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Research Article

Prevalence of Hypogonadism in a Male Population below 60 Years of Age with Metabolic Syndrome

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Introduction. A high prevalence of hypogonadism (H) has been demonstrated in patients with metabolic syndrome (MetS). There are no studies in Latin America showing the prevalence of H in MetS in men below 60 years of age. The objective of this study was to determine the association between the MetS and levels of testosterone (T) and calculated free testosterone (cfT) in men under 60 years of age. *Methodology.* 101 men were included between 18 and 60 years who met the IDF MetS criteria. The diagnosis of H was considered <70 pg/mL of cfT and <10.4 nmol/L (300 ng/dL) of T. *Results.* H with T was 17.8% and 20.7% with cfT. The H according to T had higher BMI, waist circumference, visceral fat, markers of insulin resistance, SHBG, LH, and E2. We find an inverse but weak significant correlation between T, visceral fat, and HOMA index. The linear regression analysis showed that E2 and visceral fat are determinants in H. *Conclusion.* We found a high prevalence of H using T and cfT in Chilean patients with MetS below 60 years of age, who turned out to be more insulin-resistant and have more visceral fat, waist, and E2 than non-H.

1. Introduction

The metabolic syndrome (MetS) corresponds to a series of alterations that establish an association between high blood pressure (HBP), glucose intolerance, elevated triglycerides (TGS), and reduction of high density lipoprotein (HDL) cholesterol, which determines a higher risk of developing cardiovascular disease and diabetes [1]. There is a high prevalence of MetS worldwide [2], despite the fact that the diagnostic criteria are not uniform [3]. Latin American urban populations do not escape this reality since they exhibit a high prevalence of abdominal obesity, with a consequent increase in cardiovascular risk and development of Type 2 Diabetes Mellitus (T2DM) [4]. Some genetic variations aggravated by environmental factors (sedentary lifestyle, inadequate nutrition, and migration) have been claimed as major etiological factors of this condition [5]. In our country, a study with data obtained from the National Health Survey (ENS) in 2003 determined the prevalence of MetS, in the adult Chilean population, to be 31.6% and 36.8% based, respectively, on updated ATP III and IDF criteria [6]. Furthermore, epidemiological studies have reported consistently a high prevalence of low testosterone (T) levels in men with MetS and T2DM compared to the general population, of even up to 50% of hypogonadism (H) in men with a diagnosis of T2DM [7, 8]. The etiopathogenesis is not yet clear, but the role of abdominal obesity and the increase in visceral fat have been highlighted as a common and essential pathophysiological element [5].

It is unclear whether visceral fat determines an effect on the hypothalamic level, the testicular level (Leydig cells), or a combination of both [9], although apparently the H is a factor that precedes the MetS, which is why in recent years the studies showing this important association have multiplied [10, 11].

H in men, defined as a deficit of T associated or not with symptoms, is considered a CVD risk factor [12, 13]. With age,

there is a significant drop in T [14]; however in men under 60 years old, the fall does not occur in a relevant way, unless there are concomitant factors that accelerate it, such as diabetes, obesity, and chronic and metabolic diseases [11, 15, 16].

There are no studies of hypogonadism associated with MetS in populations younger than 60 years in Chile and Latin America, so that we decided to conduct a study to determine the prevalence of this association in an urban Chilean population, determining anthropometric, metabolic, and hormonal variables.

2. Methodology

We recruited patients who sought preventive medical checkups or management of malnutrition due to excess, at a private medical center affiliated to a health insurance and a university. For this study, male patients aged between 18 and 60 years, with a BMI less than 40, being sedentary, and meeting criteria of metabolic syndrome according to IDF 2005 [17] were considered. Patients who had a history of diabetes mellitus, uncompensated hypothyroidism, tumors, surgery or radiation in the hypothalamic-pituitary area, anosmia, liver, kidney or heart disease, cancer, neuroleptic or tricyclic/IRSS use, or hormone replacement therapy (HRT) with T were excluded from the study. All patients signed informed consent approved by local ethic committee.

