

# The Dark Side of Testosterone Deficiency: I. Metabolic Syndrome and Erectile Dysfunction

## Review

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**ABSTRACT:** The metabolic syndrome (MetS) is considered the most important public health threat of the 21st century. This syndrome is characterized by a cluster of cardiovascular risk factors including increased central abdominal obesity, elevated triglycerides, reduced high-density lipoprotein, high blood pressure, increased fasting glucose, and hyperinsulinemia. These factors increase the risk of cardiovascular disease (CVD) and/or type 2 diabetes. Although the etiology of this syndrome is thought to stem from obesity and physical inactivity, the extent of interactions of the individual MetS components with one another remains poorly defined. Obesity, diabetes, hypogonadism, and specific hormone and metabolic profiles have been implicated in the pathophysiology of CVD. The evolving role of androgens in MetS and CVD is of paramount importance. Reduced androgen levels associated with hypogonadism or androgen deprivation therapy increase cardiovascular risk factors and produce

marked adverse effects on cardiovascular function. MetS has been associated with hypogonadism and erectile dysfunction (ED), and MetS may be considered a risk factor for ED. It is suggested that MetS, diabetes, and CVD will increase in the upcoming decades. Thus, it is critically important to develop a better understanding of how obesity, diabetes and hypogonadism contribute to androgen deficiency and the various pathophysiologic states of vascular disease. In this review we discuss the current literature pertaining to androgen deficiency, MetS, and ED, because the relationship of these factors is of scientific and clinical importance. Specifically, we will focus on exploring the relationships between hypogonadism, obesity, MetS, and ED.

Key words: Androgen deficiency, diabetes, insulin resistance, vascular disease, metabolic syndrome.

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The metabolic syndrome (MetS) has received considerable attention in recent years because of its association with increasingly common pathophysiologic states such as heart failure (Ingelsson et al, 2006), type 2 diabetes mellitus (Imam et al, 2007), and erectile dysfunction (ED) (Bansal et al, 2005). MetS is considered the main threat for public health in the 21st century (Taskinen, 2007) and is associated with an increased risk of cardiovascular disease (CVD), irrespective of which MetS definition is used (Table 1). Bataille et al (2006) studied over 10 000 men in France and Northern Ireland as part of the PRIME cohort, and found that MetS predicts the risk of having coronary heart disease in multiple areas of Europe. Obesity and physical inactivity are known to be risk factors for the

development of MetS (Ford and Li, 2006) and it is well known that obese individuals are more likely to develop insulin resistance than are nonobese individuals. This insulin resistance predisposes these individuals to metabolic risk factors such as elevated serum TGs, reduced high-density lipoprotein (HDL) levels, elevated fasting glucose levels, and high blood pressure (Hu et al, 2004). These metabolic abnormalities, in conjunction with abdominal (visceral) obesity, represent the classical symptoms of MetS. According to the third National Health and Nutrition Examination Survey (Ford et al, 2002), the age-adjusted prevalence of MetS in American men was 23.7%. There is considerable evidence linking MetS to androgen deficiency. In this review, we discuss the link between androgen deficiency, MetS, and ED. For brevity's sake, the relationship among androgen deficiency, type 2 diabetes, and insulin resistance as risk factors for CVD will be addressed in separate reviews.

### 1. MetS

*A. General Characteristics and Definitions*—Hanefeld and Leonhardt (1981) were the first to coin the term *metabolic syndrome*. Because this report was published

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Table 1. Diagnostic criteria for MetS in men according to various definitions

MetS Criteria	WHO <sup>a</sup>	NCEP-ATP III <sup>b</sup>	IDF <sup>c</sup>
Required for diagnosis	Criterion 1 plus 2 of the other 4	≥3 of 5 criteria	Criterion 2 plus 2 of the other 4
1. Hyperinsulinemia, hyperglycemia	FBS ≥ 110 mg/dL (≥6.1 nmol/L), ↑ insulin or IR or T2DM	FBS ≥ 110 mg/dL (≥6.1 nmol/L) or T2DM	FBS ≥ 100 mg/dL or T2DM
2. Increased body size	WHR > 0.90, WC ≥ 94 cm, BMI ≥ 30.0	WC ≥ 102 cm	WC ≥ 94 cm
3. Triglyceride	≥150 mg/dL (≥2.3 mmol/L) (combined with HDL)	≥150 mg/dL (≥ 2.3 mmol/L)	≥150 mg/dL (≥2.3 mmol/L)
4. HDL cholesterol	>35 mg/dL (>0.9 mmol/L)	>40 mg/dL (>1.03 mmol/L)	>40 mg/dL (>1.03 mmol/L)
5. BP	≥140/90 mmHg or HTN on Rx	≥130/85 mmHg or HTN on Rx	Systolic BP ≥ 130 mmHg, diastolic BP ≥ 85 mmHg, or HTN on Rx

