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*Research Article*

# Comparison of Triglyceride–Glucose (TyG) Index and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) Index in Prediction of Male Hypogonadism

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Several studies have shown the association between decreased insulin sensitivity and the risk of male hypogonadism. Homeostatic model assessment of insulin resistance (HOMA-IR) is a well-established marker of decreased insulin sensitivity. The triglyceride–glucose index (TyG), calculated as $\ln(\text{fasting triglyceride (mg/dL)} \times \text{fasting glucose (mg/dL)}/2)$, was recently suggested to be a cheaper and a reliable surrogate marker to detect insulin resistance (IR). Our aim was to compare the performance of those two indexes in the prediction of male hypogonadism. The data on 192 men from infertile couples (18–50 years; sperm concentration <20 x $10^6$/mL) and 199 population-based matched controls collected during the years 2009–2012 (baseline) were evaluated retrospectively. Half of these subjects (72 subfertile men and 122 controls) were reinvestigated 5–10 years later (median year (range): 7 (5–10)). The patients receiving any hormonal therapy were excluded. Hypogonadism was defined as fasting, morning serum testosterone below 12 nmol/L. In receiver operating characteristic curve analysis, the optimal diagnostic cutoff values for baseline HOMA-IR and TyG to predict MetS at re-examination were 2.68 (Area Under Curve (AUC) = 0.886, $p < 0.001$) and 8.60 (AUC = 0.816, $p < 0.001$), respectively. Moreover, in binary logistic regression analysis performed on the whole cohort using these thresholds for high values of HOMA-IR and high TyG, the odds-ratios (ORs) for hypogonadism were 6.48 (95% Confidence Interval (CI): 3.77–11.2; $p < 0.001$) and 3.58 (95% CI: 2.17–5.94; $p < 0.001$), respectively. Even though high HOMA-IR levels provided better risk estimates, high TyG was also highly related to the risk of hypogonadism. These markers can be utilized to identify men being at high risk of hypogonadism.

## 1. Introduction

An association between decreased insulin sensitivity and risk of male hypogonadism has been shown. Testosterone, in pancreatic B cells, triggers glucose-stimulated insulin secretion in males via binding to the androgen receptor and has protective effects against apoptosis [1]. Testosterone also regulates lipolytic responses to catecholamines and reduces lipoprotein lipase activity, especially in visceral adipose tissue, which results in increased triglyceride turnover and prevents body fat accumulation [1]. Corona et al. [2] demonstrated an increased prevalence of metabolic syndrome (MetS) and increased waist circumference, which is one of the features of MetS [3], in all age quartiles in men having low circulating testosterone values [2]. In general, these metabolic disorders are often co-existing, and the underlying mechanisms linking hypogonadism with obesity and insulin resistance (IR) are complex and possibly bi-directional. Visceral obesity may result in hypogonadism (directly or via obesity-induced IR), but hypogonadism itself can also cause obesity and IR, consequently creating a vicious circle [4].

Low total testosterone (TT) values (hypogonadism) have also been shown to be common among subfertile men [5]. Hence, infertile obese patients are considered to be at particularly high risk of presenting with low testosterone levels.

On the other hand, a recent study has shown that even nonobese metabolically unhealthy subfertile men may have

an increased risk of low testosterone levels [6]. In most clinics, assessment of semen quality is the main focus of investigation of men with fertility problems. Thus, early detection of hypogonadism and, thereby, prevention of its long-term sequelae can be missed.

This problem may be overcome with the help of biochemical markers, which have the potential to assess metabolic status. These markers, at the same time, might aid in detecting hypogonadism in subfertile males and help stratify risk groups. Therefore, this study addresses the possible use of these markers to detect hypogonadism in subfertile men.

The homeostatic model assessment of insulin resistance (HOMA-IR) is widely used for identifying subjects being at high risk of developing or having MetS [7, 8]. Recently, a new marker called the triglycerides–glucose index (TyG) has been proposed as an alternative to HOMA-IR with the added benefit of being cheaper and more user-friendly [9, 10, 11].