At the day of assessment, with 8 hours fasting, the following measurements were performed: anthropometry (weight, height, BMI, blood pressure, and waist circumference) and analysis of body composition (percentage of muscle, body fat, and visceral fat) with a bioimpedanciometry device, OMRON model HBF 510 [18, 19] and biochemical analysis consisting of glycaemia and basal and postload insulinemia (used to calculate insulin sensitivity indices: HOMA and QUICKI), lipid panel, prolactin, TSH, total testosterone, LH, SHBG, and estradiol (E2). Free testosterone (cfT) was calculated using the Vermeulen formula [20, 21].

Laboratory tests were conducted by the chemiluminescence method, with BIORAD trial (Immunoassay—MCC1, MCC2, and MCC3 Liquid) for T and SHBG and BIORAD (Immunoassay Plus) for LH, TSH, Prolactin, E2, and lipids. Both kits were with an intertrial variability of less than 10%. Those patients with elevated levels of LH and prolactin were excluded from the analysis. The diagnosis of H was considered to be below 70 pg/mL of cfT [22] and T less than 10.4 nmol/L (300 mg/dL), based on reference data from the published literature [23–26].

2.1. Statistical Analysis. The normality of variable distribution was determined using the Shapiro Wilk test. Variables with a normal distribution are expressed as mean ± standard deviation. Variables with a nonnormal distribution are expressed as median (p25–p75). The significance of differences between median values was calculated using ANOVA for variables with normal distribution and Kruskal Wallis test for nonparametric variables. Linear regression equations were used to calculate the association between the presence of hypogonadism and the rest of variables. For estimation of fasting parameters of insulin resistance we used HOMA and QUICKI. Since all these parameters had different units of measure, no effort was made to carry out concordance analyses.

Table 1: Variables expressed in average normal distribution and standard deviation. Nonnormal distribution variables, expressed as median and confidence interval.

n	101
Age (yr)	38 (17–60)
IMC (kg/mt^2)	33 ± 4.76
Waist (cm)	109 (107–113)
Body fat (%)	34.5 ± 4.75
Body lean mass (%)	30.9 (30.2–31.4)
Visceral fat (%)	16 ± 4.26
Basal glycemia (mmol/L)	5.32 (5.21–5.38)
Postload glycemia (mmol/L)	6.49 (5.9–7.15)
Basal insulin (mIU/L)	16.6 (14.7–17.9)
Postload insulin (mIU/L)	121 (99–144)
HOMA	3.8 (3.5–4.2)
QUICKI	0.31 ± 0.024
Cholesterol (mmol/L)	5.21 ± 0.92
Cholesterol HDL (mmol/L)	0.98 (0.96–1.03)
Triglyceride (mmol/L)	2.21 (1.85–2.66)
Testosterone (nmol/L)	12.4 (11.8–13.4)
SHBG (nmol/L)	24 (22–25.6)
c free testosterone (pg/mL)	89.9 (38.2–170)
LH (mU/mL)	4.28 (3.6–4.78)
Estradiol (pmol/L)	105 (98.7–110.5)
TSH (μIU/mL)	2.36 (2.18–2.7)
Prolactin (pmol/L)	435 (378.2–448)

3. Results

The prevalence of hypotestosteronemia in our population was 17.8% with T and 20.7% with cfT. Of the total evaluated patients, 101 were selected for analysis. The characteristics of subjects are presented in Table 1. The median age was 38 years, with an average BMI of 38 kg/m^2, no patient presented BMI within normal range, 28% were overweight, 63% were obese, and 9% had morbid obesity. With respect to waist circumference, only 27 patients (26%) were within the normal range (less than 102 cm).

