretion and consequently on the HPG axis should be further investigated to clarify the concomitant increase of LH and estradiol. In the meantime, our findings indicate that ED, aging, and estradiol might have a stronger connection than what is currently described in the literature.

Overall, this study underlines the importance of the collection of a full hormonal panel in ED men, as well as a detailed clinical history, to exclude the presence of other hormonal disturbances than hypogonadism and MetS. Our results yield further insights into this still unclear multidisciplinary and complex subject and raise new research opportunities on alternative factors mediating the relationship between ED, hypogonadism, and MetS.

## Disclaimer

The authors alone are responsible for the content and writing of the paper.

## Conflict of Interests

The authors report no conflict of interests and declare no competing financial interests.

## References

- [1] J. B. McKinlay, W. Wilson, S. Sharlip, M. Montague, M. Melman, and B. Broderick, "The worldwide prevalence and epidemiology of erectile dysfunction," *International Journal of Impotence Research*, vol. 12, supplement 4, pp. S6–S11, 2000.
- [2] I. A. Aytac, J. B. McKinlay, and R. J. Krane, "The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences," *BJU International*, vol. 84, no. 1, pp. 50–56, 1999.
- [3] P. S. Vendeira, N. M. Pereira, N. Tomada, and J. M. LaFuente, "Estudo EPISEX-PT/Masculino: prevalência das disfunções sexuais masculinas em Portugal," *Cadernos de Sexologia*, no. 4, pp. 15–22, 2011.
- [4] W. Zohdy, E. E. Kamal, and Y. Ibrahim, "Androgen deficiency and abnormal penile duplex parameters in obese men with erectile dysfunction," *The Journal of Sexual Medicine*, vol. 4, no. 3, pp. 797–808, 2007.
- [5] National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)., "Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report," *Circulation*, vol. 106, no. 25, pp. 3143–3421, 2002.
- [6] N. Tomada, I. Tomada, F. Botelho, F. Cruz, and P. Vendeira, "Are all metabolic syndrome components responsible for penile hemodynamics impairment in patients with erectile dysfunction? The role of body fat mass assessment," *The Journal of Sexual Medicine*, vol. 8, no. 3, pp. 831–839, 2011.
- [7] G. Hu, Q. Qiao, J. Tuomilehto, B. Balkau, K. Borch-Johnsen, and K. Pyörälä, "Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women," *Archives of Internal Medicine*, vol. 164, no. 10, pp. 1066–1076, 2004.
- [8] B. Srilatha and P. G. Adaikan, "Endocrine milieu and erectile dysfunction: is oestradiol-testosterone imbalance, a risk factor in the elderly?" *Asian Journal of Andrology*, vol. 13, no. 4, pp. 569–573, 2011.
- [9] G. Corona, E. Mannucci, G. Forti, and M. Maggi, "Hypogonadism, ED, metabolic syndrome and obesity: a pathological link supporting cardiovascular diseases," *International Journal of Andrology*, vol. 32, no. 6, pp. 587–598, 2009.
- [10] G. Corona, G. Forti, and M. Maggi, "Why can patients with erectile dysfunction be considered lucky? The association with testosterone deficiency and metabolic syndrome," *Aging Male*, vol. 11, no. 4, pp. 193–199, 2008.
- [11] V. Kupelian, S. T. Page, A. B. Araujo, T. G. Travison, W. J. Bremner, and J. B. McKinlay, "Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the metabolic syndrome in nonobese men," *The Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 3, pp. 843–850, 2006.
- [12] M. M. Miner and R. Sadovsky, "Evolving issues in male hypogonadism: evaluation, management, and related comorbidities," *Cleveland Clinic Journal of Medicine*, vol. 74, supplement 3, pp. S38–S46, 2007.
- [13] M. M. Miner and A. D. Seftel, "Testosterone and ageing: what have we learned since the Institute of Medicine report and what lies ahead?" *International Journal of Clinical Practice*, vol. 61, no. 4, pp. 622–632, 2007.
- [14] A. Rodriguez, D. C. Muller, E. J. Metter et al., "Aging, androgens, and the metabolic syndrome in a longitudinal study of aging," *The Journal of Clinical Endocrinology and Metabolism*, vol. 92, no. 9, pp. 3568–3572, 2007.
- [15] A. M. Traish, A. Guay, R. Feeley, and F. Saad, "The dark side of testosterone deficiency: I. metabolic syndrome and erectile dysfunction," *Journal of Andrology*, vol. 30, no. 1, pp. 10–22, 2009.
- [16] G. Corona, E. Mannucci, V. Ricca et al., "The age-related decline of testosterone is associated with different specific symptoms and signs in patients with sexual dysfunction," *International Journal of Andrology*, vol. 32, no. 6, pp. 720–728, 2009.
- [17] F. C. Wu, A. Tajar, J. M. Beynon et al., "Identification of late-onset hypogonadism in middle-aged and elderly men," *The New England Journal of Medicine*, vol. 363, no. 2, pp. 123–135, 2010.
- [18] H. A. Feldman, C. Longcope, C. A. Derby et al., "Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study," *The Journal of Clinical Endocrinology and Metabolism*, vol. 87, no. 2, pp. 589–598, 2002.
- [19] F. C. W. Wu, A. Tajar, S. R. Pye et al., "Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European male aging study," *The Journal of Clinical Endocrinology and Metabolism*, vol. 93, no. 7, pp. 2737–2745, 2008.
- [20] A. Mancini, D. Milardi, A. Bianchi, V. Summaria, and L. de Marinis, "Increased estradiol levels in venous occlusive disorder: a possible functional mechanism of venous leakage," *International Journal of Impotence Research*, vol. 17, no. 3, pp. 239–242, 2005.
- [21] G. Corona, F. C. Wu, G. Forti et al., "Thyroid hormones and male sexual function," *International Journal of Andrology*, vol. 35, no. 5, pp. 668–679, 2012.
- [22] M. Maggi, J. Buvat, G. Corona, A. Guay, and L. O. Torres, "Hormonal causes of male sexual dysfunctions and their management (hyperprolactinemia, thyroid disorders, GH disorders, and DHEA)," *The Journal of Sexual Medicine*, vol. 10, no. 3, pp. 661–677, 2012.
- [23] M. R. Nikoobakht, M. Aloosh, N. Nikoobakht, A. Mehryar, F. Biniaz, and M. A. Karjalainen, "The role of hypothyroidism in male infertility and erectile dysfunction," *Urology Journal*, vol. 9, no. 1, pp. 405–409, 2012.
- [24] G. Corona, E. Mannucci, A. D. Fisher et al., "Effect of hyperprolactinemia in male patients consulting for sexual dysfunction," *The Journal of Sexual Medicine*, vol. 4, no. 5, pp. 1485–1493, 2007.
- [25] C. Wang, E. Nieschlag, R. Swerdloff et al., "ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males," *International Journal of Impotence Research*, vol. 21, no. 1, pp. 1–8, 2009.
- [26] F. Montorsi, A. Briganti, A. Salonia et al., "Erectile dysfunction prevalence, time of onset and association with risk factors in 300



