Endocrinology & Metabolic Syndrome

Metabolic Syndrome, Obesity Paradox and Testosterone Level

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Abstract

Metabolic Syndrome (MetS) is a cluster of risk factors proposed as a prevalent responsible for the development of Atherosclerotic Cardiovascular Diseases (ACVD). The predominant risk factors are obesity, abdominal obesity and insulin resistance. People in middle age with MetS are at increased absolute risk for ACVD. Criticism for MetS include its imprecise in definition, its uncertain pathogenesis as a marker of ACVD risk, and questions regarding whether this "cluster" of risk factors portend risk above and beyond the its individual components. Abdominal and visceral obesity evaluated by Waist-Circumferences (WC) and Waist-Hip-Ratio (WHR) are more specific than Body Mass Index (BMI) in definition of cardiovascular risk, but the triglycerides/HDL cholesterol ratio (TG/HDL-C) is adequate and better than MetS in diagnosis cardiovascular risk. However, evidence of an obesity paradox i.e. that obesity has a protective effect in some populations led to some confusion about the role of body mass on MetS. The role of Free Fat Mass (FFM) is relevant in this context since most studies on the obesity paradox have relied on BMI rather than body composition and fat distribution. The low BMI, prevalently due to low FFM, is correlated to exercise capacity and respiratory muscle strength is inversely related with mortality rate. Furthermore the weight loss program in overweight and obese patients increases the mortality risk because detrimental to FFM and low FFM is expression of malnutrition. Testosterone plays a central role in regulation FFM and in reduction on MetS reducing insulin resistance, improving glucose control and particularly inflammatory markers. Clinical trials conducted about the effect of testosterone on MetS evidenced a significant positive effect of testosterone administration in hypogonadal and normal patients and a positive clinical outcome. Low level of testosterone should be considered a risk factor for Mets and ACVD.

Keywords: Bariatric medicine; Obesity; Biguinide; Primary care

Introduction

MetS represent a cluster of risk factors of metabolic origin that appear to directly promote the development of atherosclerotic cardiovascular disease [1]. Use of the term MetS had a somewhat controversial history. The first definition of MetS came in 1998 from a consultation group of the World Health Organization (WHO) [2]. This group emphasized insulin resistance as the major underlying risk factor and required evidence of insulin resistance for diagnosis. In the WHO group limited the term metabolic syndrome to patients with type 2 Diabetes Mellitus (DM2). A modification of the WHO definition came in 1999 by the European Group for Study of Insulin Resistance (EGIR) who used the term insulin resistance syndrome rather than MetS [3]. This group assumed that insulin resistance was the major cause and required evidence for the diagnosis. In 2001, the National Cholesterol Education Program (NCEP) and Adult Treatment Panel III (ATP III) introduced alternative clinical criteria defining the metabolic syndrome based only on the measurement of the abdominal obesity because so highly correlated with insulin resistance and other more laborious measures of insulin resistance are unnecessary. The ATP III definition is characteristic for its clinical simplicity [4]. The American Association of Clinical Endocrinologists (AACE) in 2003 refocused on insulin resistance as the primary cause of metabolic risk [5]. They used the term insulin resistance syndrome and included impaired glucose intolerance, elevated triglycerides, reduced HDL-C, elevated blood pressure, and obesity as the major criteria. No specified number of factors qualified for diagnosis, which was left to clinical judgment. In 2005 the International Diabetes Foundation (IDF) [6] published new criteria modifying the ATPIII definition including the abdominal obesity circumference because so highly correlated with insulin resistance that makes other measures unnecessary for diagnosis.. For people of European origin (Europid), the IDF specified thresholds for abdominal obesity to be waist circumferences >94 cm in men and >80 cm in women. The clinical criteria of definition for MetS are summarized in Table 1.

Obesity in not always a risk factor for mortality. In fact, obesity paradox evidences a protective effect of overweight and moderate obesity on mortality rate in heart failure patients. Other component such lean mass and testosterone level are fundamental in prevention of MetS and ACVD.

Etiological Factors

The characterization of MetS is still subject to debate, but the most prevalent etiologic factors appear to be abdominal obesity [7] and insulin resistance [8]. Other associated conditions include physical inactivity [9] and aging [10]. Hormonal imbalance also plays a fundamental role in determining metabolic disorders given that adipose tissue is considered an endocrine organ secreting leptin [11] which affects testosterone [12] and Growth Hormone (GH) secretion [13]. These hormonal responses and the increased production of inflammatory cytokines [14] have been implicated for increasing metabolic risk. A state of chronic, low-grade inflammation has been noted to be associated with MetS [15]. Some researchers speculate that inflammation of this type underlies or exacerbates the syndrome. For example, inflammatory cytokines reportedly induce insulin resistance in both adipose tissue and muscle [16,17].

The chronic positive energy balance leading to obesity increases subcutaneous adipose tissue and acts as an energy sink protecting other tissues from ectopic fat accumulation [18]. Excess caloric intake influences fat deposition in other organs, such as the liver and Visceral Adipose Tissue (VAT) leading to low-grade chronic inflammation, dyslipidemia, insulin resistance, and ultimately, type-2 diabetes and Cardiovascular Disease (CVD) [18,19]. Various observational studies

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Risk Factor	EGIR (1999) (2)	WHO (1999)	NCEP ATP III	AACE (2003)	IDF (2006)
\Body weight	Waist Circumference: - Men greater than or equal to 94 cm - Women greater than or equal to 80 cm	WHR: - Men greater than 0.90 - Women greater than 0.85 and/or BMI greater than 30 kg/m²	Waist circumference: - Men greater than 102 cm - Women greater than 88 cm	BMI greater than or equal to 25 kg/m²	Central obesity (defined using waist circumference with ethnicity specific values) and/or BMI greater than 30 kg/m²
Blood pressure	BP ≥ 140/90 mmHg	BP ≥ 140/90 mm Hg	BP ≥ 130/85 mmHg	BP ≥ 130/85 mmHg	BP ≥ 130/85 mmHg
Lipids	TG greater than or equal to 2.0 mmol/L HDL-C less than 1.0 mmol/L	TG greater than or equal to 150 mg/dL HDL: - Men less than 35 mg/dL - Women less than 39 mg/dL	TG greater than or equal to 150 mg/dL HDL: - Men less than 40 mg/dL - Women less than 50 mg/dL	TG greater than or equal to 150 mg/dL HDL: - Men less than 40 mg/dL - Women less than 50 mg/dL	TG greater than 150 mg/dL HDL: - Men less than 40 mg/dL - Women less than 50 mg/dL
Blood sugar	3 FPG greater than or equal to 6.1 mmol/L Insulin resistance defined as the top 25% of the fasting insulin values among nondiabetic individuals	Presence of Type 2 diabetes, impaired glucose tolerance, impaired fasting glucose or insulin resistance	FPG greater than or equal to110 mg/dL	FPG=110-126 mg/dL, or 2-hour post glucose challenge greater than140 mgldL.	FPG greater than 100 mg/dL, or previously diagnosed Type 2 diabetes
Insulin Resistance	Plasma insulin _75th percentile plus any 2 of the following	IGT, IFG, T2DM, or lowered insulin sensitivity* plus any 2 of the following	None, but any 3 of the following 5 features	IGT or IFG plus any of the following based on clinical judgment	None
other		Microalbuminuria: urinary albumin excretion ratio greater than or equal to 20 mg/min or albumin : creatinine ratio greater than or equal to 30 mg/g		Family history or high risk of Type 2 diabetes, hypertension, or CVD, PCOS, old age, sedentary lifestyle	

