ORIGINAL ARTICLE

Association of nocturnal penile rigidity with testosterone, metabolic syndrome, and other variables: A prospective cross-sectional pilot study

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Received 17 March 2011; accepted 18 March 2011

KEYWORDS
Erectile dysfunction; Penile rigidity; Testosterone; Metabolic syndrome; Body mass index

Abstract

Introduction: The aim was to study whether nocturnal penile rigidity (NPTR) correlates with metabolic syndrome (MetS) and testosterone in men consulting for erectile dysfunction (ED).

Materials and methods: 234 men were included in a prospective, cross-sectional pilot study. Serum total and bioavailable testosterone and other biochemical constituents were measured and compared with NPTR. Patients were classified by normal or low/abnormal penile rigidity (abnormal meaning predominant organic component of ED) and presence or absence of MetS to test the hypothesized correlations.

Results: Application of the logistic regression model to rigidity as the dependent variable showed the risk of low penile rigidity to be significantly lower for patients with higher total (OR = 0.96, 95% CI = 0.92, 0.99) or bioavailable testosterone (OR = 0.91, 95% CI = 0.84, 0.99). Patients with testosterone levels between 8 and 12 mmol/L had a quadrupled risk of low penile rigidity compared with patients with higher levels (>12 mmol/L) (OR = 3.96, 95% CI = 1.89, 8.31). Considering men without MetS, age and body mass index were associated as significant factors for low penile rigidity: age increased risk by 8% (OR = 1.08, 95% CI = 1.03, 1.13) and BMI increased it by 18% (OR = 1.18, 95% CI = 1.01, 1.38).

Conclusion: Testosterone levels are weakly associated with penile rigidity and disappear when associated with MetS.

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Introduction

Penile erection is the result of a neurovascular process modulated by psychological factors and by the hormonal status, which is at risk of suffering the same alterations as other territories of the vascular system. Literature suggesting that erectile dysfunction (ED) is an early marker for atherosclerosis, increased cardiovascular risk, and other subclinical systemic vascular diseases is very wide. ED by itself could be considered an indicator of occult cardiovascular disease (CVD) and a marker for related comorbidities, such as hypertension, dyslipidemia, and diabetes mellitus.

Obesity and abnormal distribution of fat in relation to body size are known to be risk factors for vascular disease—and are a recognized part of the metabolic syndrome (MetS) —a cluster of increased metabolic risk factors for heart disease. One consequence of MetS is endothelial dysfunction, which can be predictive of future cardiovascular alterations and involvement of the vascular system, including the penile vascular structure. The core of MetS is considered to be insulin resistance, which results in hyperinsulinism and, in conjunction with an endothelial pro-inflammatory state, in turn leads to a prothrombotic state that ultimately produces atherosclerosis. Inflammatory markers such as C-reactive protein (CRP) are high in MetS and in subjects with increased adipose tissue.

In a review, Kapoor et al. have noted that hypotestosteronemia may play a role in the pathogenesis of insulin-resistant states. Others, in experimental clinical models, reported that over a wide range of doses testosterone has no effects on insulin sensitivity. Further studies have reported an inverse association between serum fractions of testosterone and visceral obesity and insulin resistance. MetS, and the risk of type 2 diabetes mellitus. Insulin is known to inhibit sex hormone-binding globulin (SHBG), obese and insulin-resistant men with higher insulin levels, would be expected to have lower SHBG levels and consequently lower total testosterone concentrations (but not free testosterone).

Testosterone enhances sexual interest, increases frequency of sexual acts and enhances the frequency of sleep-related erections. However, studies on the effect of testosterone treatment in symptomatic patients with ED have yielded conflicting results. Age can also be considered an independent factor contributing to a decrease in circulating testosterone, and this needs to be borne in mind in all studies.

The aim of this study was to investigate whether nocturnal penile rigidity is related to serum concentrations of total testosterone, bioavailable testosterone, MetS, and other factors likely to be related to CVD.