consecutive patients with acute chest pain and angiographically documented coronary artery disease," *European Urology*, vol. 44, no. 3, pp. 360–365, 2003.

- [27] G. Corona, G. Rastrelli, L. Vignozzi, E. Mannucci, and M. Maggi, "Testosterone, cardiovascular disease and the metabolic syndrome," *Best Practice and Research*, vol. 25, no. 2, pp. 337–353, 2011.
- [28] J. Buvat, R. Shabsigh, A. Guay et al., "Hormones, metabolism, aging, and men's health," in *Standard Practice in Sexual Medicine*, H. Porst, J. Buvat, and The Standards Committee of the International Society for Sexual Medicine, Eds., pp. 225–2286, Blackwell Publishing Company, London, UK, 2006.
- [29] G. Jackson, P. Montorsi, M. A. Adams et al., "Cardiovascular aspects of sexual medicine," *The Journal of Sexual Medicine*, vol. 7, no. 4, part 2, pp. 1608–1626, 2010.
- [30] K. Blouin, J.-P. Després, C. Couillard et al., "Contribution of age and declining androgen levels to features of the metabolic syndrome in men," *Metabolism*, vol. 54, no. 8, pp. 1034–1040, 2005.
- [31] G. Corona, E. Mannucci, A. D. Fisher et al., "Low levels of androgens in men with erectile dysfunction and obesity," *The Journal of Sexual Medicine*, vol. 5, no. 10, pp. 2454–2463, 2008.
- [32] P. G. Cohen, "The role of estradiol in the maintenance of secondary hypogonadism in males in erectile dysfunction," *Medical Hypotheses*, vol. 50, no. 4, pp. 331–333, 1998.
- [33] A. Aversa, M. Caprio, A. Antelmi et al., "Exposure to phosphodiesterase type 5 inhibitors stimulates aromatase expression in human adipocytes in vitro," *The Journal of Sexual Medicine*, vol. 8, no. 3, pp. 696–704, 2011.
- [34] E. A. Greco, M. Pili, R. Bruzziches, G. Corona, G. Spera, and A. Aversa, "Testosterone: estradiol ratio changes associated with long-term tadalafil administration: a pilot study," *The Journal of Sexual Medicine*, vol. 3, no. 4, pp. 716–722, 2006.

## Clinical Study

# Trunk Fat Negatively Influences Skeletal and Testicular Functions in Obese Men: Clinical Implications for the Aging Male

**Silvia Migliaccio,<sup>1</sup> Davide Francomano,<sup>2</sup> Roberto Bruzziches,<sup>2</sup> Emanuela A. Greco,<sup>2</sup> Rachele Fornari,<sup>2</sup> Lorenzo M. Donini,<sup>2</sup> Andrea Lenzi,<sup>2</sup> and Antonio Aversa<sup>2</sup>**

<sup>1</sup> Department of Movement, Human and Health Sciences, Unit of Endocrinology, University of Rome "Foro Italico", Largo Lauro De Bosis 15, 00195 Rome, Italy

<sup>2</sup> Department of Experimental Medicine, Medical Pathophysiology, Food and Science and Endocrinology Section, "Sapienza" University of Rome, Viale Regina Elena 324, 00161 Rome, Italy

Correspondence should be addressed to Silvia Migliaccio; [silvia.migliaccio@uniroma4.it](mailto:silvia.migliaccio@uniroma4.it)