Abbreviations: BMI, body mass index; BP, blood pressure; FBS, fasting blood sugar; HDL, high-density lipoprotein; HTN, hypertension; IDF, International Diabetes Federation; IR, insulin resistance; NCEP-ATP III, National Cholesterol Education Program-Adult Treatment Panel; Rx, prescription; T2DM, type 2 diabetes mellitus; WC, waist circumference; WHO, World Health Organization; WHR, waist-hip ratio.

<sup>a</sup> European Group for the study of Insulin Resistance (2002).

<sup>b</sup> Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001).

<sup>c</sup> International Diabetes Federation (2007).

in German and behind the “Iron Curtain,” it remained unnoticed by many scientists and clinicians (Hanefeld and Leonhardt 1981). The authors stated that MetS represented the common prevalence of obesity, hyperlipoproteinemia, dyslipoproteinemia, maturity onset diabetes (type 2), gout, and hypertension associated with increased incidence of atherosclerotic vascular disease, fatty liver, and gallstones that develops on the basis of genetic susceptibility combined with overnutrition and physical inactivity. The authors suggested that if this working hypothesis could be confirmed it would provide the basis for integrated diagnostics and prevention of this cluster of diseases, which is of central importance for health care (Hanefeld and Leonhardt 1981). Interestingly, for over 2 decades after the recognition that certain metabolic risk factors seem to cluster together, there were no set criteria by which MetS could be diagnosed or characterized.

Recently, the World Health Organization (WHO) developed a working definition for MetS by defining signs and symptoms that include dyslipidemia, hyperinsulinemia, and hypertension (European Group for the Study of Insulin Resistance, 2002; Table 1). The Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP) modified the definition based on similar characteristics used by the WHO (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001; Table 1). The ATP III suggested that the primary treatment should focus on reduction of low-density lipoprotein (LDL) cholesterol levels, followed by the treatment of individual MetS symptoms that would lead to a decrease in the risk for congestive heart disease (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). More recently, a new worldwide definition

for MetS was developed based on the International Diabetes Federation (IDF) Consensus Group held in Berlin in 2005 (Table 1) (International Diabetes Federation, 2007). All 3 MetS definitions imparted similar CVD and diabetes risks in a recent comparison from the San Antonio Heart Study (Lorenzo et al, 2007a,b).

The definitions of MetS (Table 1) have provided clear criteria by which subjects can be evaluated by physicians; however, not all clinical studies have used the same definition, making comparisons among such studies difficult. There is still a difference of opinion as to whether waist circumference (WC) is superior to body mass index (BMI) as a cardiovascular (CV) risk predictor, or if any one parameter is inferior to multiple abnormalities (Lorenzo et al, 2007a,b). Ferrannini et al (2007) tried to dissect out the impact of various factors on CV risk factors, especially obesity, abdominal obesity, and insulin resistance (IR), by using a euglycemic clamp. In evaluating 1308 nondiabetic subjects, they reported that no one factor stood out as a sole driving force for CV risk; each factor was associated with multiple physiological pathways.

*B. Prevalence of MetS across Various Geographic, Ethnic, and Cultural Backgrounds*—MetS does not manifest itself uniformly in all populations. Ford et al (2002) showed that the expression of MetS is highly variable between ethnicities, with Mexican Americans exhibiting the highest prevalence of symptoms, except high blood pressure, as defined by the ATP III criteria among US adults. In addition, a patient’s lifestyle (Esposito et al, 2004), age, and sex (Ford et al, 2002) largely affect the associated risk for developing MetS. Park et al (2003) showed that cigarette smoking, carbohydrate-rich diets, and physical inactivity all increase the odds of developing this syndrome. Another practical concern in diagnosing MetS is that one definition