When evaluating subjects according to presence or absence of H, we found that the characteristics of the group varied according to the testosterone cut-off criteria used. When using T level under 10.4 nmol/L (300 ng/dL), we noticed the H patients to have more visceral fat and insulin resistance indicators (QUICKI and HOMA), as well as presenting less LH, E2, and SHBG with significant differences with the non-H group (Table 2). When using a cfT cut-off of 72 pmol/mL we observed that the H group presented greater visceral fat, BMI, waist circumference, and rates of insulin resistance, with a stronger association than the T cut-off group, also showing lower levels of E2 and SHBG. With this cut-off point, statistical significance of LH levels is lost,

Table 2: Variables expressed in average normal distribution ± standard deviation analyzed by ANOVA. Nonnormal distribution variables, expressed as median + confidence interval, analyzed by Kruskal-Wallis test.

Testosterone (cut-off < 10.4 nmol/L)	Hypogonadism (18)	No hypogonadism (83)	p
Age (yr)	45 (31–55)	37 (34–40)	NS
IMC (kg/mt^2)	35 ± 4.5	33 ± 4.7	NS
Waist (cm)	114 ± 11	108 ± 10	NS
Body fat (%)	35.5 ± 4.8	34 ± 4.2	NS
Body lean mass (%)	29 ± 2.6	30 ± 2.5	NS
Visceral fat (%)	18 ± 4.4	15 ± 4.0	0.003
Basal glycemia (mmol/L)	5.49 (4.99–5.71)	5.27 (5.21–5.38)	NS
Postload glycemia (mmol/L)	6.32 ± 1.23	7.10 ± 2.22	NS
Basal insulin (mIU/L)	19.9 (16–32)	15.4 (13–17)	0.01
Postload insulin (mIU/L)	107 (92–218)	127 (97–152)	NS
HOMA	4.2 (3.9–7.27)	3.7 (3.1–3.9)	0.01
QUICKI	0.31 (0.29–0.31)	0.32 (0.31–0.32)	0.02
Cholesterol (mmol/L)	5.30 ± 0.88	5.18 ± 0.98	NS
Cholesterol HDL (mmol/L)	0.89 (0.88–0.98)	0.89 (0-93–1.26)	NS
Triglyceride (mmol/L)	2.40 (1.67–3.46)	2.20 (1.70–2.67)	NS
c free testosterone (nmol/L)	16.3 (12–20)	25 (23–27)	0.001
SHBG (nmol/L)	67 ± 13	96 ± 22	0.000
LH (mU/mL)	3.65 (2.05–4.74)	4.37 (3.81–4.9)	0.04
Estradiol (pmol/L)	89.2 (78.9–106)	106.4 (99–117.4)	0.01
TSH (μIU/mL)	2.4 (1.6–2.88)	2.35 (2.14–2.88)	NS
Prolactin (pmol/L)	432 (282–435)	347 (421–430)	NS

Table 3: Variables expressed in average normal distribution ± standard deviation, analyzed by ANOVA. Nonnormal distribution variables, expressed as median + confidence interval, analyzed by Kruskall Wallis test.

c free testosterone (cut-off < 72 pmol/mL)	Hypogonadism (21)	No hypogonadism (80)	p
Age (yr)	41 ± 13	37 ± 11	NS
IMC (kg/mt^2)	35 ± 5.05	32.9 ± 4.5	0.04
Waist (cm)	114 ± 11	108 ± 10	NS
Body fat (%)	36 ± 5.2	34 ± 4.5	NS
Body lean mass (%)	30 (27–31.2)	31.3 (30–31.8)	0.03
Visceral fat (%)	17.9 ± 4.9	15.4 ± 3.9	0.017
Basal insulin (mIU/L)	20.1 (16–28)	15.1 (13.3–17.1)	0.01
HOMA	4.55 (3.9–6.3)	3.7 (3.0–3.9)	0.01
QUICKI	0.30 ± 0.02	0.317 ± 0.023	0.034
SHBG (nmol/L)	16.4 (13.7–19.8)	25.5 (23–27.9)	0.0001
LH (mU/mL)	3.7 (2.2–4.96)	4.3 (3.7–4.9)	NS
Estradiol (pmol/L)	97.2 (78.9–106.8)	107 (99–117.4)	0.04

although they continue to be low (Table 3). While analyzing the composition of these groups, we observed that they were not composed of the same subjects, adding significance to the findings.