Received 5 August 2013; Accepted 13 September 2013

Academic Editor: Roberto LaCava

Copyright © 2013 Silvia Migliaccio et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Osteocalcin (OSCA) seems to act as a negative regulator of energy metabolism and insulin sensitivity. Evidence from male rodents suggests that OSCA may also regulate testosterone (T) synthesis. Using a cross-sectional design, we evaluated OSCA, 25(OH) vitamin D, T, 17 $\beta$ -estradiol (E2), homeostasis model assessment of insulin resistance (HOMA-IR), and body composition in 86 obese (mean BMI = 34) male subjects (18–69 yr old). Independently from BMI, an inverse relationship between trunk fat percentage and plasma T ( $r^2 = -0.26$ ,  $P < 0.01$ ) and between HOMA-IR and OSCA levels ( $r^2 = -0.22$ ,  $P < 0.005$ ) was found. OSCA levels, as well as vitamin D, decreased significantly for higher BMI with significant differences above 35 ( $P < 0.01$ ). A direct correlation between T and bone mineral density at lumbar (BMDL) and neck (BMDH) ( $P < 0.001$ ,  $r^2 = -0.20$ ;  $P < 0.001$ ,  $r^2 = -0.24$ ) was found, independently from age. An inverse correlation between E2 levels, BMDL, and BMDH ( $P < 0.001$ ,  $r^2 = -0.20$ ;  $P < 0.001$ ,  $r^2 = -0.19$ ) was observed. These data provide new evidences that a relationship between trunk fat mass, insulin sensitivity, OSCA and T synthesis occurs. This new relationship with skeletal health has relevant implications for the aging male, suggesting OSCA as a novel marker of metabolic and gonadal health status.

## 1. Introduction

Emerging data suggest that bone mass, energy metabolism, and reproduction may be coordinately regulated. It is now accepted that bone is an endocrine organ favouring whole-body glucose homeostasis and energy expenditure. These functions of bone are, at least in part, mediated by an osteoblast-specific secreted molecule, osteocalcin (OSCA), that, when uncarboxylated (ucOSCA), acts as a hormone favouring  $\beta$  cell proliferation, insulin secretion and sensitivity, and energy expenditure. Also, the recent study by Oury et al. reveals that, in rodents, the bone is a positive regulator of male fertility, and that this action may be mediated through OSCA, via binding to a specific receptor present on Leydig cells that favours testosterone (T) biosynthesis [1]. OSCA-deficient mice show a decrease in testicular, epididymal, and

seminal vesicles weights and sperm count, and Leydig cell maturation appears to be halted in absence of OSCA. Those results, along with others previously published, support the hypothesis that regulations of bone remodelling, energy metabolism, and reproduction are linked [2, 3].

Ageing decreases circulating levels of sex steroid hormones in men [4, 5], and it is associated with visceral fat accumulation at the abdominal level. Male obesity might be associated with a reduction of T levels, as well as with sexual disturbances [6]. At present, the effects of raising T levels on bone mineral density (BMD) in men with metabolic syndrome (central obesity) have been investigated by our group demonstrating that a 5%/year increase in bone mineral density occurs in this population. However, in that previous study, OSCA levels were not evaluated [7].

Thus, the aim of the present study was to evaluate the potential relationship between circulating levels of OSCA and T with adipose tissue and BMD in obese men.

## 2. Materials and Methods

**2.1. Subjects.** A cross-sectional study was made in 86 consecutive outclinic male adult subjects. Physical examination and routine biochemistry were performed to exclude significant diseases. Some of the obese subjects had an impaired glucose tolerance test (according to WHO criteria), but none was overtly diabetic [8]. Some had moderate hypertension. None of the subjects had modified prior medications and body weight over six months or reported excessive alcohol consumption before clinical investigation. Smokers were not considered as a separate group. Exclusion criteria were chronic medical conditions, vitamin D supplementation, or the use of medications affecting bone metabolism, hormonal and nutritional status, recent weight loss, and prior bariatric surgery interventions. All subjects provided informed consent before taking part in the study, and the local ethical committee approved the research protocol.

**2.2. Study Protocol.** Body mass index (BMI) was calculated dividing weight (kilograms) by the square of length (meters). Blood samples were obtained in the morning (07.00–08.00 am) after an overnight fast. Sera were frozen at  $-80^{\circ}\text{C}$  until analysis. All subjects underwent an oral glucose (75 g) tolerance test, and samples were taken at 0, 30, 60, 90, 120, and 180 minutes for glucose and insulin determinations, as well as routine assay for total and HDL cholesterol and triglycerides. To assess insulin sensitivity, we calculated the HOMA-IR using the formula (fasting insulin in  $\text{mU/L} \times \text{fasting glucose in mmol/L}/22.5$ ). The hormonal evaluation included OSCA,  $17\beta$ -estradiol (E2), T, 25-OH vitamin D (vitamin D), parathyroid hormone (PTH), sex hormone binding globulin (SHBG), thyroid stimulating hormone (TSH), free T3 (fT3), free T4 (fT4), and prolactin (PRL). Nonspecific inflammatory markers as fibrinogen and C reactive protein (CRP) were also evaluated.

**2.3. Assays.** OSCA, T, E2, TSH, fT3, and fT4 were measured with solid phase commercial RIAs (provided by Diagnostic Products, Los Angeles, CA, and Diagnostics Systems Laboratories, Inc., Webster, TX). TSH, PRL, PTH, and SHBG levels were measured by immunoradiometric assay (provided by Diagnostic Products, Diagnostics Systems Laboratories, Inc., and Radim, Pomezia, Italy). Plasma glucose, serum total cholesterol, HDL cholesterol, and triglycerides were measured by an automated clinical chemistry analyser (Modular P, Roche Diagnostics GmbH, Mannheim, Germany). Insulin and vitamin D levels were measured by radioimmunoassay while CRP circulating levels were measured by latex agglutination. The intra- and interassay coefficients of variations for all hormonal assays ranged between 3.4–6.2% and 3.6–8.4%, respectively. All determinations were performed in duplicate.