Abbreviations: BMI: Body Mass Index, BP: Blood Pressure, cm: Centimeter, CVD: Cardiovascular Disease, dL: Deciliter, EGIR: European Group for the Study of Insulin Resistance, FPG: Fasting Plasma Glucose, g: gram, HDL-C: High Density Lipoprotein Cholesterol, IDF: International Diabetes Federation, kg: Kilogram, L: liter, m: Meter, min: minute, mmHg: Millimeters mercury, mmol: Millimole, NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III, PCOS: Poly Cystic Ovary Syndrome, TG: Triglyceride, WHO: World Health Organization, WHR: Waist.

Table 1: The Clinical criteria for definitions of the metabolic syndrome.

identify obesity [20,21] as an independent predictor of MetS and obesity appears to play a key role in the pathophysiology of all MetS components [22]. Obesity is associated with insulin resistance [23] but insulin resistance can influence several MetS components independent from obesity level, [24,25]. Some investigators give a greater priority on insulin resistance rather than obesity in the major underlying cause of the syndrome [26]. VAT is more correlated with incidence of type 2 diabetes [27]; it is predictive of type 2 diabetes [28] and of inflammatory factors [27,29]. VAT is also a strong determinant of insulin sensitivity and β-cell function and may contribute to the increased prevalence of type 2 diabetes in older populations [30]. Furthermore, an association between insulin resistance and hypertension has been documented using experimental manipulation in normal rats that developed hypertension after induction of insulin resistance and hyperinsulinemia [31]. The plasma concentrations of several inflammatory markers are also elevated in insulin resistant subjects, the first step in the process of atherogenesis. [32]. Finally, type-2 diabetes is a strong CHD risk factor [33] and represent a duration-dependent risk factor for cardiovascular events [34].

The Inflammatory Cytokines

Abdominal adipose tissue is a major source of inflammatory and thrombotic cytokines. In all women, visceral fat volume was negatively related to gene expression of leptin, adiponectin, tumor necrosis factor-α (TNF-α), fasting insulin and interleukin-6 (IL-6) [14] and reactive oxygen species [35]. The Plasminogen Activator Inhibitor-1 (PAI-1) is increased [36] and the potentially protective effect of adiponectin reduced. Adiponectin expression from adipose tissue is higher in lean subjects and women, and is associated with higher degrees of insulin sensitivity and lower TNF-alpha expression [37].

Recently, a growing interest is collected by Osteoprotegerin (OPG),

a cytokine member of the TNF receptor superfamily, binds to two ligands: RANKL (receptor activator of nuclear factor kB ligand) and TRIAL (TNF-related apoptosis-inducing ligand) [38]. OPG inhibits the nuclear factor kB effect on inflammation, skeletal and vascular system and prevent TRAIL-induced apoptosis. OPG is highly expressed in heart, lung, liver, kidney and bone marrow and is produced by vascular endothelial and smooth muscle cells. OPG is also known as Osteoclastogenesis Inhibitory Factor (OCIF) that regulates bone resorption [39]. OPG and RANKL are important regulators of mineral metabolism in both bone and vascular tissues [40]. In patients with MetS, OPG is significantly elevated and may trigger adipose tissue proinflammatory changes in MetS high-fat-diet-induced obesity [41]. Gunn et al. [42] found that OPG was increased in women with osteoporosis compared to subjects with normal BMD and osteopenia. BMD was negatively correlated with OPG and positively with weight, dairy intake of protein, vitamin B12, zinc, potassium intake. It has been suggested that OPG is a possible mediator of vascular calcification and have a potential protective or detrimental role on both vascular pathologies and tumourigenesis [43]. A strong association between serum OPG levels and cardiovascular risk factors, vascular calcification, and diabetes has been observed. Plasma OPG levels have been demonstrated to be an independent risk factor for the 10 year incidence of CVD and vascular mortality [44]. OPG is present in atherosclerotic plaques in the area of calcification and the expression pattern of OPG during atherogenesis might suggest a regulatory role of these proteins not only in osteo-clastogenesis but also in atherosclerotic calcification [45]. An increased serum OPG level is more frequently found in patients with carotid plaques [46] and predicts a significant increased risk of major cardiovascular events [47,48]. The link between vascular calcification and increased mortality is now well established [49] and OPG may potentially be a biomarker for cardiovascular risk/

damage in the MS [50].

Body Fat Distribution and MetS

Body fat determines positive or negative effects on health depending on its body distribution. The subcutaneous obesity is causing less negative effects to the patient's metabolic profile whereas patients with an excess of visceral fat are characterized by the worst metabolic profile [51-54]. The distribution of body fat is independently associated with the MetS in older men and women, particularly among those of normal BMI. Subcutaneous abdominal adipose tissue and intermuscular adipose tissue are associated with MetS only in normal-weight and over-weight men and women [22]. A dysfunctional subcutaneous adipose tissue expansion and ectopic triglyceride storage is closely related to clustering cardiometabolic risk factors [55] and is responsible of the predisposition to insulin resistance [56] and dyslipidemia [25].

Excessive fat deposition as observed in obesity represents a risk factor for Coronary Heart Disease (CHD) and is associated with a cluster of conditions that contribute to the progression of CVD [57], with HF risk in a dose dependent fashion [58] and with an increased risk of death [59]. Levitan et al. [60] analyzing two population of Swedish men and women found that not only higher BMI but higher WC and WHR were associated with higher HF hospitalization and mortality. An increased WHR, as a marker of the relative amount of abdominal fat, was associated with a significant increased risk of myocardial infarction [61]. An increased WC is associated with an elevated CHD risk, whereas a large hip girth appears to protect against CHD [62]. Canoy et al. [63] demonstrated that both WC and BMI were independently associated with incident CHD; within each BMI category (<25, 25-29.9, ≥30 kg/m^2); CHD risk increased with increasing waist circumference and within each waist circumference category (<70, 70-79.9, ≥79 cm), CHD risk increased with increasing BMI. However, the excess adiposity was associated with an increased risk of incident CHD but not necessarily death [64]. The volume of VAT (calculated using a multi-detector CT to evaluate the entire volume of abdominal visceral) was correlated imperfectly with BMI and WC and gender conferred large differences in VAT that represent a strong, independent predictor of all-cause mortality in men [65] and an important driver of cardiometabolic risk in patients with DM2 [66]. Correlation of VAT with MetS was strong for men, but absent in women [67].