Materials and methods

Subjects

Men consulting on account of clinical ED and older than 18 years were randomly allocated to the study. Before enrolment, all participants gave written informed consent to participate in the protocol, which had previously been approved by the institutional review committee.
Main outcome measures

All patients underwent a complete physical examination and a mean of two measurements of blood pressure in the sitting position. Body mass index (BMI) and waist circumference (WC) were recorded.

Exclusion criteria were: the presence of local penile deformities, such as Peyronie’s disease; previous treatment or surgical intervention for prostate disease; a diagnosis of or current treatment for mental or other systemic illness; and elevated prolactin levels.

Definition of the metabolic syndrome

For the purpose of the present study, diagnosis of MetS was made on the basis of the NCEP-ATPIII criteria. The presence of three or more of the following was required: abdominal obesity (waist circumference > 102 cm), fasting blood glucose (FBG) ≥ 6.1 mmol/L; triglycerides ≥ 1.7 mmol/L; high-density lipoprotein cholesterol (HDL-C) < 1.04 mmol/L; systolic blood pressure (SBP) ≥ 130 mmHg and diastolic blood pressure (DBP) ≥ 85 mmHg. Moreover, all individuals previously diagnosed with or currently in receipt of any pharmacologic therapy for type 2 diabetes, hypertension, hypertriglyceridemia, or low HDL cholesterol were considered afflicted with these factors.

Prothrombotic variables, BMI, glycosylated hemoglobin (HbA1C), and other hormonal and inflammatory markers not included in the NCEP-ATP III consensus, we measured and studied, because they are proposed to be risk determinants for CVD.

Measurement of biochemical constituents and determination of testosterone and its fractions

Blood samples were withdrawn from 8 to 10 a.m. Laboratory determinations included: complete blood count, glucose, urate, creatinine, total cholesterol, HDL-C, LDL-C, triglycerides, total protein, albumin, AST (SGOT), ALT (SGPT), HbA1c, prolactin, total testosterone, SHBG, high-sensitive C-reactive protein (hsCRP), plasminogen activator inhibitor type 1 (PAI-1) activity, and adiponectin.

Serum glucose, serum cholesterol, serum triglycerides, serum HDL-C and serum albumin were measured using a Cobas Integra 700 analyzer (Roche Diagnostics). LDL-C was calculated using the Friedewald equation, excluding patients with triglycerides > 4.52 mmol/L (400 mg/dL).

Glomerular filtration rate (GFR) was calculated with the Levey equation. HbA1c was measured using the Bio-Rad D-10 analyzer (Hercules, CA). Serum total testosterone, SHBG, and hsCRP were determined using a chemiluminescent method (Immulite 2000, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). Bioavailable testosterone was calculated using the equations proposed by Vermeulen.14 PAI-1 was tested with the Zymutest PAI-1 activity kit (HYPHEN BioMed Neuville-sur-Oise, France). Adiponectin concentrations were measured using the ELISA kit (bioVendor, Czech Republic).

Study of nocturnal penile erections

To quantify penile rigidity, all patients underwent a three-night study for nocturnal penile tumescence and rigidity (NPTR) with the Rigiscan® (Timm Medical, Minneapolis, MN, USA). This method allows for quantification and verification of the relation of spontaneous nocturnal erections with all the studied variables. Criteria for normality were: at least one episode of erection with duration of more than 5 min and with rigidity equal to or higher than 60%.15 For data analysis, men were classified as having normal or abnormal penile rigidity. The first group, men with normal penile rigidity, was considered to have minimal or no organic compromise of erection; in these patients, ED was regarded as being of central psychogenic origin and for the purpose of the study we refer to this patient set, as the group without ED. The second group, with less than 60% rigidity (low/abnormal penile rigidity), were considered to have ED with a predominantly peripheral, organic origin.