As seen in the tables, our population of hypogonadal subjects presented decreased levels of LH, a difference that is statistically significant, despite remaining within the ranges of normality of the measurement. We did not perceive an association between levels of LH and the rest of the variables analyzed. Once evaluating the association between the cfT and the rest of the variables, a weak but statistically significant correlation is noticeable with visceral fat percentage (r –0.27, p 0.007) (Figure 1) and HOMA index (r –0.20, p 0.04).

As expected, the relationship between testosterones and LH level is significant in the overall group (r 0.76, p 0,000), if analyzed separating the hypo- versus normogonadal group (using different cut-off points); we find that despite remaining significant, the association is much more direct in the hypogonadal group (data not shown), correlation that is not modified when analyzed along with other factors.

Table 4: Regression analysis is noted as the determinating variables of hypogonadism estradiol and 303 visceral fat. R^2 0.10, p 0.02.

Hypogonadism (cut-off 72 pmol/mL)	Coefficient	$p > \|t\|$
Estradiol	−0.0071	NS
Visceral fat	0.0253	0.014
Age	−0.0004	NS
Constant	0.0255	NS

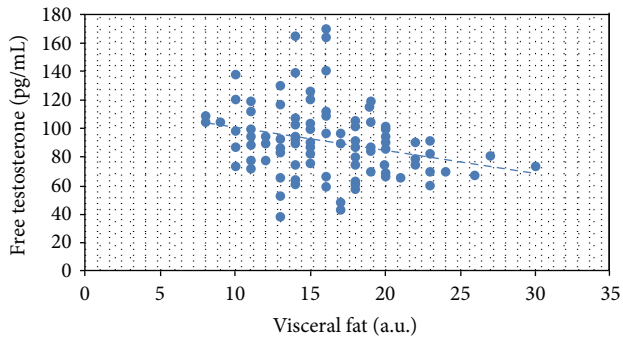

Figure 1: Relationship between visceral fat and free testosterone levels measured by impedance 299 measurement. (r −0.28, p 0.01).

After performing linear regression analysis, we see that the levels of E2 and visceral fat are determining factors in the presence of H, leaving the rest of the variables without statistical significance (Table 4). Furthermore, the correlation between the levels of E2 and the percentage of body fat and BMI is significant (r 0.24, p 0.01 and r 0.26, p 0.01, resp.), not detecting in this sample correlation between E2 levels and other biochemical parameters such as glycaemia, insulinemia, or cholesterol.

4. Discussion

Various studies have shown prevalence of H, linked to obesity and diabetes, defined by low T with associated symptoms, in ranges from 17% to 30% [27, 28], reaching up to 42% when considering levels of cfT [28]. Since Dhindsa et al. [29] published his study of H in T2DM, it has been shown that H is associated with diabetes, independent of adiposity. Suggesting that low androgen levels may be a risk factor for diabetes in men [27, 30]. Our study population below 60 years of age presented H at a higher percentage than the general population, which is approximately 1.5% [31, 32]. In recent studies, the prevalence in healthy men above 60 years of age with late onset hypogonadism (LOH) is described to be between 2 and 4% [33, 34]. It is worth mentioning that our patients with MetS exhibit more H and earlier than the elder population. Several studies on nondiabetic obese patients show prevalence rates of 15% to 57% [14, 20, 35, 36].

The recognition and pursuit of H in young MetS carriers can be of great importance in identifying subpopulations with increased CVD risk, since H is considered another factor that complements CVD risk in the MetS [1, 37, 38]. Our series is the first to describe hypotestosteronemia as being related to MetS in an urban young male population of Chile.