The primary aim of this study was, therefore, to compare TyG, in comparison to HOMA-IR performs in defining men as being at particularly high risk of hypogonadism. The special focus was on their usefulness in men, who were categorized according to their state of fertility or body mass index (BMI).

## 2. Materials and Methods

*2.1. Subjects.* During the period 2009–2012 (baseline), 391 males were included in a study of metabolic parameters in subfertile men at the Reproductive Medicine Centre, Skåne University Hospital in Malmö, Sweden [5]. The study cohort included two different subgroups:

(i) Group 1: Men from couples attempting unsuccessfully, for at least 12 months, to achieve pregnancy ($n = 192$). Those being 18–50 years old and having sperm concentration $<20 \times 10^6$/mL in at least two consecutive semen samples were identified as subfertile. A sperm concentration of $20 \times 10^6$/mL was used as a cutoff since, at the start of the study, according to the latest World Health Organization (WHO) semen manual [12], this level was considered the lowest level of normozoospermia. As an alternative definition of subfertile men, the cutoff values from the two most recent versions of the WHO semen manual, $15 \times 10^6$/mL [13] and $16 \times 10^6$/mL [14], respectively, were also tested. Patients with a history of obstructive azoospermia, diagnosed with normal reproductive hormone levels and testicular volume, as well as normal spermatogenesis in the testicular biopsy, were not included.

(ii) Group 2: Population-based age-matched controls ($n = 199$). The Swedish Population Registry was used for the study to select subjects for the control group. Invitation was sent to 977 men, and 199 of them, matching our age criteria and having no previous or present fertility problems and no untreated metabolic problems, were accepted to participate in the study.

Twenty-four men were excluded from the study due to treatment with one of the following: antidiabetic medication (subfertile men, $n = 3$; control group, $n = 1$), androgens (subfertile men, $n = 9$), lipid-lowering medication (subfertile men, $n = 4$; control group, $n = 3$) or corticosteroids (subfertile men, $n = 3$; control group, $n = 3$). Two patients were using different drugs at the same time. No patients were taking other drugs with an impact on androgen levels, such as opioids or aromatase inhibitors. Thus, finally, 175 subfertile men and 192 controls were included in the study, respectively.

The study had ethical approval from the regional ethical review board at Lund University (Dnr. 2010/660). Following detailed written and oral information about the study, all participants gave written consent.

*2.2. Study Outline.* At baseline fasting blood samples were taken from all subjects between 8.00 am and 10.00 am and used for analyses of metabolic markers and reproductive parameters.

The subjects who participated in the first part of the study (baseline investigation) were asked to be part of a follow-up examination carried out from 2018 to 2019. Approximately half of the participants (76 subfertile men and 128 controls) accepted to be reinvestigated.

*2.3. Semen Analysis.* Semen samples were collected at the Reproductive Medicine Centre, Skåne University Hospital in Malmö, Sweden. The samples were obtained only from subfertile patients, following sexual abstinence intervals of 2–7 days. Semen analysis was carried out according to the 1999 WHO semen manual, which was the most recent version at the time of recruitment of study subjects [12].

*2.4. Biochemical Markers.* All measurements were performed by routine methods at the Department of Clinical Chemistry, Skåne University Hospital, Malmö (Sweden). TT, luteinizing hormone (LH), fasting glucose, triglycerides, HbA1c, and insulin levels were included in our study. The analytical methods for laboratory tests, the lowest limit of detection, and the range of reference values are illustrated in Table S1.

We also computed the following parameters related to IR: the HOMA-IR (glucose $\times$ insulin)/22.5 ) [7] and the triglycerides/glucose index (TyG: ln ( fasting triglyceride (mg/dL) $\times$ fasting glucose (mg/dL)/2)) [10].

*2.5. Biochemical Hypogonadism.* Biochemical hypogonadism was defined as TT < 12.0 nmol/L [15]. Men with LH > 8.6 IU/L and TT $\geq$ 12 nmol/L were considered as presenting with compensated (subclinical) hypogonadism (i.e., normal TT with elevated LH). The LH cutoff level was set according to the normal reference values of the laboratory (normal range for men <50 years: LH 1.7–8.6 IU/L) as previously described [5].

