Hypogonadism and metabolic syndrome

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ABSTRACT. Background: The relationship between metabolic syndrome (MetS), male hypogonadism and their possible interaction in cardiovascular (CV) risk stratification are not completely understood. Aim: We reviewed relationships between testosterone (T) and MetS emphasizing their possible interaction in the pathogenesis of CV diseases. Materials and methods: A systematic search of published evidence was performed using Medline (1969 to January 2011). Results: Cross-sectional data have shown that subjects with MetS have lower levels of total T (TT) (about 3 nmol/l), as hypogonadism is more evident in subjects with than in those without erectile dysfunction (ED) than in those without. Longitudinal evidence shows that low T is allocated with a higher risk of subsequent development of MetS, although the reverse condition is also possible. Which are the factors in MetS responsible for the low T is not completely clarified. In clinical studies, increased waist circumference is the major determinant of MetS-associated hypogonadism. Our experiments in rabbits do not support the idea that visceral fat is the main determinant of MetS-associated male hypogonadism. Only few randomized clinical trials have evaluated the impact of testosterone replacement therapy (TRT) in patients with MetS. Available evidence suggests that TRT decreases visceral fat accumulation and ameliorates insulin sensitivity, whereas androgen deprivation increases abdominal adiposity. Conclusions: The clinical significance of the MetS-associated hypogonadism needs further clarifications. In particular, it has not been completely clarified if low T might be considered a cause or a consequence of MetS. The benefit of TRT in term of the reduction of CV risk needs to be confirmed in larger and longer studies.

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INTRODUCTION

The term metabolic syndrome (MetS) refers to a constellation of pathological conditions (hypertension, obesity, hyperglycemia, and dyslipidemia) reflecting insulin resistance and associated with an increased cardiovascular (CV) and metabolic risk. It is well known that hypertension is a major risk factor for CV morbidity and mortality (1, 2); its prevalence is increasing worldwide, particularly in developing countries (1-3). Data from the National Health and Nutrition Examination Survey (NHANES) study (2) reported an absolute increase of 3.7% in the US in 1999-2000 up from 1988-1991. The European Male Aging Study (EMAS), a population-based survey performed in 8 European countries, showed that hypertension was the most commonly reported concomitant disease with an overall prevalence of 29% (3). The increased prevalence of hypertension could be due, at least partially, to the increasing incidence and prevalence of obesity both in Europe and in the US (4). Hypertension and obesity, along with dyslipidemia and hyperglycemia, have been found to frequently cluster together. Such grouping of risk factors for CV diseases (CVD) occur together more often than would be expected by chance alone, giving rise to a clinical entity termed MetS (5). The syndrome has been shown to be significantly associated with increased mortality (5, 6). Recent data have suggested that low testosterone (T) might be considered an additional MetS component in males (5). Cross-sectional data have shown that subjects with MetS have lower levels of T, whereas in longitudinal studies low T is allocated with a higher risk of subsequent development of MetS (7). Despite this evidence, the clinical significance of MetS and its association with male hypogonadism has not been completely clarified (4, 8). In particular, it has been reported that MetS adds little or nothing to the careful assessment of its components in predicting CVD (4, 8). In addition, within the association between low T, CVD, and MetS, it is not apparent which one is the cause and which one the consequence. While low T could contribute to the pathogenesis of CVD and MetS, the reverse is also possible (5, 9). The aim of the present review is to clarify the relationship between T and MetS in men emphasizing their possible interaction in the pathogenesis of CVD.

METS CLASSIFICATIONS

Any definition of MetS is, at present, largely arbitrary. In fact, some Authors developed their diagnostic criteria for MetS in order to identify insulin-resistant subjects, while others aimed at predicting clinical events, ranging from incident diabetes to CVD. In epidemiological studies, the National Cholesterol Education Program-Third Adult Treatment Panel (NCEP-ATPIII) criteria have been used much more often than the alternative definitions of MetS,
due to their simplicity, rather than to an intrinsic superiority (Table 1) (5). Besides the NCEP-ATPIII criteria, many other definitions also exist, including that proposed by the World Health Organization (WHO) in 1999 and the American College of Endocrinology (ACE), which requires the presence of insulin resistance or impaired glucose tolerance (5). In 2005, the International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) attempted to reconcile the different clinical definitions. In spite of this effort, their separate recommendations contained differences related to waist circumference (Table 1) (5). Recently, IDF and AHA/NHLBI representatives held discussions to attempt to resolve the remaining differences between definitions of MetS (10). Both sides agreed that abdominal obesity should not be a prerequisite for diagnosis (as considered in the 2005 IDF definition) but that it is 1 of 5 criteria, so that the presence of any 3 of 5 risk factors constitutes a diagnosis of MetS. The final results are summarized in Table 1.