The measures of central obesity is more strongly associated with the Coronary Artery Calcium (CAC) score than either the parameters assessing overall obesity or other more direct measures of visceral adiposity VAT. [68,69] and abdominal obesity is an independent predictor of CAC progression [70]. These results point to the importance of using clinical measurements of abdominal obesity to identify individuals at increased risk for atherosclerosis [71-74]. The association of longer duration of overall and abdominal obesity was associated with subclinical ACVD disease and its progression through midlife independent of the degree of adiposity [75]. In middle-aged European men, waist-to-height ratio identifies coronary risk more strongly than WC, WHR or BMI, though the difference is marginal [76]. In the Framingham heart study [77] the general measures of obesity as BMI and measures of central abdominal fat were related to the CAC and abdominal aortic calcium levels in the age- and gender-adjusted models.

Although WC is a better marker of abdominal fat accumulation than the BMI, an elevated waistline alone is not sufficient to diagnose visceral obesity. An elevated fasting triglyceride concentration could be represent when WC is increased, a simple clinical marker of excess visceral/ectopic fat but a clinical diagnosis of visceral obesity

or of the metabolic syndrome is not sufficient to assess global risk of cardiovascular disease [78]. The visceral obesity may partly be a marker of a dysmetabolic state and partly a cause of the MetS.

WC could be considered a simple and inexpensive methodology to assess for abdominal obesity and predict cardiovascular risk in general population [79] and of the most prevalent manifestation of MetS [18]. There is a great correlation between BMI and WC so that the higher the BMI, the higher will generally be the waistline WC and BMI correlations were highest for fat mass and subcutaneous adipose tissue compared to VAT [80]. WC is fairly good correlating to the amount of total abdominal fat and alone cannot distinguish between subcutaneous and visceral obesity. Waist girth is not only a crude marker of abdominal adiposity; it is also largely influenced by the patient's total adiposity [81]. Despite the importance given to WC, it is relevant to point out that an elevated BMI is not a trivial phenotype with any risk.

MetS and Risk Assessment of Atherosclerotic Cardiovascular Disease (ACVD)

People in middle age with the MetS are at increased risk for long-term cardiovascular outcomes [82,83] also in young women [84] and in different populations including Japanese [85], Chinese [86], Taiwanese [87], US Asian Indians [88] and Mediterranean hypertensive subjects [89]. MetS, defined by the WHO, ACE and IDF criteria, was associated with an increased risk of CHD mortality [90]. However, among the single components of the MetS, impaired fasting glucose, impaired glucose tolerance, low HDL cholesterol, and microalbuminuria, ACVD mortality was predicted equally or better than the composite definitions of the MetS. Mozaffarian et al. [91] suggested a limited utility of MetS for predicting total or CVD mortality in older adults compared with assessment of fasting glucose and blood pressure alone. The IDF definition has a higher prevalence of Mets compared with NCEP-ATPIII and EGIR definition but was not superior to these definitions for prediction of ACVD events for both genders. In addition, single risk factors had an equal prediction as the Mets [92]. Lawler et al. [93] in a study conducted on 3589 elderly British women found that the MetS, defined by any of the three methods, is only modestly associated with CHD risk. Socioeconomic position appears to be an important confounder in the association of the metabolic syndrome with CHD risk. Interestingly, there is a high prevalence of clustering of cardiometabolic abnormalities among normal-weight US adults, and a small but prevalent proportion of overweight and obese individuals who are metabolically healthy. The physiologic mechanisms underlying these different phenotypes and their impact on health need further investigation [94]. A recent meta-analysis showed that MetS is associated with a 2-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality [95] and others found that MetS is an independent determinant of angiographically significant coronary artery disease only among individuals at low 10-year risk for future coronary events and the individual components of the syndrome, such as impaired fasting glucose, have a stronger association with coronary artery disease than the syndrome as a whole [96]. Thus, the global cardiometabolic risk resulting from traditional risk factors combined with the additional contribution of MetS should be considered individually. The contribution of abdominal obesity to global cardiometabolic risk is an important underlying mechanism including adipocytokine, insulin resistance, lipotoxicity and ectopic fat deposition [97].

Limitation of MetS in prediction ACVD

The MetS is not more effective in identifying insulin resistance

individuals and the relationship between BMI and WC with the MetS and its components appears to be comparable. Application of the ATP-III metabolic syndrome criteria provides good specificity but low sensitivity to screen asymptomatic white adults for insulin resistance [98,99]. Thus, it seems reasonable to conclude that the MetS criteria do not necessarily provide an effective way to identify individuals who are insulin resistant. Kahn et al. [100] found that of the single components of the MetS, particularly impaired glucose intolerance and microalbuminuria, but also impaired fasting glucose and low HDL cholesterol were predictive of ACVD mortality. These findings emphasize the importance of being critical of MetS in its current form as a marker of ACVD especially in women, and advocate for a redefinition of MetS [101].

Various prospective studies have shown that microalbuminuria predicts CHD and ACVD morbidity and mortality and all-cause mortality independently of other risk factors [90,102]. Proteinuria has predicted ACVD mortality independently of the presence of MetS in non-diabetic and diabetic subjects [103]. The study of Wang [90] suggested that the MetS does not predict CHD and ACVD above and beyond its components. Although WC is a better marker of abdominal fat accumulation than BMI, a large waistline alone is not sufficient to diagnose visceral obesity. An elevated fasting triglyceride concentration could be present when WC is increased, a could be a simple clinical marker of excess visceral/ectopic fat but a clinical diagnosis of visceral obesity or the metabolic syndrome is not sufficient to assess global risk of cardiovascular disease [78]. The visceral obesity may partly be a marker of a dysmetabolic state and partly a cause of the MetS.

Flegal et al. [104] showed that the obesity-associated disease risk does not necessarily translate into higher mortality. Their meta-analysis including 97 studies, representing more than 2.88 million individuals, showed that, while obesity classes 2 and 3 (BMI >35) are associated with a significantly higher all-cause mortality compared to normal weight individuals, no difference was observed between obesity class 1 (BMI 30 to <35) and normal weight individuals. Most intriguingly, overweight (BMI 25 to <30) was associated with a significantly lower all-cause mortality compared to normal weight.