*2.6. MetS.* We defined the MetS utilizing the National Cholesterol Education Program Adult Treatment Panel III 2002 (NCEP-ATP III) criteria [3].

*2.7. Statistical Analysis.* SPSS Statistics 28.0 (IBM, Somers, IL, USA) package was used for performing statistical analyses. Group characteristics were given as medians and ranges.

TABLE 1: The baseline characteristics of the participants.

| Variables | Subfertile men, $n = 175$ | Healthy controls, $n = 192$ | Variables | Men who participated in the follow-up, $n = 204$ | Men who did not participate in the follow-up, $n = 163$ |
|---|---|---|---|---|---|
| Age (years) | 34.6 (22.7–48.4) | 37.9 (24.1–49.6) | Age (years) | 36.4 (24.1–49.6) | 35.2 (22.7–48.4) |
| Height (cm) | 180 (154-–204) | 182 (164–199) | BMI (kg/m$^2$) | 25.3 (18.4–40.4) | 25.7 (18.2–50.3) |
| Weight (kg) | 86.8 (47.6–145) | 82.2 (55.8–139) | Glucose (mmol/L) | 5.20 (4.20–6.60) | 5.20 (4.10–19.1) |
| BMI (kg/m$^2$) | 26.1 (18.4–50.3) | 24.8 (18.2–46.4) | Insulin (mIE/L) | 7.10 (2.00–53.0) | 7.95 (2.00–58.0) |
| FSH (IE/L) | 8.20 (1.20–73.4) | 3.50 (1.00–15.9) | Triglycerides (mmol/L) | 1.00 (0.30–6.70) | 1.10 (0.40–7.20) |
| LH (IE/L) | 6.30 (1.80–43.0) | 4.50 (0.90-–11.6) | | | |
| Testosterone (nmol/L) | 14.1 (1.90–40.9) | 16.0 (5.40–41.7) | Testosterone (nmol/L) | 15.1 (1.90–41.7) | 15.1 (4.00–32.0) |
| TyG | 8.37 (7.25–11.2) | 8.34 (7.39–10.2) | | | |
| HOMA-IR | 1.87 (0.40–14.2) | 1.71 (0.44–12.4) | | | |

BMI: body mass index; TyG: triglyceride–glucose index; HOMA-IR: homeostatic model assessment of insulin resistance. Medians (ranges) are shown.

(i) Receiver operating characteristic (ROC) analysis was performed to define cutoff values of HOMA-IR and TyG at baseline investigation to predict MetS at follow-up. For that analysis, men who had MetS at baseline ($n = 25$) were excluded. Fifteen subjects with newly diagnosed MetS were identified at follow-up.

(ii) Based on the cutoff levels, defined at point 1, a logistic regression analysis was performed, including all subjects ($n = 367$), to test the association between HOMA-IR or TyG below/above the cut-off level and ±hypogonadism. Subsequently, the same analysis was done with compensated hypogonadism as an endpoint.

(iii) Additionally, in order to assess if HOMA-IR and TyG perform differently according to BMI and fertility status of the subject, we reperformed logistic regression analyses based on various study groups, namely subfertile men, controls, overweight-obese (BMI > 25) and nonoverweight (BMI ≤ 25), respectively. To define subfertility, three sperm concentration thresholds (i.e., 20 x $10^6$/mL, 15 x $10^6$/mL, and 16 x $10^6$/mL) were independently tested.

(iv) Spearman Rho correlation test was applied to assess whether HOMA-IR and TyG were associated with sperm concentrations. Additionally, Kruskal–Wallis test was used to compare TyG and HOMA-IR in three different sperm concentration categories: (I) nonobstructive azoospermia (NOA); (II) severe oligospermia (> 0 x $10^6$/mL and ≤ 5 x $10^6$/mL); and, (III) moderate oligospermia (> 5 x $10^6$/mL and <20 x $10^6$/mL).

The analysis, including sperm concentration, was only performed on data from the subfertile group, as semen data were not available for men from the background population.

The statistical significance level was defined as $p < 0.05$.