**2.4. Measurements.** Anthropometric measurements included weight and height; body weight was measured as the

subjects were fasting overnight and wearing underwear. Body fat mass, fat-free mass (kg), and both lumbar and femoral BMD were measured by dual-energy X-ray absorptiometry (DEXA) (Hologic 4500 RDR), with coefficient of variation of  $<1\%$  for bone density and  $<1.5\%$  for fat mass [9]. Amount of trunk fat mass was distinguished from peripheral and appendicular fat mass as a measure of abdominal adiposity. In particular, trunk fat was defined as the adipose tissue localized within the region below the chin, delineated by vertical lines within the left and right glenoid fossae bordering laterally to the ribs and by the oblique lines that cross the femoral necks and converge below the pubic symphysis [10].

**2.5. Statistical Analysis.** Data are presented as the mean  $\pm$  SD of absolute value except for skewed variables, which were presented as median (interquartile range 25–75%). Continuous variables were normally distributed (Shapiro-Wilk test) and were analysed using Student's *t*-test for paired or unpaired data, Pearson's  $\chi^2$  test, Wilcoxon's signed-rank test, and Spearman's correlation analysis, as appropriate. Multiple stepwise regression analysis was performed to determine the associations between serum OSCA, BMD, T, and E2 concentration after adjusting for potential confounders. A *P* value  $<0.05 \pm$  SD was considered statistically significant. Statistical analysis was performed using the computer statistical package SPSS/10.0 (SPSS, Chicago, IL, USA) and SAS/6.4 (SAS Institute Cary, NC, USA).

## 3. Results

Baseline characteristics of the study population are shown in Table 1. Eighty-six adult men (mean age 45 yrs) were subdivided, according to their BMI, into overweight (BMI  $< 30$ ), class-I obesity (BMI  $> 30 \leq 35$ ), class-II obesity (BMI  $> 35 \leq 40$ ), and class-III obesity (BMI  $> 40$ ). Each group showed normal levels of total and HDL cholesterol and triglycerides (Table 1). No significant difference in the percentage of smokers and hypertensive men among the groups was present. Increased HOMA index ( $P < 0.0001$ ), plasma fibrinogen, and C reactive protein ( $P < 0.0001$ ) but lower levels of vitamin D ( $P < 0.0001$ ) were found (Table 1). As expected, both trunk fat and HOMA increased for higher BMIs ( $P < 0.0001$ , resp.); regression analysis demonstrated that trunk fat was found to be the independent variable from BMI (Table 2).

T levels were evaluated in different BMI subgroups, and, as expected, they were significantly lower in the higher BMI categories (BMI  $> 35 \leq 40$ ,  $P < 0.01$ ; BMI  $> 40$ ,  $P < 0.001$ ; Table 1) but independent of age. Also, T showed an inverse relationship with trunk fat ( $P < 0.01$ ,  $r^2 = -0.26$ ; Figure 1(a)) but a direct relationship with OSCA ( $P < 0.0001$ ,  $r^2 = 0.23$ ; Figure 1(c)). Noteworthy, OSCA levels showed the same trend to decrease in the groups with a higher BMI (BMI  $35 \leq 40$ ,  $P < 0.01$ ; BMI  $> 40$ ,  $P < 0.0001$ ; Table 1) showing also an inverse relationship with HOMA index ( $P < 0.001$ ,  $r^2 = -0.20$ ; Figure 1(d)) and trunk fat ( $P < 0.001$ ,  $r^2 = -0.17$ ; Figure 1(b)). A direct correlation between T and bone mineral density at lumbar (BMDL) and neck hip site (BMDH) ( $P < 0.001$ ,  $r^2 = -0.20$ ,  $P < 0.001$  Figure 2(a);

TABLE 1: Biochemical and hormonal characteristics of the patients according to different BMI. Values are expressed as means  $\pm$  SD.

|                        | BMI < 30<br>(n = 20) | BMI 30 $\leq$ 35<br>(n = 22) | BMI 35 $\leq$ 40<br>(n = 22) | BMI > 40<br>(n = 22) |   |
|------------------------|----------------------|------------------------------|------------------------------|----------------------|---|
| BMI                    | 27 $\pm$ 1.2         | 32 $\pm$ 1.6**               | 38 $\pm$ 1.5***              | 44 $\pm$ 4***        | **P < 0.001<br>***P < 0.0001              |
| Mean age (yrs)         | 51 $\pm$ 12          | 42 $\pm$ 18                  | 47 $\pm$ 10                  | 46 $\pm$ 13          | —   |
| Total chol. (mg/dL)    | 195 $\pm$ 43         | 197 $\pm$ 42                 | 215 $\pm$ 34                 | 202 $\pm$ 39         | —   |
| HDL (mg/dL)            | 42 $\pm$ 10          | 42 $\pm$ 7                   | 41 $\pm$ 6                   | 44 $\pm$ 4           | —   |
| TGL (mg/dL)            | 119 $\pm$ 53         | 131 $\pm$ 54                 | 126 $\pm$ 52                 | 151 $\pm$ 58         | —   |
| Fibrinogen (mg/dL)     | 263 $\pm$ 81         | 303 $\pm$ 70                 | 366 $\pm$ 76                 | 402 $\pm$ 133**      | **P < 0.001                               |
| CRP (ng/mL)            | 3 $\pm$ 1.5          | 3 $\pm$ 1.8                  | 4 $\pm$ 2.4                  | 5.5 $\pm$ 2.1**      | **P < 0.001                               |
| HOMA                   | 2.7 $\pm$ 1.4        | 4.4 $\pm$ 2.1***             | 5.7 $\pm$ 2.5***             | 6.4 $\pm$ 2.2***     | ***P < 0.0001                             |
| OSCA ( $\mu$ g/L)      | 25.34 $\pm$ 10.7     | 19 $\pm$ 10.1                | 16.6 $\pm$ 9.1*              | 12.5 $\pm$ 7.1***    | *P < 0.01<br>***P < 0.0001                |
| SHBG (nmol/L)          | 25 $\pm$ 10          | 24 $\pm$ 13                  | 25 $\pm$ 10                  | 27 $\pm$ 12          | —   |
| PTH (pg/mL)            | 38 $\pm$ 14          | 39 $\pm$ 13                  | 39 $\pm$ 13                  | 49 $\pm$ 14          | —   |
| Vitamin D (ng/mL)      | 29 $\pm$ 7           | 23 $\pm$ 5*                  | 19 $\pm$ 8**                 | 14 $\pm$ 9***        | *P < 0.01<br>**P < 0.001<br>***P < 0.0001 |
| 17 $\beta$ -E2 (pg/mL) | 29 $\pm$ 11          | 32 $\pm$ 9                   | 31 $\pm$ 13                  | 35 $\pm$ 16          | —   |
| Testosterone (ng/mL)   | 4.4 $\pm$ 1.06       | 4.5 $\pm$ 1.24               | 3.17 $\pm$ 1.32*             | 2.69 $\pm$ 1.1**     | *P < 0.01<br>**P < 0.001                  |
| Trunk fat (%)          | 25.5 $\pm$ 6.6       | 33.74 $\pm$ 6.1***           | 37.11 $\pm$ 5.2***           | 41.86 $\pm$ 7.1***   | ***P < 0.0001                             |