A new cardiometabolic risk: the TG/HDL-C ratio

Salazar et al. [105] evaluated cardiometabolic data obtained from 926 apparently healthy individuals and they found that visceral abdominal index does not identify individuals with an adverse cardiometabolic profile any better than the triglycerides/HDL-cholesterol ratio (TG/HDL-C). An elevated TG/HDL-C ratio appears to be just as effective as the MetS in predicting the development of ACVD [106]. Sung et al. [107] measuring various cardio-metabolic risk factors, including coronary calcium scores on 12,166 apparently healthy Korean adults found that determination of the plasma TG/HDL-C concentration ratio provides a simple way to identify individual at increased cardio-metabolic risk. The elevated TG/HDL-C ratio is useful to identify identified a greater number of "high risk" subjects, comparable to that achieved using the more complicated MetS [108-110] and predicts CHD and ACVD mortality as well as or better than MetS [111].

The Obesity Paradox

Despite evidence that overweight and obesity is correlated with the development of CHD, higher all-cause mortality [112], and increased risk of HF in both genders [113] many studies have shown that obesity may paradoxically be associated with a better prognosis in particular patients with existing CHD and other conditions [57,114,115] this has been termed the "obesity paradox". The obesity paradox has been

reported in a number of chronic diseases [116], in renal disease [117], including HF [114,118], chronic obstructive pulmonary disease [119], diabetes [120], hypertension, coronary artery disease [121], and acute coronary syndromes [122].

Obesity paradox in HF patients

The obesity paradox is particularly evident is HF patients. Despite the known adverse effects of obesity on both systolic and particularly diastolic function, along with an higher prevalence of left ventricular structural abnormalities, many studies have demonstrated that obese HF patients have a better prognosis compared to lean and normal weight patients [123] (Figure 1). Lavie et al. [124] reported an inverse relationship between BMI and all-cause mortality in over 30,000 patients with preserved LV systolic function referred for echocardiography. A meta-analysis including 28,209 HF patients followed up for an average of 2.7 years, showed that overweight and obese HF patients had reductions in CV (19% and 40%, respectively) and all-cause (16% and 33%, respectively) mortality compared to individuals with normal BMI [125]. Likewise, in an analysis of BMI and in-hospital mortality for 108,927 decompensated HF patients, a higher BMI was associated with lower mortality [126]. For every 5-unit increase in BMI, the risk of mortality was 10% lower. In a large cohort of patients with advanced HF of multiple etiologies, obesity was not associated with increased mortality: in fact obesity conferred a more favorable prognosis [123]. A favorable outcome in patients with advanced HF was associated with a high BMI and WC [114]. Patients with chronic HF and obesity have significantly lower sympathetic activation and this finding may partially explain the obesity paradox described in chronic HF [127].

The obesity paradox has been most commonly described using BMI as criteria for obesity. Romero-Corral et al. [128] studied 250,000 patients with CHD and reported that the BMI-mortality curve is typically U-shaped, with increasing mortality at the extremes of obesity. In a study conducted on 581 consecutive patients with CAD, De Schutter et al. [129] found that the mortality was U shaped, being highest in the underweight group (25%) and lowest in the overweight group (2.3%), with intermediate mortality in the normal (6.4%) and
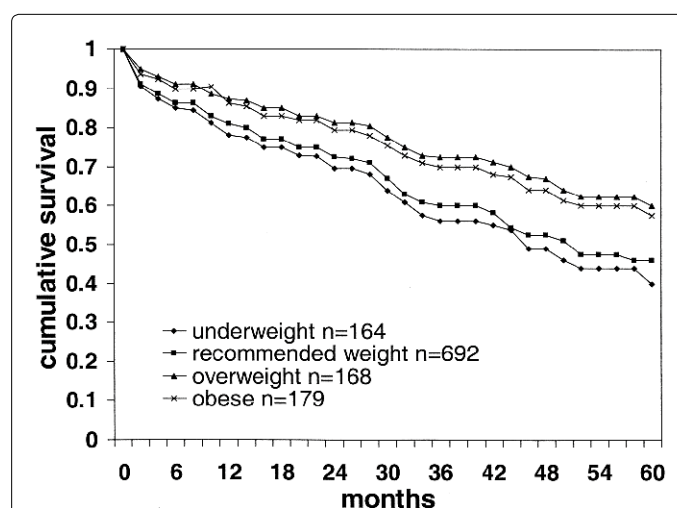
Figure 1: Risk-adjusted survival curves for the four Body Mass Index (BMI) categories at five years. The variables entered into the equation were age, gender, hypertension, diabetes mellitus, left ventricular ejection fraction, hemodynamic variables, peak VO2), mitral regurgitation, tricuspid regurgitation, medications and serum sodium, creatinine and lipid levels. Survival was significantly better for the overweight and obese BMI categories.(reproduced with permission from Horwich (Horwich, et al. [123]).

obese (3.6%) groups. The better outcomes for cardiovascular and total mortality seen in the overweight and mildly obese groups did not change after adjustment for confounding factors [130] (Figure 2). The highest mortality ratio was found in the group with the lowest BMI < 18.

Obesity paradox and mortality

In 413,673 patients hospitalized with acute myocardial infarctions, morbidly obese patients had lower odds of in-hospital mortality, compared to those not morbidly obese [131]. Lavie et al. [132] found that low BMI and low body fat subgroup of patients had a particularly high mortality rate (11% vs. 4%) suggesting than lean subjects do worse than obese. These authors [133] later showed that FFM and BF were independently protective and low FFM was associated with a higher mortality rate (3.1-3.9 times) compared to subjects with low body fat (2.6 times). In patients with stable CHD, both LMI and BF predict mortality and mortality was particularly high in those with low LMI/ Low BF and lowest in those with high LMI/High BF.

In the ambulatory care setting study overweight and obese patients reported worse self-rated health, more co-morbidities and biological risk factors [134]. However, compared with non-obese participants a lower risk of all-cause mortality was observed in those who were in overweight. After 8 years of follow up, Uretsky et al. [135] reported an obesity paradox in individuals referred for exercise testing and the obese showed the lowest all-cause cardiac mortality. Yamauchi et al. [136] studied 263,940 patients who were identified the in-hospital mortality and found that overweight and obese patients had a lower mortality than low-normal weight patients, supporting the obesity paradox. The mortality rates were 14.3% and 4.4% in the BMI groups with values of >18.5 and >30 respectively.

The role of abdominal obesity in the obesity paradox has been investigated. A recent meta-analysis demonstrated that WHR and WC are significantly associated with the risk of incident CVD events. These simple measures of abdominal obesity should be incorporated into CVD risk assessments. Coutinho et al. [137] (5) has explained this question reporting robust evidence that central obesity was associated with higher mortality in the subset of subjects with normal BMI. In subjects with CAD, including those with normal and high BMI, central obesity but not BMI is directly associated with mortality. This study underscores the fact that the central obesity in subjects with normal BMI is an expression of intra-abdominal fat.