## 3. Results

### 3.1. Characteristics of Subjects at Baseline and Follow-up.
Table 1 details the baseline characteristics of all men. Surgical correction for varicocele was previously performed on five subfertile subjects (2.8%) and on one person (0.5% of the cohort) in the control group.

As shown in Table 1, median age, BMI, glucose, insulin, triglyceride, and testosterone levels were also calculated in participants and nonparticipants at follow-up assessment. The median (ranges) age of participants and nonparticipants at baseline was 36.4 (24.1–49.6) and 35.5 (22.7–48.4) years, respectively. The number of subjects with MetS and hypogonadism at baseline and follow-up was 16 and 14, respectively. The median value of insulin was within the normal reference range in both groups (7.10 (2.00–53.0) mIE/L for participants vs. 7.95 (2.00–58.0) mIE/L for nonparticipants, respectively).

### 3.2. Defining Cutoff Levels for HOMA-IR and TyG for the Prediction of Developing MetS.
According to the ROC analysis (Figure 1), the baseline cutoff values of the TyG index and HOMA-IR in relation to MetS at follow-up were 8.60 and 2.68, respectively.

### 3.3. Association between HOMA-IR and TyG above Cutoff and Hypogonadism in the Entire Cohort.
At binary logistic regression analysis based on all study participants, both HOMA-IR (Odds Ratio (OR) = 6.48; 95% Confidence Interval (CI): 3.77–11.2; $p < 0.001$) and TyG (OR = 3.58; 95% CI: 2.17–5.94; $p < 0.001$) above cut-offs were associated with significantly increased OR of hypogonadism ($n = 88$).

Levels above the respective cutoffs for HOMA-IR (OR = 0.49; 95% CI: 0.17–1.46; $p = 0.201$) and TyG (OR = 0.24; 95% CI: 0.07–0.79; $p = 0.020$) were not associated with risks of compensated hypogonadism ($n = 31$).

### 3.4. Subgroup Analysis of HOMA-IR and TyG with Subfertility.
HOMA-IR above cut-off was significantly associated with hypogonadism in both groups (i.e., OR = 11.0 (95% CI: 5.09–23.7; $p < 0.001$) in the subfertile group and OR = 2.82 (95% CI: 1.18–6.74; $p < 0.001$) in the control group), respectively. Conversely, for TyG the figures were OR = 4.59 (95% CI: 2.30–9.16; $p < 0.001$) and OR = 2.84 (95% CI: 1.29–6.25; $p < 0.001$), respectively (Table 2).

No statistically significant association was observed for compensated hypogonadism.
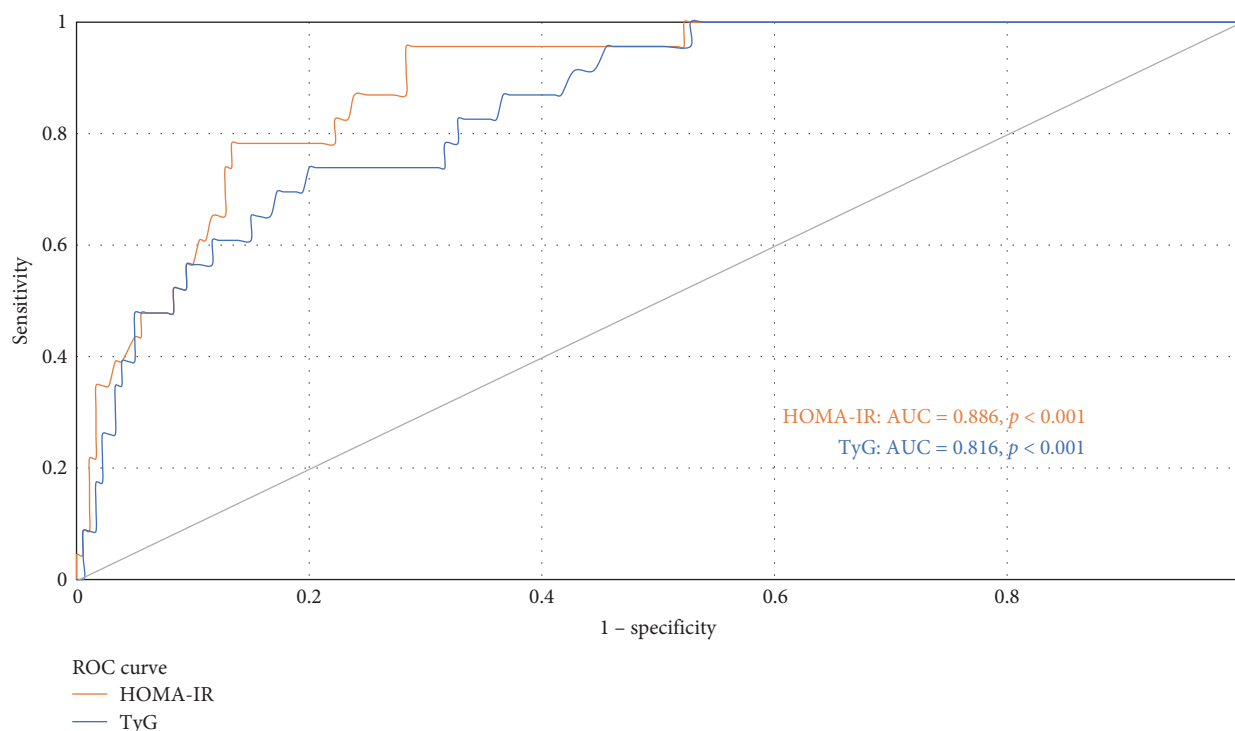
FIGURE 1: ROC curve of sensitivity versus specificity of HOMA-IR and TyG in future metabolic syndrome. The reference curve is also shown.