TABLE 2: (a) Regression analysis: Trunk fat is an independent variable from BMI. (b) Regression analysis: total T levels is an independent variable from age.

(a)

| Coefficients <sup>a</sup> |                             |            |                           |        |       |
|---------------------------|-----------------------------|------------|---------------------------|--------|-------|
| Model                     | Unstandardized coefficients |            | Standardized coefficients | t      | Sig.  |
|                           | B                           | Std. error | Beta                      |        |       |
| (Constant)                | 25.611                      | 5.582      |                           | 4.588  | 0.000 |
| OSCA                      | 0.015                       | 0.080      | 0.027                     | 0.185  | 0.854 |
| HOMA                      | -0.130                      | 0.297      | -0.069                    | -0.437 | 0.665 |
| Total_T                   | 0.492                       | 0.499      | 0.147                     | 0.985  | 0.330 |
| FBN                       | -0.002                      | 0.008      | -0.036                    | -0.208 | 0.836 |
| PCR                       | -0.329                      | 0.332      | -0.154                    | -0.990 | 0.328 |
| Trunk_Fat                 | 0.224                       | 0.100      | 0.330                     | 2.253  | 0.030 |

<sup>a</sup>Dependent variable: BMI.

(b)

| Coefficients <sup>a</sup> |                             |            |                           |        |       |
|---------------------------|-----------------------------|------------|---------------------------|--------|-------|
| Model                     | Unstandardized coefficients |            | Standardized coefficients | t      | Sig.  |
|                           | B                           | Std. error | Beta                      |        |       |
| (Constant)                | 71.519                      | 15.074     |                           | 4.745  | 0.000 |
| OSCA                      | -0.098                      | 0.216      | -0.068                    | -0.454 | 0.652 |
| HOMA                      | -0.441                      | 0.802      | -0.088                    | -0.550 | 0.585 |
| Total_T                   | -3.447                      | 1.348      | -0.387                    | -2.558 | 0.014 |
| FBN                       | 0.006                       | 0.023      | 0.043                     | 0.244  | 0.808 |
| PCR                       | 0.271                       | 0.897      | 0.048                     | 0.302  | 0.764 |
| Trunk_Fat                 | -0.290                      | 0.269      | -0.160                    | -1.078 | 0.288 |

<sup>a</sup>Dependent variable: Age.