Sample size

It was calculated that a sample size of at least 192 patients (96 with ED and 96 without ED) would be required to guarantee an 80% power to detect a difference in the prevalence of MetS (in percentage terms) between the ED population (low/abnormal penile rigidity) and the population without ED (normal penile rigidity). The test was performed using a two-tailed $\chi^2$ statistic for independent samples with a 5% significance level, assuming that the success rate must be at least 43% for the ED population and 24% for the population without ED.

Statistical analysis

To assess whether serum levels of testosterone, MetS, and their biochemical markers were related to ED (low rigidity), various statistical tests were performed. Descriptive statistics was used to study patient data, proportions for categorical variables, and mean and standard deviations for continuous variables.

Total testosterone was categorized following guideline recommendations16; less than 8, between 8 and 12, or greater than 12 mmol/L. Calculated bioavailable testosterone was stratified by quartiles: less than or equal to 6.90, between 6.91 and 8.77, between 8.78 and 11.40, or greater than 11.40 mmol/L. Comparisons between continuous variables were performed using Student’s t-test when conditions were satisfied and the Mann–Whitney–Wilcoxon test when they were not. Also, when conditions were satisfied, the relationships between categorical variables were studied using the chi-square test or, alternatively, the likelihood test or Fisher’s exact test. Multivariate logistic regression models were used to assess factors associated with ED, and the rates of change in ED were studied. Different models were used for total and stratified fractions. Age and MetS were also added into the model.

The statistical analyses were performed using PASW Statistics v17.0 for Windows and SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA). The level of significance was set at $p \leq 0.05$. 
Results

Initially, 235 men consulting for ED were included in the study, but one was omitted because of refusal to undergo the nocturnal study of erections. There were no missing data.

A total of 234 men, ranging in age from 22 to 85 years and complaining of clinical ED at consultation, completed the study protocol: 78 patients had evidence of neither MetS nor abnormal nocturnal erections (ED); 23 patients without MetS presented ED; 69 patients had MetS but these were without ED; and 64 patients had both MetS and ED. We found that MetS and ED were not independent \((p < 0.001, \text{ Fisher’s exact test})\). As the proportion of patients with ED was not the same for those with and without MetS, we decided to study these groups separately. There were no statistical differences among the groups with respect to WC, triglycerides, HDL-C, or diastolic blood pressure (Table 1). In the group without MetS, statistically significant factors for ED were (Table 2): age, BMI, SHBG, and bioavailable testosterone; that is, comparing men who had high penile rigidity (without ED) with those who had lower rigidity (mainly peripheral ED), the latter were older and had a lower level of bioavailable testosterone and higher BMI and SHBG. In the group with MetS, men with ED were also significantly older, had a lower stratified total testosterone, and had higher systolic blood pressure, blood fasting glucose, and HbA1c. We could not find statistically significant differences in adiponectin, PAI-1, PCR, or GFR between men with lower rigidity and men without lower rigidity in either the group with or the group without MetS.

Tables 3 and 4 display the results obtained with the logistic regression model using as the dependent variable the presence of normal nocturnal erections. Co-variables included in the model were total testosterone, bioavailable testosterone, and their stratified fractions. It was evident that following control for age and MetS, the effects of total testosterone, bioavailable testosterone, and their fractions were not significant in men presenting lower penile rigidity (ED). More specifically, however, Table 3 shows that the risk of ED was significantly lower for those men with higher values of total testosterone (OR = 0.96, 95% CI = 0.92, 0.99) or bioavailable testosterone (OR = 0.91, 95% CI = 0.84, 0.99). With respect to stratified total testosterone, patients with levels between 8 and 12 nmol/L had a quadrupled risk of ED compared with patients with higher values (>12 nmol/L) (OR = 3.96; 95% CI = 1.89, 8.31). After adjusting for age and MetS, the magnitude of the ORs was attenuated, significance being retained only in the group with total testosterone levels between 8 and 12 nmol/L (OR = 2.63; 95% CI = 1.20, 5.76). There was not a demonstrable correlation between the patients with testosterone levels of less than 8 nmol/L and ED. When the sample was divided according to the presence or absence of MetS, the differences between patients with testosterone levels of 8–12 nmol/L and those with higher levels (>12 nmol/L) were clearly evident in the group with MetS (Table 4). However, it should be stressed that when applying the logistic regression model stratified by MetS and with the presence of other biochemical markers, testosterone was not found to be a significant factor (Table 5). When patients were grouped according to the presence or absence of MetS, age and BMI in men without MetS were the
Table 2  Characteristics of the 234 men consulting for ED: comparison of further variables (not used in the diagnosis of MetS according to NCEP-ATPIII) and testosterone among groups with and without normal nocturnal erections and MetS criteria.