Obesity paradox in revascularized patients

Overweight and obese patients have similar or lower short- and long-term mortality rates post-coronary revascularization and patients undergoing percutaneous coronary intervention with a low BMI have increased risks for adverse outcomes [138-140]. Overweight patients have better early hospital outcomes and improved survival after cardiac surgery [140]. Patients with extreme obesity who present with STEMI at younger ages and have less extensive coronary artery disease and better left ventricular systolic function [141].

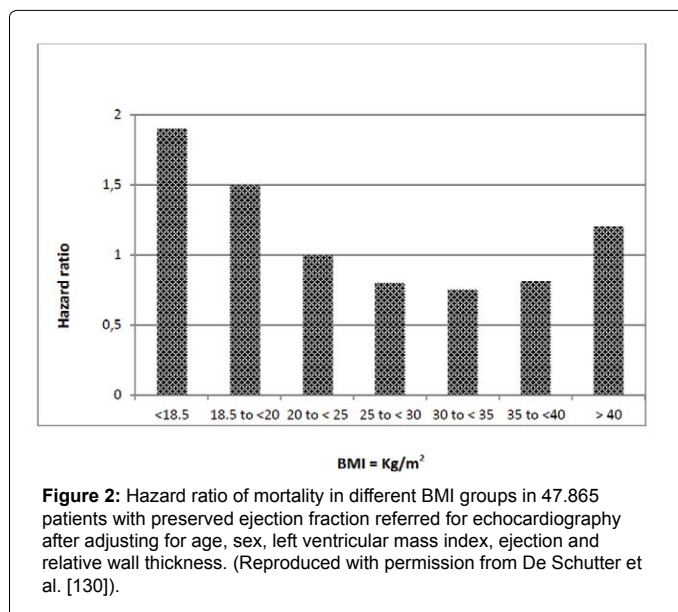## Obesity paradox in rehabilitation programs

Although an "obesity paradox" exists using either baseline BMI, it is supported the safety and potential long-term benefits of purposeful weight loss in overweight and obese patients with coronary heart disease [142]. Following cardiorespiratory training, obese patients had small, but statistically significant, improvements in obesity indices, including weight, BMI, and percentage of fat, a significant improvements in exercise capacity. The prevalence of MetS fell from 62% to 51% with only a non-significant trend for lower mortality [143].

Weight Loss and Mortality Rate

Weight loss in overweight and obese individuals with CVD is associated with increased mortality suggesting that weight loss may be detrimental in these patients [144,145] and also an increased mortality rate has been observed [146]. A meta-analysis did not find any benefit for a reduction in mortality risk with weight loss among healthy obese [147]. Weight loss among the overweight or obese appeared detrimental to survival particularly among those who remained physically inactive [144]. Nanri et al. [145] found that a large weight change, both loss and gain, was associated with an increased risk of mortality and was predictors of early death in apparently healthy adult Japanese. Weight loss in cardiac rehabilitation is a marker for favorable long-term outcomes, regardless of initial BMI [148]. Whereas unintentional weight loss is associated with increased adverse cardiovascular events, intentional weight loss is associated with lower clinical events. These results suggest that the underlying mechanism of weight loss (ie, intentional or unintentional) affects its impact on subsequent risk in persons with known CAD [149]. Low BMI was associated with poorest survival, similar to previous observations in patients with left ventricular systolic dysfunction. Cachexia is an ominous and often missed sign in patients with CHF. Morbid obesity (BMI>45 kg/m^2), however, also represented an increased risk, and a U-shaped relationship between BMI and mortality was described [150]. Non-voluntary weight loss should be recorded and managed aggressively. If overlooked or ignored, a vicious circle of body wasting and eventually cachexia may ensue [151].

Inaccuracy of BMI

BMI is the most widely used measure of obesity because of its practicality. BMI is an aggregate of varying amounts of Fat Free Mass (FFM) and Body Fat (BF), which contributes in its own way to an individual's metabolic profile. BMI does not discriminate between FFM and FM and has received a lot of criticism in terms of its accuracy to define obesity [152,153]. This may explain the controversial findings that link mild elevations of BMI to better survival and fewer cardiovascular events in patients with CAD. Numerous techniques may be more accurate to define obesity including WC, WHR, Bioelectrical Impedance Analysis (BIA) and Dual-Energy X-ray Absorptiometry

Figure 2: Hazard ratio of mortality in different BMI groups in 47.865 patients with preserved ejection fraction referred for echocardiography after adjusting for age, sex, left ventricular mass index, ejection and relative wall thickness. (Reproduced with permission from De Schutter et al. [130]).

(DEXA) [154]. The gold standards for assessing body composition are Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) [155] that is limited by expense. Body composition techniques to accurately diagnose obesity in patients with CAD are necessary because the inaccuracy might help explain the obesity paradox [152,153]. The obesity paradox could be considered a BMI paradox because the excess visceral fat is identified clinically by what has been termed "hypertriglyceridemic waist" [156]. Hypertriglyceridemic waist as a marker of visceral obesity and related metabolic abnormalities is a useful and practical clinical phenotype to screen persons at risk for CAD and type 2 diabetes. It has been suggested as an alternative to MetS for predicting future diabetes [157].

The Free Fat Mass (FFM)

Nutrition influences on loss of muscle mass [158], exercise capacity [159] and wound healing [160]. Patients with a low BMI, prevalently due to low FFM, show lower exercise capacity on submaximal and maximal exercise tests [161]. FFM associated with muscle strength enjoys a widespread acceptance as a positive prognostic and protective factor in the general and CHD population [162] nutritional status [163] and cardiorespiratory fitness. Sabino and Silva [163] found that overweight/obese patients had greater FFM, exercise capacity and respiratory muscle strength and that FFM was the main predictor of exercise capacity. FFM remained stable up to 60 years of age and was lower during the 75 years of age, while FM is higher among older compared with younger groups [164]. The mortality is inversely related to Lean Mass Index (LMI) in patients with stable CHD and the higher LMI is at least strongly associated with better survival [133]. The best survival was noted in those patients with High BF/High LMI ratio, and the highest mortality was noted in those with Low BF/Low LMI group with a 4.24-fold increase in mortality [165]. A higher LMI is associated with muscular strength, which is associated with better survival [166], even independently of aerobic fitness [167]. LMI seems to remain protective in obese patients even when BMI is not [130,165]. A marked survival benefit has been noted with increasing weight in patients with CHF and the risk of cachexia Anker et al. [168,169]. The cachectic state is a strong independent risk factor for mortality in patients with CHF and undoubtedly this is a factor in studies on the obesity paradox in CHF. In nonagenarian men, low BMI and low WC predict increased mortality [170].