The diagnosis of H, in addition to decreased levels of T, includes the existence of associated sexual symptoms. It is important to note that men with low T are not always symptomatic. A recent study determined the association between the MetS and T levels in patients with erectile dysfunction (ED) [39]; this study included 280 patients above 40 years of age, 16.4% had hypotestosteronemia and this was even more frequent in patients with MetS (22.9% versus 11.7%); however the presence of H was not decisive for the levels of symptomatic ED and the correlation was low between T levels and the occurrence of symptoms. The decline in T will therefore not always reflect on symptoms and it is not appropriate to wait for these to appear in order to search for hypotestosteronemia [38].

Although the pathophysiology of H in the MetS is not entirely clear, the inhibitory effect is preferably at a hypothalamic-pituitary level, but direct inhibitory effects on Leydig cell secretion have been described [9, 11]. Our data support the hypothesis of a hypothalamic-pituitary effect because, in our group, the H patients presented lower values of LH and a negative correlation with the T compared to the non-H. Although age has a negative correlation, there are no significant differences between the ages of the H and the non-H.

It is noteworthy that the correlations of total and visceral fat were neither relevant nor significant and that there was only slightly positive one between the cfT and visceral fat measured by bioimpedanciometry. It is possible that the sensitivity of our bioimpedanciometry measuring instrument might have affected certain values, although it is a validated method [18, 40]. However the correlations with the waist measurement, weight, and BMI were also unimportant, although H patients were significantly more obese and had greater waist circumference and more insulin resistance, determined by values of basal insulin, HOMA, and QUICKI.

Androgen receptors are expressed in the visceral adipocytes, liver, and muscle among other tissues, determining tissue specific responses to androgens [32]; the dilemma of determining which is first, the H, defined by hypotestosteronemia, or the increase in total and visceral fat, is not yet clear; however, in insulin resistance conditions, the inverse interaction between the visceral fat and T seems to increase [7, 11, 41]. Several factors have been studied: TNFa, adipokines, regulation of fat signal by neuropeptide Y, and elevated leptin acting on hypothalamic kisspeptin which have been proposed as intermediaries in this connection [9]. Direct inhibitory effects of some of these factors on the Leydig cell, especially leptin and insulin, have also been suggested in this connection [42–44].

Insulin itself has direct hypothalamic axis stimulating effects in *in vitro* conditions [45]; however hyperinsulinemia has negative correlations with the T *in vivo* [46]. In our work we did not observe these relationships. In our study the values of E2 resulted in normal-low ranges for males, but significantly higher ones in non-H patients compared to H, and the linear regression analysis showed that the E2 was one

of the determinant variables of the presence of hypogonadism (Table 4). The increase in circulating and tissue-specific E2 due to increased aromatase activity is one of the etiological mechanisms associated with H in obese patients [35]. The INCHIANTI study [47], using 574 Italian patients above 65 years old, showed a positive association between the levels of E2 (total and free) with the components of the MetS, independent of age. Williams [48] in a recent article suggests that the activation of aromatase in tissues (FAT, breast) leads to an increase of cell E2, which along with increased insulin and leptin, could induce H, metabolic syndrome, and mitogenic prostatic growth, via activation of estrogen receptors. It is possible that, in conditions of insulin resistance, the decrease of SHBG allows the presence of less plasmatic E2 but free E2 at a hypothalamic level acting as an LH inhibition factor and producing lower levels of testosterone. The role of E2 in men and its influence on the MetS are still unclear; yet we think that in our population it may itself be a determining factor. In conclusion, in our sample of young obese men, with metabolic syndrome, we identified a high prevalence of H. These men turned out to be more insulin-resistant and have more visceral fat and greater waist circumference than the nonhypogonadal, although the correlations with the parameters of the Mets were not significant.