<table>
<thead>
<tr>
<th></th>
<th>All (n = 234)</th>
<th>Without MetS Nocturnal erections(^a)</th>
<th>With MetS Nocturnal erections(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (n = 78)</td>
<td>Abnormal (n = 23)</td>
<td>Normal (n = 69)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53 (44–61)</td>
<td>45.9 (12.1)</td>
<td>56.7 (11.4)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>26.1 (4.5)</td>
<td>23 (22–26)</td>
<td>26 (24–28)</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>7 (4.6–9)</td>
<td>7.1 (5–8.7)</td>
<td>7.7 (5.9–12)</td>
</tr>
<tr>
<td>PAI-1</td>
<td>16 (9.4–26)</td>
<td>11 (7.6–19)</td>
<td>13 (6.5–18)</td>
</tr>
<tr>
<td>hsCRP</td>
<td>0.2 (0.1–0.4)</td>
<td>0.1 (0.06–0.2)</td>
<td>0.2 (0.1–0.3)</td>
</tr>
<tr>
<td>HbA1c (g%) (normal &lt; 5.8%)</td>
<td>5.7 (5.3–6.9)</td>
<td>5.4 (5.1–5.8)</td>
<td>5.4 (5.2–6.6)</td>
</tr>
<tr>
<td>GFR</td>
<td>91.4 (20.4)</td>
<td>94.2 (17.0)</td>
<td>90 (29.3)</td>
</tr>
<tr>
<td>Albumin</td>
<td>41 (39–43)</td>
<td>41 (39–43)</td>
<td>41 (39–43)</td>
</tr>
<tr>
<td>SHBG</td>
<td>31 (22–40)</td>
<td>29 (24–40)</td>
<td>39 (33–43)</td>
</tr>
<tr>
<td>Total T (nmol/L)</td>
<td>18 (14–22)</td>
<td>20 (15–24)</td>
<td>17 (15–20)</td>
</tr>
<tr>
<td>Stratified total T (nmol/L)(^b)</td>
<td>8 ≤ 8 ≥ 12 &gt;12</td>
<td>2.1 – 15.8 82.1</td>
<td>8 ≤ 8 ≥ 12 &gt;12</td>
</tr>
<tr>
<td>Bio T (nmol/L)</td>
<td>8.8 (6.9–11.3)</td>
<td>10 (7.8–12)</td>
<td>7 (5.9–11.4)</td>
</tr>
<tr>
<td>Stratified Bio T (nmol/L)(^c)</td>
<td>6.90 ≤ 6.90 ≥ 8.77 &gt;8.77</td>
<td>25.2 25.6 25.6</td>
<td>6.90 ≤ 6.90 ≥ 8.77 &gt;8.77</td>
</tr>
</tbody>
</table>

Results are expressed in percentages for nominal data and means (SD) or median (quartiles) for continuous data.
Chi-square test (1) was used for nominal data and Student’s t-test (2) or the Mann–Whitney–Wilcoxon test (3) for continuous data for bivariate comparisons between patients with normal and patients with abnormal nocturnal erections in the two groups with or without MetS.

\(^a\) Nocturnal erections were measured using Rigiscan® (NPTR test). Rigidity ≥60% was considered as normal, and rigidity <60% or absence of rigidity as abnormal.