TABLE 2: Logistic regression analysis: OR for hypogonadism ($n = 88$) and compensated hypogonadism ($n = 31$) according to high/normal HOMA-IR and TyG: subfertile men and healthy controls.

| | Subfertile group ($n = 175$) | | | | Control group ($n = 192$) | | | |
|---|---|---|---|---|---|---|---|---|
| | $p$ | Odds ratio ($B$) | 95% CI | | $p$ | Odds ratio ($B$) | 95% CI | |
| | | | Lower | Upper | | | Lower | Upper |
| Hypogonadism | | | | | | | | |
| HOMA-IR | <0.001 | 11.0 | 5.09 | 23.7 | 0.020 | 2.82 | 1.18 | 6.74 |
| TyG index | <0.001 | 4.59 | 2.30 | 9.16 | 0.010 | 2.84 | 1.29 | 6.25 |
| Compensated hypogonadism | | | | | | | | |
| HOMA-IR | 0.050 | 0.29 | 0.08 | 0.99 | 0.686 | 1.60 | 0.16 | 15.9 |
| TyG index | 0.013 | 0.15 | 0.03 | 0.67 | 0.871 | 0.83 | 0.08 | 8.13 |

Hypogonadism: total testosterone < 12 nmol/L; Compensated hypogonadism: total testosterone ≥ 12 nmol/L, and LH > 8.6 IU/L.

Moreover, the risk estimates were almost identical when the WHO 2010 and 2021 criteria, $<15 \times 10^6$/mL and $<16 \times 10^6$/mL, respectively, were applied.

3.5. Subgroup Analysis of HOMA-IR and TyG with Obesity. In the entire cohort, according to HOMA-IR, the ORs for hypogonadism were 4.42 (95% CI: 2.35–8.32; $p < 0.001$) in the overweight-obese group and 8.73 (95% CI: 2.07–36.9; $p < 0.001$) in the non-overweight group, respectively. Moreover, whilst TyG above cut-off was associated with significant increased OR of hypogonadism in overweight–obese group (OR = 3.08; 95% CI: 1.67–5.66; $p < 0.001$), this was not the case in the non-overweight group (OR = 2.14; %95 CI: 0.68–6.72; $p = 0.193$) (Table 3).

At subgroup levels, there was no significant association between those indexes and compensated hypogonadism (Table 3).

3.6. Association between HOMA-IR and TyG and Sperm Concentration. TyG index (Spearman's $p$ correlation = −0.021, $p = 0.779$) and HOMA-IR (Spearman's $p$ correlation = −0.145, $p = 0.055$) were not associated with sperm concentration. Neither HOMA-IR nor TyG differed significantly among the three sperm concentration groups (Table 4).