The choice of parameters to be included among components of MetS is arbitrary; in fact, other metabolic alterations, linked with insulin resistance, increased the risk for CVD and diabetes, and clustering with hypertension, obesity, and dyslipidemia could be added [e.g. hyperuricemia, non-alcoholic fatty liver disease, polycystic ovary syndrome, etc. (11-13)]. Furthermore, the relative weight attributed to each component and for the diagnosis is arbitrary. Finally, thresholds for each diagnostic parameter are also arbitrary, and, in fact, they have changed over time.

**CLINICAL SIGNIFICANCE OF METS**

The prevalence of MetS depends on the criteria applied for the diagnosis. Figure 1 shows the prevalence of MetS, according to different definitions, in a large series of subjects (n=2195, mean age 57.5±9.8 y) consulting our Andrology Unit, seeking medical care for erectile dysfunction (ED), a clinical condition characterized by a high CV risk (see below). In this sample of ED subjects, prevalence of MetS ranges from 33% to 44% when NCEP-ATPIII (modified or not) or IDF criteria are used, which is more than double the prevalence reported in the general population in the same geographical area (14).

In Northern European and US populations, MetS confers a 1.5 to 3-fold increased risk of coronary artery diseases (CAD), CV death and death from any cause in the general population, as well as in patients with known CAD (15) or ED (6, 8). Considering that individual components of MetS are all CV risk factors, it is quite obvious that their combination would lead to an elevated CV risk. However, the hypothesis that the overall CV risk conferred by MetS could be greater than the sum of the risks associated with each of its individual components has not been confirmed by epidemiological studies (4, 8, 16). MetS itself is a poor indicator of absolute short term CV risk, because it does not contain key determinants of such risk, including age, serum cholesterol, gender, and smoking status (4, 5). Hence, the clinical use of this category, and in particular its utility as a predictor of CVD, has been the subject of vigorous criticisms (4, 5, 8). Accordingly, recent data from the Vascular Risk in Navarre (RIVANA) study, a survey involving 880 community dwelling men, supported the concept that MetS is no better than each of the individual components in predicting CV risk (17). We recently confirmed these observations in a subset of the aforementioned cohort of ED subjects (n=1687) followed longitudinally for 8 or 10 years at the University of Florence (6, 8) (Fig. 2). In particular, we found that having MetS at baseline (as defined by using NCEP-ATPIII criteria) increased the chance of having major CV events.

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**Table 1 - Comparisons of definitions of metabolic syndrome: National Cholesterol Education Program-Third Adult Treatment Panel (NCEP-ATPIII) and International Diabetes Federation (IDF), World Health Organization (WHO), American College of Endocrinology (ACE), American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) and common definition by IDF and AHA/NHLBI.**

<table>
<thead>
<tr>
<th>NCEP-ATPIII</th>
<th>IDF</th>
<th>WHO</th>
<th>ACE</th>
<th>AHA/NHLBI</th>
<th>IDF&amp;AHANHLBI</th>
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<tbody>
<tr>
<td>3 or more of the following</td>
<td>Central obesity (waist circumference &gt;102 cm) and 2 or more of the following</td>
<td>Central obesity (waist circumference &gt;29 cm)</td>
<td>Central obesity (waist circumference &gt;102 cm) and 2 or more of the following</td>
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<tr>
<td>Hypertriglyceridemia: triglycerides ≥150 mg/dl (1.7 mmol/l) or treatment</td>
<td>Fasting insulin in top 25%; fasting glucose ≥100 mg/dl (6.1 mmol/l); 2 h glucose ≥140 mg/dl (7.8 mmol/l) and 2 or more of the following</td>
<td>Obesity waist/hip ratio &gt;0.9 or body mass index ≥30 kg/m²</td>
<td>High risk of insulin resistance: 2h plasma glucose ≥140 (7.8 mmol/l) and &lt;200 mg/dl (11 mmol/l) and 2 or more of the following</td>
<td>3 or more of the following</td>
<td>Central obesity (population- country-specific definitions)</td>
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<tr>
<td>Hypertension: blood pressure ≥130/85 mmHg or treatment</td>
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<td>Fasting plasma glucose ≥110 mg/dl (6.1 mmol/l) or diabetes</td>
<td>Fasting plasma glucose ≥100 mg/dl (6.1 mmol/l) or diabetes</td>
<td>Microalbuminuria: urine albumin/urinary creatinine ratio ≥3.39 mg/mmol (30 mg/g)</td>
<td>Fasting plasma glucose ≥100 mg/dl (5.6 mmol/l) or treatment</td>
<td>Fasting plasma glucose ≥100 mg/dl (5.6 mmol/l) or treatment</td>
<td>Fasting plasma glucose ≥100 mg/dl (5.6 mmol/l) or treatment</td>
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