\(^b\) Stratified values: Nieschlag et al.\(^{16}\)

\(^c\) Distribution by quartiles.

\(^\ast\) p < 0.05.
Table 3  Results of univariate logistic regression models (unadjusted and adjusted for age and MetS) for the association of total and bioavailable testosterone with prevalence of ED.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted for age and MetS OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total T (nmol/L)</td>
<td>0.96 (0.92, 0.99)</td>
<td>0.99 (0.95, 1.04)</td>
</tr>
<tr>
<td>Stratified total T&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8</td>
<td>1.43 (0.23, 8.79)</td>
<td>0.72 (0.11, 4.89)</td>
</tr>
<tr>
<td>8-12</td>
<td>3.96 (1.89, 8.31)</td>
<td>2.63 (1.20, 5.76)</td>
</tr>
<tr>
<td>&gt;12 (reference patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioavailable T (nmol/L)</td>
<td>0.91 (0.84, 0.99)</td>
<td>1.00 (0.91, 1.10)</td>
</tr>
<tr>
<td>Stratified bioavailable T&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6.90</td>
<td>2.95 (1.35, 6.46)</td>
<td>1.43 (0.59, 3.43)</td>
</tr>
<tr>
<td>6.91-8.77</td>
<td>1.90 (0.87, 4.17)</td>
<td>1.09 (0.46, 2.59)</td>
</tr>
<tr>
<td>8.78-11.40</td>
<td>0.97 (0.42, 2.21)</td>
<td>0.67 (0.27, 1.64)</td>
</tr>
<tr>
<td>&gt;11.40 (reference patients)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

T, testosterone.
<sup>a</sup> Odds ratio (OR) and 95% confidence intervals (95% CI).
<sup>b</sup> See Nieschlag et al. 16
<sup>c</sup> Distribution by quartiles.
<sup>*</sup> p < 0.05.

only significant factors: age increased the risk of ED by 8% (OR = 1.08, 95% CI = 1.03, 1.13) and BMI increased it by 18% (OR = 1.18, 95% CI = 1.01, 1.38). In men with MetS, age and HbA1c higher than 5.5% were the only significant factors: age increased the risk of ED by 5% (OR = 1.05, 95% CI = 1.01, 1.10) and HbA1c ≥5.5% increased it by 68% (OR = 1.68, 95% CI = 1.28, 2.22).

Discussion

In the present study, we investigated the relation between spontaneous nocturnal penile rigidity, the metabolic syndrome (MetS), and other variables, including total testosterone, bioavailable testosterone, and their stratified fractions. Furthermore, MetS was not used alone as an independent risk factor but it was also used to divide the sample based on its presence or absence.

In order to assess penile rigidity, we employed a three-night study for nocturnal penile tumescence and rigidity using the Rigiscan<sup>®</sup>. This diagnostic modality has high sensitivity and specificity and is currently considered one of the best available tools for this purpose<sup>17</sup>; nevertheless, it is the subject of some controversy<sup>18</sup>. We decided to use it because allows quantification and correlation of all variables, unlike standardized questionnaires.

Table 4  Results of univariate logistic regression models (unadjusted and adjusted for age) for the association of total and bioavailable testosterone with the prevalence of ED in groups with and without MetS.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Adjusted for age OR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>MetS = No</td>
<td>MetS = Yes</td>
<td>MetS = No</td>
</tr>
<tr>
<td>Total T (nmol/L)</td>
<td>0.97 (0.91, 1.04)</td>
<td>0.97 (0.93, 1.02)</td>
</tr>
<tr>
<td>Stratified total T&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8</td>
<td></td>
<td>0.90 (0.14, 5.66)</td>
</tr>
<tr>
<td>8-12</td>
<td>3.89 (0.89, 17.02)</td>
<td>3.02 (1.25, 7.28)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>&gt;12 (reference subjects)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioavailable T (nmol/L)</td>
<td>0.90 (0.78, 1.04)</td>
<td>0.96 (0.85, 1.07)</td>
</tr>
<tr>
<td>Stratified bioavailable T&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6.90</td>
<td>5.72 (1.58, 20.66)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>1.56 (0.55, 4.36)</td>
</tr>
<tr>
<td>6.91-8.77</td>
<td>1.37 (0.35, 5.40)</td>
<td>1.75 (0.62, 4.97)</td>
</tr>
<tr>
<td>8.78-11.40</td>
<td>0.45 (0.08, 2.56)</td>
<td>0.93 (0.32, 2.68)</td>
</tr>
</tbody>
</table>