## 4. Discussion

Current findings demonstrate that both HOMA-IR and TyG can predict an increased risk of male hypogonadism. As a whole, risk estimates emerged to be higher for HOMA-IR than for TyG. In non-overweighted men, only high levels of HOMA-IR showed significantly increased OR of testosterone levels suggestive for hypogonadism. As compared with controls, the risk estimates seemed to be higher among subfertile men, regardless of which specific threshold for normalcy in terms of sperm

TABLE 3: Logistic regression analysis: OR for hypogonadism ($n = 85$) and compensated hypogonadism ($n = 30$) according to high/normal HOMA-IR and TyG: overweight and nonoverweight men.

| | *Overweight group ($n = 199$) | | | | *Non-overweight group ($n = 153$) | | |
| | | | 95% CI | | | | 95% CI | |
| | $p$ | Odds ratio | Lower | Upper | $p$ | Odds ratio | Lower | Upper |
|---|---|---|---|---|---|---|---|---|
| Hypogonadism | | | | | | | | |
| HOMA-IR | <0.001 | 4.42 | 2.35 | 8.32 | 0.003 | 8.73 | 2.07 | 36.9 |
| TyG index | <0.001 | 3.08 | 1.68 | 5.66 | 0.193 | 2.14 | 0.68 | 6.73 |
| Compensated hypogonadism | | | | | | | | |
| HOMA-IR | 0.240 | 0.50 | 0.16 | 1.58 | | Not valid | | |
| TyG index | 0.050 | 0.28 | 0.08 | 1.00 | | Not valid | | |

*In this analysis, missing values of the body mass index in 15 patients altered the number of men with hypogonadism and those with compensated hypogonadism. Not valid: OR cannot be calculated because the high HOMA-IR/TyG index categories are lacking in subjects with compensated hypogonadism.

TABLE 4: TyG index and HOMA-IR in subfertile patients categorized according to sperm concentration.

| Metabolic markers | NOA | Severe oligospermia | Moderate oligospermia | $p$ |
|---|---|---|---|---|
| Total included ($n$) | 57 | 62 | 49 | — |
| TyG index median (range) | 8.32 (7.25–11.2) | 8.34 (7.49–9.80) | 8.36 (7.45–10.2) | 0.792 |
| HOMA-IR median (range) | 2.08 (0.69–14.2) | 1.89 (0.40–13.8) | 1.52 (0.40–9.50) | 0.097 |

NOA, nonobstructive azoospermia; Severe oligospermia: $>0 \times 10^6$/mL and $\leq 5 \times 10^6$/mL; Moderate oligospermia: $>5 \times 10^6$/mL and $<20 \times 10^6$/mL.

concentration was implemented ($<20 \times 10^6$/mL, $<15 \times 10^6$/mL, or $<16 \times 10^6$/mL). However, no significant associations were observed in relation to compensated hypogonadism and sperm concentration.

Overall, both HOMA-IR and TyG have been utilized as metabolic markers of MetS [7, 10]. Associations between risk of sexual dysfunction, serum testosterone levels, and MetS have previously been reported [2]. MetS has been shown to be an independent risk factor for male hypogonadism [16]; in this context, testosterone therapy may improve metabolic parameters and prevent the sequelae of hypogonadism [17, 18]. However, androgen replacement may suppress sperm production and, thereby, worsen the infertility problem. The administration of human chorionic gonadotropin will not have such side effects [19], but more studies would be needed in order to evaluate its effect on metabolism. In any case, reliable predictive markers for hypogonadism are of clinical importance, and HOMA-IR has been shown to be increased among subfertile men [20] who were also found to have 10-fold increased OR of concomitant hypogonadism [5].