We believe that the search for H in young patients with MetS is fully justified given its high prevalence in different urban populations worldwide and the fact that it can identify a population with greater comorbidity and cardiovascular risk, especially with increasing age. Correction of the H and its role in the etiology of the MetS is pending evaluation, but it seems to open a very promising future in the reduction of morbidity.

Conflict of Interests

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

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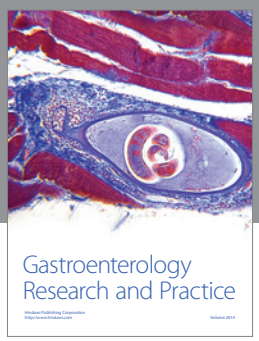

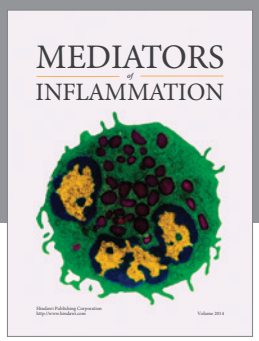

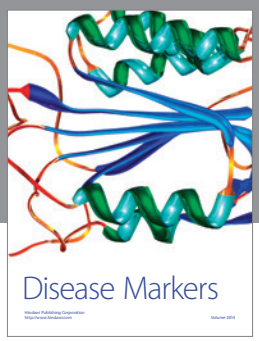

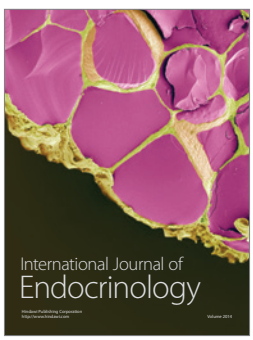

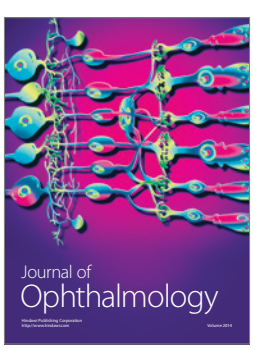

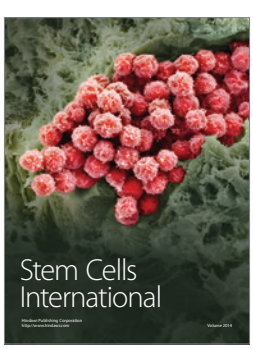

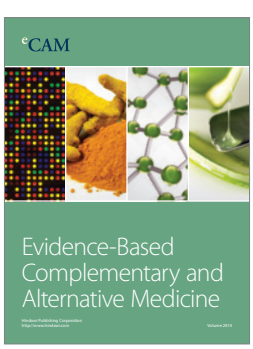

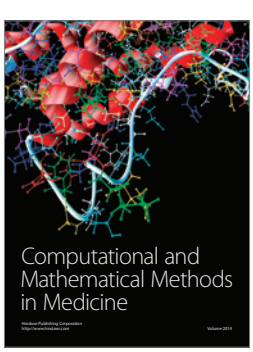

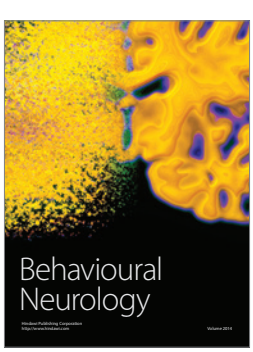

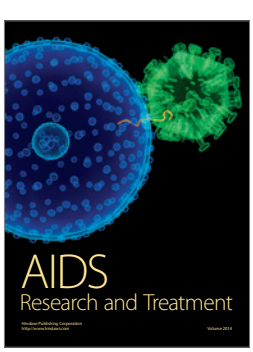

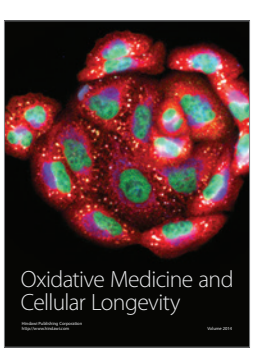

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