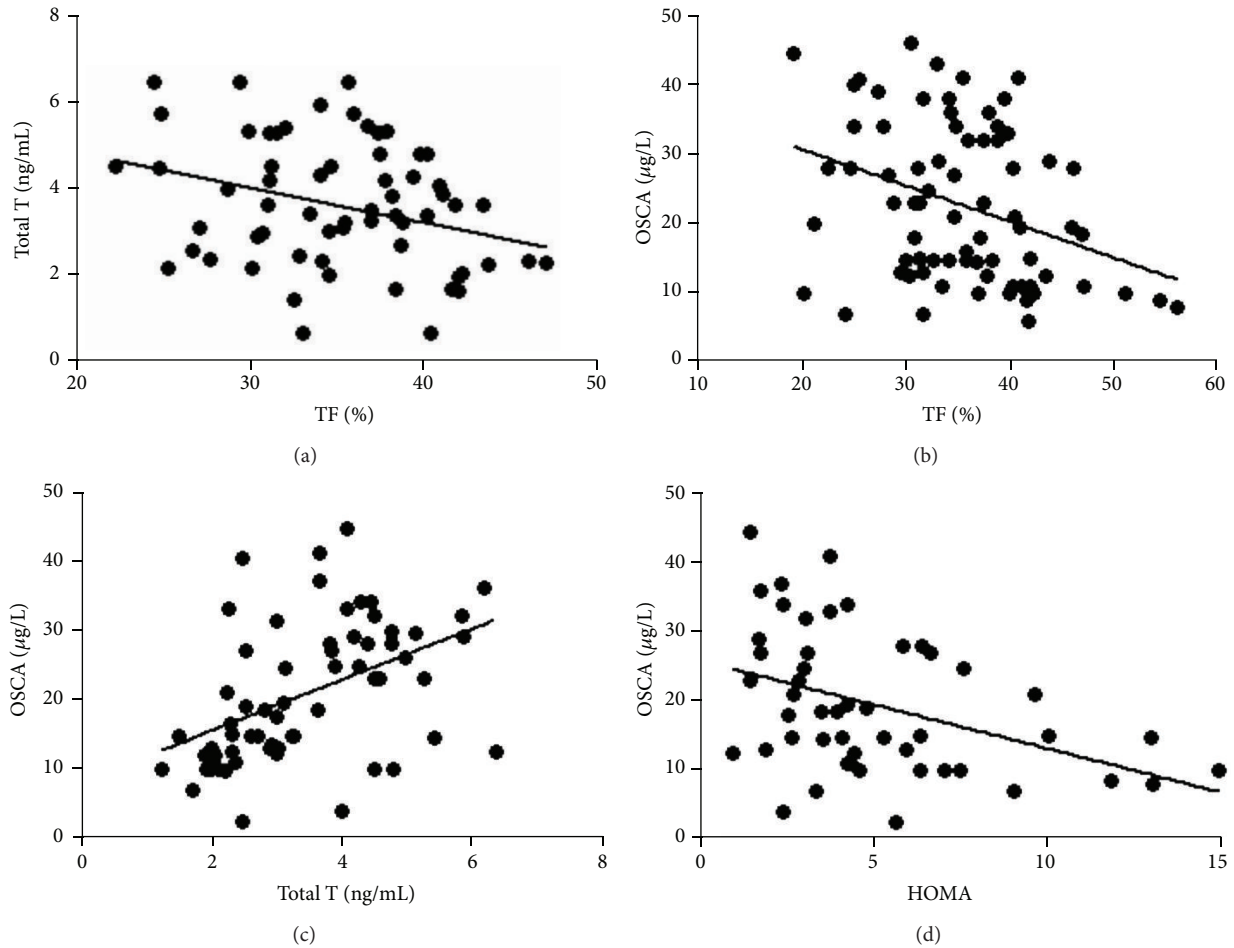


FIGURE 1: Correlation between (a) total testosterone (total T) and trunk fat (TF) ( $P < 0.01$ ,  $r^2 = -0.26$ ), (b) osteocalcin (OSCA) and TF ( $P < 0.001$ ,  $r^2 = -0.17$ ), (c) OSCA and Total T ( $P < 0.0001$ ,  $r^2 = 0.23$ ), (d) OSCA and HOMA ( $P < 0.001$ ,  $r^2 = -0.20$ ).

$r^2 = -0.24$ , Figure 2(c), respectively) was found; regression analysis showed that T levels were independent from age (Table 2(b)). On the contrary, an inverse correlation between  $17\beta$ -estradiol (E2) serum levels and BMDL and BMDH ( $P < 0.001$ ,  $r^2 = -0.20$ ,  $P < 0.001$  Figure 2(b);  $r^2 = -0.19$ , Figure 2(d), respectively) was observed.

#### 4. Discussion

As far as we are aware, this is the first study that demonstrates a relationship between metabolic, bone, and testicular functions in humans. In particular, our retrospective analysis carried out in a series of overweight and obese outclinic patients shows that OSCA, a product protein produced by osteoblasts [11], involved in multiple regulatory pathways, might play a pivotal role in the regulation of glucose metabolism, energy expenditure, and testosterone synthesis in humans. Trunk-fat mass influences cardiovascular diseases because of its impact on glucose and lipid metabolism [12, 13].

Elevated OSCA levels have been associated with improved glucose tolerance and with increased  $\beta$  cell function and insulin sensitivity [14]. Indeed, the uncar-

boxylated forms of OSCA (ucOSCA) appear to be associated with improved glucose tolerance in healthy men [15]. Thus, the balance between cOSCA and ucOSCA seems to be a key factor in this paradigm. Alfadda et al. [16] found a relationship between OSCA and lipid indices in patients with T2DM, and both OSCA and ucOSCA were significantly lower in patients with metabolic syndrome (MetS) compared to those without MetS, independently of BMI. In patients with MetS, ucOSCA was significantly and positively correlated with HDL cholesterol, while OSCA was significantly and negatively correlated with serum triglycerides [16, 17].

In the present study, we did not investigate whether this carboxylation plays an active role in biological actions of OSCA. However, it is known that circulating OSCA concentration is associated with parameters of glucose metabolism, insulin sensitivity, and fat mass in humans [18]. These observations clearly suggest a role of OSCA as a regulator of systemic energy metabolism so that we can speculate that the skeleton might act as an endocrine organ by secreting OSCA, which leads to increased insulin secretion, lowering blood glucose, and increasing insulin sensitivity and energy expenditure. The endocrine interplay between insulin, osteoblast,