Likewise, TyG is a new promising metabolic marker in the prediction of hypogonadism [21, 22, 23]. In a study of 726 white-European primary infertile men, TyG and HOMA were significantly correlated with each other, and patients with TyG above the threshold had greater BMI, lower sperm concentration, and lower TT [9]. Current findings seem to confirm previous observations showing that high levels of HOMA-IR and TyG in subfertile men were both associated with increased ORs for hypogonadism. Even though HOMA-IR seems to be a better predictor than TyG, in terms of cost-effectiveness, the latter sounds as a more affordable option since measuring plasma insulin levels is relatively expensive [10]. For instance, in Sweden, the estimated cost of HOMA-IR

is approximately two times higher than TyG's; however, the OR for HOMA-IR in subfertile men is approximately twice as strong as for TyG. Nevertheless, such cost difference is non-negligible, especially in less developed countries or countries where the patients are obliged to use private services.

A cross-sectional study of 942 males showed that obesity could cause decreased levels of total and free testosterone [24], and testosterone levels markedly rose following weight loss in 2,736 men aged 40–79 years [25]. However, in obesity, free testosterone levels may reflect the hypogonadal status more accurately than TT, as sex hormone-binding globulin is usually lower. A slight decline in weight does not impact free testosterone [25]. Our data demonstrated that HOMA-IR and TyG can be used as valuable tools in predicting hypogonadism in obese males.

Interestingly enough, current findings also show that in males with a BMI below 25 kg/m$^2$, in whom the phenotype may not rise suspicion of hypogonadism, high HOMA-IR may also be indicative of low TT levels.

A previous Danish study based on data from almost 5,000 men investigated due to infertility has shown a negative association between semen quality and the risk of hospitalization due to diabetes [26]. Here, we observed that among subfertile men, sperm concentration was not significantly associated with levels of HOMA-IR or TyG. This might indicate that in men with impairment of fertility, other factors than those related to sperm output may have a negative impact on metabolic status.

The study, however, has some limitations. The exclusion of patients undergoing hormonal treatment and the 50% decrease in the number of patients in follow-up may have lowered the statistical strength of this study. We defined hypogonadal patients based on biochemical parameters and did not take

into consideration the presence or absence of clinical symptoms related to androgen deficiency, which are important factors in terms of clinical evaluation in hypogonadism [27]. Immunoassays were used to analyze TT levels, even though liquid chromatography—tandem mass spectrometry has been suggested as being the gold standard for sex hormone analyses in the research setting [28]. However, despite some uncertainties, these assays are routinely used confidently to identify men having subnormal levels of testosterone since both methods have similar outcomes concerning predicting cardiac and metabolic disease risk in adult men [29]. Moreover, we had the option to acquire a single blood sample only. However, all samples were obtained in the morning in a fasting condition, as recommended by existent guidelines [27, 30]. Finally, we did not include waist circumference in the definition of overweight–obesity, and free testosterone in identifying hypogonadal men. What should be emphasized is that our findings are only applicable to a selected group of subfertile men and not, necessarily, to the broader community in whom hypogonadism may be of concern.

The main strength of this study is that infertile subjects and population-based controls were distributed homogeneously, eliminating the risk of selection bias. We used a sample of participants who were at a relatively young age and had a low prevalence of concurrent systemic disease, which allowed us to observe how biomarkers of metabolic status were able to foresee hypogonadism in specific subgroups, such as subfertile patients without the risk of this association being mediated by comorbidity.

## 5. Conclusions

Taking into account the high risk of hypogonadism and long-term risk of metabolic disease in men with impaired fertility, current findings provide evidence that both HOMA-IR and TyG are user-friendly markers of metabolic status, which may help not only to define men with early signs of metabolic disease but even those at increased risk of testosterone deficiency.

## Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Disclosure

An earlier version of this study was presented as a poster presentation at the 12th European Congress of Andrology in Barcelona.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

Berk Hazir was responsible for the data collection or management, data analysis, manuscript writing/editing, and final approval of the version to be published. Andrea Salonia was responsible for the conception or design of the work, critical revision of the article, and final approval of the version to be published. Aleksander Giwercman was responsible for the manuscript writing/editing, conception or design of the work, critical revision of the article, and final approval of the version to be published. Angel Elenkov was responsible for the manuscript writing/editing, critical revision of the article, and final approval of the version to be published.

## Supplementary Materials

Table S1: The features of analysis of all biomarkers in the study. (*Supplementary Materials*)

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