De Schutter et al. [171] emphasize the impact of cardiorespiratory fitness and a number of mechanisms which may offer potential explanations for this puzzling phenomenon. In a recent review Lavie et al. [172] suggest to give a greater emphasis on improving fitness rather than weight loss per se in the primary and secondary prevention of cardiovascular diseases, at least in patients with overweight and class I obesity (BMI 30-35 kg/m^2).

Potential Interpretation of the Obesity Paradox

Low BMI can be due to catabolic condition and represent a high mortality risk [173]. Advanced HF is a catabolic state and obese patients with HF may have more metabolic reserve [174,175]. The presence of the "malnutrition-inflammation complex syndrome" in CHF patients may explain the presence of reverse causality. Protein-energy malnutrition is an important public health problem [176] impairing a number of physiological processes including hematopoesis and the immune response- the production of interleukin-4 and interleukin-10 in response to lipolisaccaride as well as leucopenia and a severe reduction in bone marrow, [177]. A low-protein diet compared with control diet resulted in a decrease in red blood cells, Hb concentration and reticulocytopenia, as well as severe bone marrow and splenic atrophy [178]. The incidence of malnutrition is not recognized in overweight or obese subjects who are usually considered to be well-nourished. It is also important to consider the weight loss program can sometimes results in malnutrition and increase mortality.

It has been suggested that the obesity paradox may be modified by overall physical wellness or by unmeasured confounding factors [179]. High levels of fitness significantly alter the association between BMI and other parameters related to obesity with subsequent higher mortality [180]. Even after adjustment for fitness, BF and LMI are independent predictors of mortality. Weight loss but not weight gain is associated with increased mortality and morbidity in the study [181]. These data contrast to common thinking and to current guideline recommendations that are based on mere translation from primary prevention data and may not be applicable in patient populations with established chronic diseases.

Diet Intervention

Lowering body fat is important for health and improve cardiac function but low-carbohydrate diets have been suggested to have a potentially negative effect on long-term vascular health [182]. In addition, low-carbohydrate diets may result in unfavorable changes in low-density lipoprotein cholesterol when using such diets to induce weight loss [183]. An increase in protein content up to 25% of total energy may contribute to reducing total energy intake [184] and adequate carbohydrates ingestion should be maintained. In chronic kidney disease patient in which catabolic risk is present, a dietary protein and caloric intake of 1.2-1.4 gr/kg body weight and 30-35 kcal/kg body weight respectively are recommended [185] along with correction of fluid administration. Low-carbohydrate diets are associated with a significantly higher risk of all-cause mortality although they do not appear to be significantly associated with a higher risk of CVD mortality and incidence [186]. Lowering body weight by switching to low fat diet in obese mice with heart failure is associated with decreased cardiac hypertrophy, and improvements in both insulin sensitivity and diastolic function, suggesting that weight loss does not negatively impact heart function in the setting of obesity [187]. In human the results of a meta-analysis do not allow for an unequivocal recommendation of either low-fat or high-fat diets in the primary prevention of cardiovascular disease. It was found that lower total cholesterol level was associated with lower intakes of saturated fat and higher intakes of polyunsaturated fat, and increases in HDL cholesterol levels is related to higher amounts of total fat largely derived from monounsaturated fat [188]. Elimination of high-fat dairy decreases the risk of impaired fasting glucose and improve some metabolic syndrome components [189]. Dietary strategies should be flexible and individualized based on metabolic profile. Al-Najjar and Clark [190] demonstrated that 23% of the ambulatory CHF patients are at risk of malnutrition and some elderly subjects become severely malnourished. The nutritional risk index is a uni-variable predictor of mortality so that the nutritional risk index could be considered a useful prognostic marker in patients with CHF.

Exercise intervention. Resistance exercise and cardiorespiratory fitness play an important effect on longevity [191,192] and on the obesity paradox. Various clinical studies have shown that the obesity paradox is attenuated in fitness groups, while the obesity paradox is more apparent in patients with lower cardiorespiratory fitness [193,194]. This suggests that that higher exercise capacity attenuates the obesity paradox. Clark et al. [194] observed that at 2 years, BMI category was significantly associated with outcomes for the low peak VO2 group (≤14 ml/kg/minute), while among patients with high peak VO2 (>14

ml/kg/minute) the obesity paradox was attenuated. Overweight and obese men with moderate fitness had mortality rates similar to those of the highly fit normal-weight reference group. Fitness altered the obesity paradox. McAuley et al. [195] reported that overweight and obese men had increased longevity only if they had high fitness.

Role of Androgen on Cardiovascular Diseases and Mortality

Human androgens comprise testosterone, Dihydrotestosterone (DHT), androstenedione and De-hydroepiandrosterone (DHEA) and its sulfate (DHEAS). Testosterone is prevalently secreted by the testis in males and by the ovary in females. Approximately 5% of serum testosterone is transformed in DHT by a 5α-reduction process, with DHT having a threefold greater affinity than T and a 15- to 30-fold greater affinity than adrenal androgens for androgen receptors. DHEA and DHEAS, the most abundant adrenal steroids in humans, are precursors of the intracellular production of androgens and estrogens in non-reproductive tissues. Most testosterone (50-60%) is bound to plasma proteins, namely Sex Hormone Binding Globulin (SHBG), while 40-50% is bound to albumin and 1-2% is free [196].

Epidemiological studies have found that men with low serum testosterone are at an increased risk of mortality [197-199]. Cardiovascular diseases account for the greater proportion of these deaths [200-202]. In patients with CHD, testosterone deficiency is common and negatively impacts survival [203].

Optimal androgen levels are a biomarker for survival because older men with midrange levels of testosterone and DHT had the lowest death rates from any cause, whereas those with higher DHT had lower IHD mortality. Further investigations of the biological basis for these associations including randomized trials of testosterone supplementation are needed [204]. In men with type 2 diabetes low serum levels of testosterone were associated with an increased risk of death [205]. Men with COPD have clinically relevant lower than normal total testosterone levels [206] suggesting that testosterone therapy improves exercise capacity outcomes [207,208].

Androgen therapy improves insulin sensitivity and decreases leptin level in healthy adult men with low plasma total testosterone [209]. These results suggested an association between low serum testosterone and metabolic impairment, which has implications for the effects of testosterone treatment on components of the metabolic syndrome [210]. Testosterone dosing in a MetS animal model positively affects VAT functions. This could reflect the ability of testosterone in restoring insulin sensitivity in VAT, thus counteracting metabolic alterations [211]. Testosterone replacement therapy has positive effect on various chronic diseases such as renal chronic disease and cancer, for more detail on the effect of testosterone and mortality see the review by Muraleedharan et al. [212]. Low testosterone is associated with adverse effects on cardiovascular risk factors which include central obesity, dyslipidaemia, insulin resistance, hyperglycaemia, coagulation, endothelial dysfunction and inflammation [213]. In obese men with Obstructive Sleep Apnea (OSA) testosterone administration improved several important cardiometabolic parameters but did not differentially reduce overall weight or the metabolic syndrome. Longer term studies are required to explore this further [214].