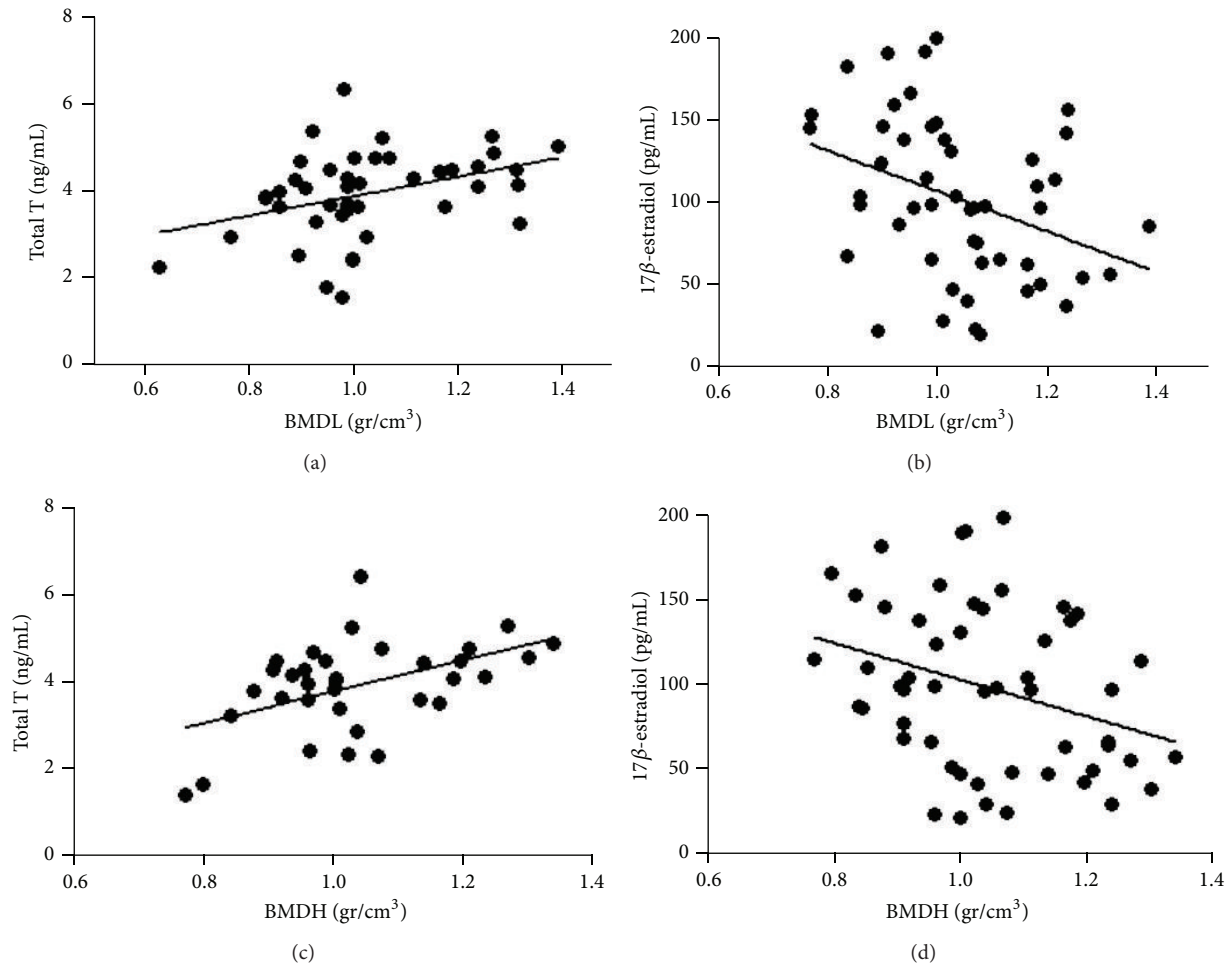


FIGURE 2: Correlation between (a) total testosterone (total T) and lumbar bone mineral density (BMDL) ( $P < 0.001$ ,  $r^2 = -0.20$ ), (b) 17- $\beta$ -estradiol and BMDL ( $P < 0.001$ ,  $r^2 = -0.20$ ), (c) total T and hip BMD (BMDH) ( $P < 0.001$ ,  $r^2 = -0.24$ ), (d) 17 $\beta$ -estradiol and BMDH ( $P < 0.001$ ,  $r^2 = -0.19$ ).

and OSCA seems to represent a complex regulatory pathway. In this loop, we were able to demonstrate that additional components may be added and that OSCA may represent a positive regulator of T production. Additionally, our data show that our patients were vitamin D deficient according to their BMI, and, thus, vitamin D deficiency might have also played a role in the reduced T levels. Interestingly, trunk fat more than BMI was an independent predictor factor of vitamin D levels, and, furthermore, reduced T levels resulted to be independent of age. It must be pointed out that, as previously shown by others [16], we have not found significant correlation between E2 levels and bone mineral density at both lumbar and femoral sites. Indeed, previous studies have suggested a pivotal role of estrogens in the regulation of skeletal homeostasis in men [19, 20]. However, our data do not support a correlation between E2 levels and higher bone mineral density and are in agreement with recent findings on the positive regulatory role of E2 in body composition and sexual function in men [21]. On the contrary, lower levels of T significantly correlate with lower bone mineral density in obese male. These data strongly

indicate that androgens, more than estrogens, play a pivotal role in the maintenance of male skeletal health.

Finally, an alteration of vitamin D levels and low OSCA level altered insulin sensitivity strongly suggesting the existence of an important interplay between bone tissue, energy metabolism, and gonadal status, likely for the presence of a common pathogenic mechanism leading to the development of metabolic and skeletal diseases.

## 5. Conclusions

Our data provide, for the first time, new lines of evidence of the role of OSCA. In fact, a relationship between visceral fat mass (not BMI), insulin sensitivity, OSCA, and testosterone synthesis occurs in humans, which significantly correlates with skeletal health. Furthermore, OSCA may exert different actions on metabolic and gonadal health status, other than the well-established function as marker of bone remodelling. In our view, these findings have relevant implications for the ageing male in that they clearly suggest OSCA as a

novel marker for metabolic, skeletal, and testicular health throughout the life.

## Acknowledgments

This work was partly supported by Grants from PRIN 2009 (Programmi di Ricerca di Rilevante interesse Nazionale no. 2009KENS9K.004 to Lorenzo M. Donini) and PRIN 2011 (Programmi di Ricerca di Rilevante interesse Nazionale no. 052013 to Silvia Migliaccio).