T, testosterone.
<sup>a</sup> Odds ratio (OR) and 95% confidence intervals (95% CI).
<sup>b</sup> Guideline recommendations.<sup>16</sup>
<sup>c</sup> Distribution by quartiles.
<sup>*</sup> p < 0.05.
Table 5  Relative risk of prevalence of ED: results of multivariate logistic regression models for the association of biochemical markers grouped according to the presence (model 1) or absence (model 2) of MetS.

<table>
<thead>
<tr>
<th>Model 1</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.08 (1.03, 1.13)</td>
</tr>
<tr>
<td>BMI</td>
<td>1.18 (1.01, 1.38)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 2</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05 (1.01, 1.10)</td>
</tr>
<tr>
<td>HbA1c (g%) ≥ 5.5</td>
<td>1.68 (1.28, 2.22)</td>
</tr>
</tbody>
</table>

Response variable: NPTR. Only significant factors are listed.

* Odds ratio (OR) and 95% confidence intervals (95% CI).

Our results confirm previous reports by other authors who have found a significantly higher incidence of MetS in men with ED. Lipid markers were not significantly different from those in men without ED, probably as a consequence of previous treatment with lipid-lowering agents. This condition was taken into account when classifying patients at risk of MetS, as explained in the Methods section.

The mitogen-activated kinase pathway is considered to mediate the expression of PAI-1, a prothrombotic and profibrotic factor in part derived from endothelial cells and associated with an increased risk of diabetes and endothelial disease. Analyzing our results with respect to inflammatory and thrombotic markers according to the presence or absence of MetS, there were no differences between groups. It is open to speculation whether this absence of differences in our study may have been due to the limited size of the sample or to the anti-inflammatory or antithrombotic effect of the lipid-lowering agents usually taken for treatment.

Adiponectin is a protein hormone produced and secreted only by adipose tissue and causes an increased sensitivity to insulin. It has been reported to have a direct anti-atherosclerotic effect but, in contrast to others, we did not find significant differences in adiponectin among the groups. These results may be a consequence of the size of the studied sample or may be due to another currently unknown factor.

Animal models and laboratory studies have previously demonstrated that testosterone plays a role in the peripheral modulation of erectile function and the composition of penile tissue. The role of testosterone replacement therapy is, however, the subject of some debate. It is not clear whether such therapy is effective and safe in aging men, and while some reports have claimed that testosterone treatment improves symptoms in patients with ED and hypogonadism, others have yielded inconsistent results. Testosterone may ameliorate the expression of phosphodiesterase-5 (PDE5) inhibitors, and its use in conjunction with PDE5 inhibitors has yielded some positive results. However, a systematic review and meta-analysis of 17 trials by Boloña et al. showed that testosterone replacement in men was associated with minimal improvements in satisfaction in erectile function and only moderate improvements in sex drive. It should also be noted that while clearly low testosterone levels are consistent with a diagnosis of hypogonadism, the threshold value, especially in the older population, is the subject of debate; moreover, it is possible to speculate that variations are a consequence of the use of different methods of determination.