Testosterone and MetS

Endogenous androgen such as testosterone has been shown to have a protective effect against obesity and MetS [12,215]. In men with low serum testosterone levels a greater incidence of MetS was found [216]. A study including 467 elderly individuals showed that low serum testosterone levels were inversely associated with components of the MetS including abnormal waist circumference, high-sensitivity C-reactive protein, insulin, and HDL cholesterol levels in men [217]. The hypo gonadotrophic hypogonadism syndrome appears be related to the two major conditions associated with insulin resistance: type-2 diabetes and the MetS. In addition, epidemiological studies have shown that endogenous androgens, such as testosterone, DHT and DHEA-S, possess a protective effect against obesity and MetS in men [215,218,219]. Low total testosterone and SHBG levels independently predict development of the metabolic syndrome and diabetes in middle-aged men. Thus, hypoandrogenism is an early marker for disturbances in insulin and glucose metabolism that may progress to the MetS or frank diabetes and may contribute to their pathogenesis [220]. Furthermore, the low serum of SHBG is a reliable marker of MetS [220-222] and type-2 diabetes [223]. Chubb et al. [222] in a cross-sectional study of 2502 community-dwelling men aged ≥70 years without known diabetes showed that lower SHBG is more strongly associated with MetS than lower total testosterone. A small study conducted for 24 week on 42 CHD patents showed that testosterone administration improved Mets parameters, a decrease in serum aldosterone but no changes in echocardiographical variables [224].

A meta-analysis supports the presence of a sex-dependent association between testosterone and MetS: total testosterone and free testosterone levels are lower in men with MetS, whereas they are higher in women with MetS. In both men and women, MetS is associated with lower SHBG levels [225]. A strong association between total testosterone and SHBG with increased likelihood of having metabolic syndrome, independent of traditional cardiovascular risk factors and insulin resistance has been demonstrated by the Third National Health and Nutrition Examination Survey (NHANES III) [226]. Corona et al. [227] demonstrated that MetS, and in particular visceral adiposity (as assessed by increased waistline and hypertriglyceridemia), is specifically associated with hypo-gonadism in subjects seeing for sexual dysfunction. The high prevalence of MetS among men with testosterone deficiency highlights the opportunity to evaluate testosterone treatment in MetS [228,229] Erectile dysfunction, age male symptoms (such as weakness, loss of libido, depression), and MetS prevalence were 97.4%, 94.9%, and 69.6% so that the severity of testosterone deficiency symptoms may indicate higher cardiovascular risk in men with low testosterone. Testosterone has an effective therapy in treatment of obesity in men with testosterone deficiency. Also in premenopausal overweight/obese women it was found that total testosterone contributed to the variance in systolic and diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, and apolipoprotein B [230]. The effect of testosterone on visceral adipose tissue and insulin resistance has been shown in patients with nonalcoholic fatty liver disease and the association remains unchanged even after controlling for visceral fat and insulin resistance [231]. In HIV-positive men with abdominal obesity and low testosterone level a greater decrease in whole body, total, and abdominal fat mass and a greater increase in lean mass in the T group compared to placebo was observed [232]. While overall treatment of obesity was unsuccessful, testosterone treatment of hypogonadal men may be effective, in part because it improves mood, energy, reduces fatigue and may motivate men to adhere to diet and exercise regimens designed to combat obesity [233]. Furthermore, the administration of testosterone im (Testosterone Undecanoate, TU) was more effective than oral TU for reaching the target for testosterone levels and to improve MetS parameters [234].

Interventional studies have shown beneficial effects of testosterone

administration on type-2 diabetes including glucose utilization and glucose uptake, glycolysis and mitochondrial phosphorylation promoting major insulin-responsive target tissues such as liver and muscle [218]. Interventional studies have shown beneficial effects of testosterone administration on type-2 diabetes, including promoting glucose utilization and glucose uptake, glycolysis and mitochondrial phosphorylation promoting major insulin-responsive target tissues such as liver and muscle [218]. In a recent review Traish et al. [235] suggested that testosterone therapy in management of obesity in men with testosterone deficiency produced a sustained weight loss without recidivism. These findings provide strong foundations for testosterone therapy in obese men with T deficiency particularly given that alternative therapeutic approaches other than bariatric surgery failed to produce significant and sustained outcome.

Effects of Testosterone Therapy on MetS

Many clinical trials have showed the favorable effect of testosterone administration in hypogonadal men on components of the MetS [210,214,234,236-245]. In the majority of these studies Testosterone Undecanoate (TU) 1000 mg every 12 weeks was administered; in one study on a total of 332 patients testosterone esters (Sustanon) 250 mg every 3 weeks was employed [241]; in in study testosterone 200 mg every 2 weeks was given and in another testosterone gel (50 mg) once daily for 52 weeks was administered [243]. The duration of the studies varied widely, with a duration ranging from 3 weeks to 5 years. All studies reported a significant improvement in body weight, waist circumference, BMI, total cholesterol, triglycerides, fasting blood glucose, HbA1c, and blood pressure. Only Sonmez et al. [241] al found a negative effect with an increased prevalence of MS and unfavorable effects of testosterone replacement in young patients with congenital hypogonadal hypogonadism. The studies are summarized in Table 2. In the study of Kalichenko et al. [240] significant decreases in weight, BMI and WC in the TU vs. placebo group were observed. The leptin and insulin levels also decreased, but there were no changes in serum glucose or lipid profile. The inflammatory markers, IL-1beta, TNF-alpha and CRP decreased, while IL-6 and IL-10 did not change.

Heufelder et al. [243] evaluated the effects of a supervised diet and exercise program in hypogonadal men with MetS and type-2 diabetes with or without transdermal testosterone administration. Testosterone administration reported therapeutic improvements of glycemic control and insulin sensitivity, adiponectin, and high-sensitivity C-reactive protein after 52 weeks of treatment (Figure 2).

Associations of testosterone and SHBG with MetS provide further insights into the pathophysiological mechanisms linking low testosterone and SHBG concentrations to cardiometabolic risk [246]. These studies demonstrate that it is possible to break the metabolic vicious circle by raising testosterone levels in diabetic men with androgen deficiency. Re-instituting physiological levels of testosterone that has an important role in reducing the prevalence of diabetic complications [236]. Testosterone supplementation has been shown to result in a greater reductions in regional adiposity associated with improved insulin sensitivity, lower LDL-C and fasting triglycerides, but lower HDL-C [247]. Similar results were shown with oxandrolone, an androgen anabolic steroid derivate from testosterone [248]. Multivariate analysis revealed that the total testosterone median value of <4.0 ng/mL was the only significant marker for the detection of MetS. Among various testosterone values, total testosterone appears to be the most reliable indicator of MetS in middle-aged Japanese men [12] and the testosterone decline is the main driver of the association between sex hormones and MetS [249]. Finally, higher total testosterone levels were associated with a reduced prevalence of MetS in men and an elevated prevalence of MetS in women suggesting a sex differences in the associations of endogenous testosterone and SHBG with MetS [250].