## References

- [1] F. Oury, G. Sumara, O. Sumara et al., "Endocrine regulation of male fertility by the skeleton," *Cell*, vol. 144, no. 5, pp. 796–809, 2011.
- [2] P. Ducy, M. Amling, S. Takeda et al., "Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass," *Cell*, vol. 100, no. 2, pp. 197–207, 2000.
- [3] N. K. Lee, H. Sowa, E. Hinoi et al., "Endocrine regulation of energy metabolism by the skeleton," *Cell*, vol. 130, no. 3, pp. 456–469, 2007.
- [4] A. Gray, J. A. Berlin, J. B. McKinlay, and C. Longcope, "An examination of research design effects on the association of testosterone and male aging: results of a meta-analysis," *Journal of Clinical Epidemiology*, vol. 44, no. 7, pp. 671–684, 1991.
- [5] R. L. Ferrini and E. Barrett-Connor, "Sex hormones and age: a cross-sectional study of testosterone and estradiol and their bioavailable fractions in community-dwelling men," *American Journal of Epidemiology*, vol. 147, no. 8, pp. 750–754, 1998.
- [6] G. Corona, G. Forti, and M. Maggi, "Why can patients with erectile dysfunction be considered lucky? the association with testosterone deficiency and metabolic syndrome," *Aging Male*, vol. 11, no. 4, pp. 193–199, 2008.
- [7] A. Aversa, R. Bruzziches, D. Francomano et al., "Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study," *Journal of Sexual Medicine*, vol. 7, no. 10, pp. 3495–3503, 2010.
- [8] K. G. Alberti and P. Z. Zimmet, "Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation," *Diabetic Medicine*, vol. 15, no. 7, pp. 539–553, 1998.
- [9] E. A. Greco, R. Fornari, F. Rossi et al., "Is obesity protective for osteoporosis? Evaluation of bone mineral density in individuals with high body mass index," *International Journal of Clinical Practice*, vol. 64, no. 6, pp. 817–820, 2010.
- [10] E. A. Greco, D. Francomano, R. Fornari et al., "Negative association between trunk fat, insulin resistance and skeleton in obese women," *World Journal of Diabetes*, vol. 4, no. 2, pp. 31–39, 2013.
- [11] E. Puchacz, J. B. Lian, G. S. Stein, J. Wozney, K. Huebner, and C. Croce, "Chromosomal localization of the human osteocalcin gene," *Endocrinology*, vol. 124, no. 5, pp. 2648–2650, 1989.
- [12] G. R. Hajer, T. W. Van Haeften, and F. L. J. Visseren, "Adipose tissue dysfunction in obesity, diabetes, and vascular diseases," *European Heart Journal*, vol. 29, no. 24, pp. 2959–2971, 2008.
- [13] M. Gössl, U. I. Mödder, E. J. Atkinson, A. Lerman, and S. Khosla, "Osteocalcin expression by circulating endothelial progenitor cells in patients with coronary atherosclerosis," *Journal of the American College of Cardiology*, vol. 52, no. 16, pp. 1314–1325, 2008.
- [14] Y.-C. Hwang, I.-K. Jeong, K.-J. Ahn, and H.-Y. Chung, "Circulating osteocalcin level is associated with improved glucose tolerance, insulin secretion and sensitivity independent of the plasma adiponectin level," *Osteoporosis International*, vol. 23, no. 4, pp. 1337–1342, 2011.
- [15] Y.-C. Hwang, I.-K. Jeong, K. J. Ahn, and H. Y. Chung, "The uncarboxylated form of osteocalcin is associated with improved glucose tolerance and enhanced  $\beta$ -cell function in middle-aged male subjects," *Diabetes/Metabolism Research and Reviews*, vol. 25, no. 8, pp. 768–772, 2009.
- [16] A. A. Alfadda, A. Masood, S. A. Shaik, H. Dekhil, and M. Goran, "Association between osteocalcin, metabolic syndrome, and cardiovascular risk factors: role of total and undercarboxylated osteocalcin in patients with type-2 diabetes," *International Journal of Endocrinology*, vol. 2013, Article ID 197519, 6 pages, 2013.
- [17] C. Lormeau, B. Soudan, M. D'Herbomez, P. Pigny, B. Duquesnoy, and B. Cortet, "Sex hormone-binding globulin, estradiol, and bone turnover markers in male osteoporosis," *Bone*, vol. 34, no. 6, pp. 933–939, 2004.
- [18] B. Ongphiphadhanakul, R. Rajatanavin, S. Chanprasertyothin, N. Piaseu, and L. Chailurkit, "Serum oestradiol and oestrogen-receptor gene polymorphism are associated with bone mineral density independently of serum testosterone in normal males," *Clinical Endocrinology*, vol. 49, no. 6, pp. 803–809, 1998.
- [19] V. Rochira, M. Faustini-Fustini, A. Balestrieri, and C. Carani, "Estrogen replacement therapy in a man with congenital aromatase deficiency: effects of different doses of transdermal estradiol on bone mineral density and hormonal parameters," *Journal of Clinical Endocrinology and Metabolism*, vol. 85, no. 5, pp. 1841–1845, 2000.
- [20] J. P. Bilezikian, A. Morishima, J. Bell, and M. M. Grumbach, "Increased bone mass as a result of estrogen therapy in a man with aromatase deficiency," *The New England Journal of Medicine*, vol. 339, no. 9, pp. 599–603, 1998.
- [21] J. S. Finkelstein, H. Lee, S. M. Burnett-Bowie et al., "Gonadal steroids and body composition, strength, and sexual function in men," *The New England Journal of Medicine*, vol. 369, pp. 1011–1022, 2013.