The results of the present study suggest that ED is related more closely to MetS than to testosterone levels. In the absence of MetS and controlling for age, we were unable to demonstrate that either total or bioavailable testosterone is associated with penile rigidity and ED. It must be stressed that in our patient group only five patients had testosterone values below 8 nmol/L and all of them were in the MetS group. On the other hand, when controlling for age, higher levels (>12 nmol/L) of total testosterone appeared to be a protective factor against ED in patients with MetS. We could not demonstrate a correlation between testosterone levels less than 8 nmol/L and ED. It is to be borne in mind that our statistical model may have had insufficient power to demonstrate the hypothesis and that the results may be due to the low sample size. Low testosterone levels were not as frequent in our patients as in other studies and correlated poorly with low penile rigidity. The present results are in line with a recently published cross-sectional studies showing that when confounding factors such as age, BMI, and other coexisting illness were controlled for, the symptoms of sexual dysfunction associated with the testosterone level were attenuated. It is to be noted that while the authors of that study employed questionnaires that can be subject to bias, in our study we employed an objective measurement of penile rigidity.

A variety of mechanisms have been suggested to influence the decline in testosterone levels in aging men. In this context, a word of caution is warranted over measurements of total testosterone and testosterone fractions when employing algorithms such as that proposed by Vermeulen because results can vary considerably, and it is suggested that there is a necessity to revalidate them in the local setting.

We found MetS to be more frequent in patients with lower penile rigidity than in those with higher rigidity (74% vs 47%). However, the first group was older than the second (57 years vs 49 years) and following adjustment for age, the difference disappeared. This indicates that ED is related more closely to age than to MetS. Similarly, while serum levels of some biochemical markers differed in those with and those without MetS, the differences disappeared when applying a logistic regression model, with age persisting as a risk factor.

There are many biological processes that occur concomitantly with male aging, and changing testosterone levels have been postulated to be at least partially responsible for a number of the observed symptoms of MetS. Examples include a decline in bone density mass with increase in fracture risk, a decline in muscular mass and strength, a decrease in physical performance, an increase in abdominal adiposity and insulin resistance, impairments in cognition and mood, and, finally, reduction in sexual function. It has been observed that testosterone treatment in intermediate-frail and frail elderly men with low to borderline-low testosterone may prevent age-associated loss of lower limb muscle strength and improve body composition, quality of life, and physical function. It has also been speculated that testosterone and its fractions may be responsible for endothelial dysfunction, which is associated with MetS.
With respect to ED, our findings may explain the absence of a clear response to testosterone treatment or supplementation in older men with normal or low-normal testosterone levels, reported by some authors. Based on our results and those of others, it may be hypothesized that testosterone influences some aspects of sexual response, but is not a determining cause. It can be speculated that the detected changes are a consequence of variation in testosterone production, plasma transport, or receptor changes. Also, it can be hypothesized that the variation in testosterone should be considered more as an epiphenomenon, a modulator, than a determinant of erection. Currently available data and evidence are insufficient to justify the use of the levels of testosterone or testosterone fractions as a marker on which to base clinical decisions, including treatment.

This study has some limitations, since it was cross-sectional. Longitudinal studies following subjects might add some further relevant information. A population bias could be possible because a wide age range and health status differences will obviously influence the prevalence of each of the components of MetS in elderly patients. Additional studies are needed to further clarify the direction of causality in the observed relationships and to determine the possible scope for preventive intervention.

Conclusions

The results of the present study show that MetS is strongly associated with ED. Classic components of MetS, such as fasting blood glucose level and blood pressure, and also factors not included in the definition of MetS, such as BMI and HbA1c, together represent significant risk factors for ED. Age must probably be considered a clear determinant of ED. In contrast, testosterone and its stratified fractions seem weakly associated with ED, especially when other risk factors are taken into account. Our results may explain the poor long-term benefits when using testosterone treatment in patients with ED; nevertheless, with higher testosterone levels, ED is less likely to appear.

It can be concluded that penile rigidity is related to age and is influenced by factors related to MetS. Future studies should aim to identify the molecular basis for the relation of testosterone with ED. Identifying and manipulating the metabolic disturbances that lead to ED would help in preventing and treating this common health problem in men.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

A Rick Mills, who technical assistant, helped in preparing the manuscript.

This work was made possible thanks to the institutional support.

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