Androgens and Inflammation

Androgens seem to have a significant effect on inhibition of the inflammatory processes. Steffen et al. [251] have demonstrated in rats that low testosterone predominantly increases the inflammatory response and high testosterone promotes a higher osteoblast-derived RANKL: OPG ratio. Testosterone down regulates osteocalcin, RANKL and OPG in primary murine osteoblasts suggesting a direct role of inflammation in osteoblast function. OPG levels decreases during testosterone therapy influencing changes in regional fat distribution and decreasing cardiovascular risk [252]. Testosterone replacement treatment decreases also leptin and adiponectin levels in type-2 diabetic men. Kapoor et al. [253] found that low levels of testosterone in men are associated with pro-inflammatory profile, though testosterone treatment over 3 months had no effect on inflammatory markers. A cross-sectional study showed that higher androgen and lower estrogen concentrations may have an anti-inflammatory effect in men [254]. In late postmenopausal women not on hormone replacement therapy, SHBG was negatively associated with CRP and IL-6. SHBG and estradiol are, negatively and positively respectively, associated with a pro-inflammatory state [255]. Haring et al. [256] demonstrated inverse associations between sex hormone concentrations and markers of inflammation and oxidative stress in men. SHBG and total testosterone were inversely associated with CRP among hormonal therapy nonusers. The inverse relationship between SHBG and CRP is stronger among leaner women [257]. These studies show the important role of androgen in reducing the inflammatory process but additional researches are warranted to elucidate potential mechanisms underlying these associations.

Conclusion

MetS represent a cluster of risk factors of metabolic origin correlated with CVD and is a strong, independent predictor of all-cause mortality in men. However MetS does not predict CHD and ACVD above and beyond its individual components. The obesity paradox underscore the importance of adipose tissue in maintaining health. Underweight and extremely obese patients are at risk of CVD and LMI seems to remain protective in obese patients even when BMI is not. FFM has been shown to be more useful than the BMI in identifying subjects with protein-energy malnutrition, and it has been shown to be more accurate for classifying disease severity [258]. FFM is also an independent predictor of mortality irrespective of fat mass [119] and in clinical management of HF patients LMI should be considered as a marker for health. In advanced stages of chronic disease, low FFM has been clearly identified as a primary determinant of perceived disability, handicap, and health care costs, and it is therefore considered an important target for therapy [259-261]. Furthermore serum testosterone level plays a fundamental role in maintaining FFM and prevents MetS. Low serum testosterone level is a risk factor for CVD and mortality. Testosterone administration should be included in the primary management of MetS along with caloric restriction, increased physical activity and improved nutritional choices. A strong evidence suggests for a role of lifestyle interventions with diet and exercise, and testosterone administration to improve FFM, reduce the inflammatory response and prevent cachexia.

Acknowledgements

Authors	No. patient	Age	Type of study	Dose mg	Duration	Effects
Janjgava, (Janjgava, Zerekidze et al. [236])	125 T2D, M	49.7	randomized in a placebo-controlled study	TU 1000 every 3 months	6 months	Important effect in reducing diabetic complications
Francomano, (Francomano, Lenzi et al. [237])	20 HM	57± 8	n.n.	TU 1000 every 3 months	5 years	Improved obesity, glycemic control, blood pressure, lipid profile, and BMD
Yassin, (Yassin, Doros et al. [238])	261 HM	59.5 ± 8.4	prospective, observational, and longitudinal registry study	TU 1000 every 3 months	5 years	Waist circumference, BMI, total cholesterol, triglycerides, fasting blood glucose, HbA1c , and blood pressure significantly improved
Hoyos, (Hoyos, Yee et al. [214])	67 M	49 ± 12	double-blind, placebo-controlled study	TU 1000	18 weeks	Increased insulin sensitivity, arterial stiffness decreased, no weight loss observed
Goncharov, (Goncharov, Katsya et al. [224])	42 M, CHF	>40	double-blind, placebo-controlled trial	TU 1000 every 3 months	24 weeks	Improvements of variables of the MetS, notably of aldosterone.
Bhattacharya, (Bhattacharya, Khera et al. [244])	849 HM	52.1 ± 12.3	multicenter, prospective observational study	Testim 1% testosterone gel (5-10 g/day)	12 months	Significant decreases in waist circumference, fasting blood glucose levels, and blood pressure
Jones, (Jones, Arver et al. [245])	22 HM T2D	59.9 ± 9.1	multicenter, prospective, randomized, double-blind, placebo-controlled study	transdermal 2% testosterone gel	6 months	Improvements in total and LDL cholesterol and insulin resistance, and sexual health
Giltay, (Giltay, Tishova et al. [239])	184 M	52.1 ± 9.6	randomized, double-blinded placebo-controlled,	1000/6-12 wk	30 weeks	Depressive symptoms, aging male symptoms and sexual dysfunction improved
Kalichenko, (Kalinchenko, Tishova et al. [240])	105 M	51.6 ± 1.8	randomized, double-blinded placebo-controlled,	1000/6-18 wk	30 weeks	Significant decreases of weight, BMI and WC, leptin and insulin, no changes in serum glucose or lipid
Aversa, (Aversa, Bruzziches et al. [234])	50 HGM	57 ± 8	Randomized, double-blinded, double-dummy study	1000 mg/12 weeks	12 months	Fasting glucose, waist circumference, and markers of atherosclerosis improved
Sonmez,2011 (Sonmez, Haymana et al. 2011)	332 CHH	21.68 ± 2.0	Retrospective analysis	250 mg/3 weeks (sustanon)	3 weeks	Increased prevalence of MetS and unfavorable effects of testosterone
(Heufelder, Saad et al. 2009)	32 HM	57.3 ± 1.4	randomized clinical trial	testosterone gel 50 mg daily	52 weeks	Improved insulin sensitivity, adiponectin, CPR, glycemic control and reverses the MetS
Kapoor, 2006 (Kapoor, Goodwin et al. 2006)	30 HM, T2D	64 ± 1.34	double-blind placebo-controlled crossover	200 mg every 2 weeks	3 months	Insulin resistance, glycaemia, total cholesterol and visceral adiposity reduced

Table 2: Effect of testosterone administration on metabolic syndrome. M: Men; HM: Hypogonadal Men; CHH: Congenital Hypogonadal Hypopituitarism; T2D: Type 2 Diabetes; CHF: Chronic Heart Failure.

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