of MetS may not be applicable to a population of a different geographic area. To estimate global prevalence, a flexible definition of MetS is needed. This was demonstrated by Lee et al (2004), who measured the prevalence of MetS in 26 528 men from Seoul and Kyung-Gi provinces of North Korea and found that the NCEP ATP III criteria, as compared with the Asian-Pacific criteria for abdominal obesity based on WC and BMI, underestimated the true prevalence of MetS. Given that this population tends to be naturally leaner in physique, the authors reasoned that they should use lower central obesity threshold criteria for MetS in the Asian-Pacific region. Oh et al (2004) assessed the prevalence of MetS in a similar Korean population and confirmed the aforementioned observations that the ATP III criteria may not capture the prevalence of MetS in this population. He et al (2007) found that in an aging Chinese population many individuals were both overweight and had MetS and that BMI alone, as a measure of overall adiposity, was strongly associated with an increased prevalence of CVD, independent of MetS. Tanomsup et al (2007) compared the ATP III and the IDF definitions in Thailand, and did this with a specific Asian WC cutoff. In this circumstance, the ATP III definition produced a higher prevalence of MetS and a stronger association with both CV and all-cause mortality. It was further qualified that although the findings support the theory that obesity is a definite CV risk, they did not feel that central obesity, as reflected in the WC, was a necessary component of MetS.

### *II. Is There a Relationship Between MetS and Hypogonadism?*

Although geography, ethnicity, lifestyle, age, and sex all affect the development of MetS, low testosterone (T) and sex hormone-binding globulin (SHBG) levels are considered risk factors for MetS in men (Muller et al, 2005; Kupelian et al, 2006a,b). Miner and Sadovsky (2007) and Miner and Seftel (2007) reported that hypogonadism is more prevalent than previously thought, is strongly associated with MetS, and may be a risk factor for diabetes and CVD. In aging men, it is well established that endogenous androgens decline with age. Blouin et al (2005, 2006) have addressed whether the decline in androgens or the aging process itself accounts for the increased risk of MetS. The authors showed that the effects of declining dehydroepiandrosterone sulfate on the metabolic profile were age dependent, whereas those of T were not. They also observed that patients with higher T values were more likely to have fewer than 3 components of MetS in comparison with those having lower T values. This finding is in accordance with observations made by Kaplan et al (2006), in which they found an inverse

relationship between mean baseline total T levels and number of NCEP-ATP III components expressed in 864 men (mean age 52 years). Laaksonen et al (2003) further supported a role for declining T levels in MetS, suggesting an inverse relationship between total T levels and odds ratios for having MetS in 1896 nondiabetic men. Rodriguez et al (2007) related their experience with the Baltimore Longitudinal Study of Aging, in which men were followed for a mean of 5.8 years. This longitudinal study confirmed what others have found in cross-sectional studies—that is, the prevalence of MetS increased with age, and that this was associated with lower androgen levels. They also found that lower total T levels, along with lower SHBG levels, predicted a higher incidence of MetS. These observations strongly suggest a link between T levels and MetS. The diagram in the Figure outlines potential interplay among androgen deficiency, endothelial dysfunction in the development, progression of the pathologic state of MetS, and the relationship to ED.

Clearly, low circulating androgen levels are a risk factor for MetS, and Laaksonen et al (2005) showed the reverse relationship to be true as well—namely, that patients with MetS at baseline, whether defined by the WHO or by the NCEP-ATP III, will have increased odds of developing hypogonadism (total T < 11 nmol/L) during an 11-year follow-up period. Makhsida et al (2005) argued that hypogonadism is a central feature of MetS and that T treatment, in addition to restoring eugonadal hormone concentrations, is of beneficial impact on MetS itself, slowing the progression to diabetes and CVD. In contrast, Chen et al (2006) argued that although total T levels are inversely related to the likelihood of having MetS, testosterone does not have a role in the development of type 2 diabetes. Increasing insulin levels have also been found to be associated with a statistically significant increase in the prevalence of MetS components (Hu et al, 2004). The authors showed that the prevalence of individual components of MetS, according to cohort-specific quartiles of plasma insulin levels in the pooled DECODE study data (6156 men from 11 European cohort studies, mean follow-up 8.8 years), all increased significantly with an increase in insulin quartile.

### *III. Central Obesity, Waist Circumference, and Androgen Deficiency*

The prevalence of obesity in men between the ages of 20 and 72 in the United States has consistently risen over the past several decades, starting at ~10% between 1960 and 1962 and rising to ~30% in 2000 (Ogden et al, 2003). Other countries, such as Spain, have also shown a high prevalence of overweight (49%) and obese (31.5%) men over the age of 60 (Gutierrez-Fisac et al, 2004).

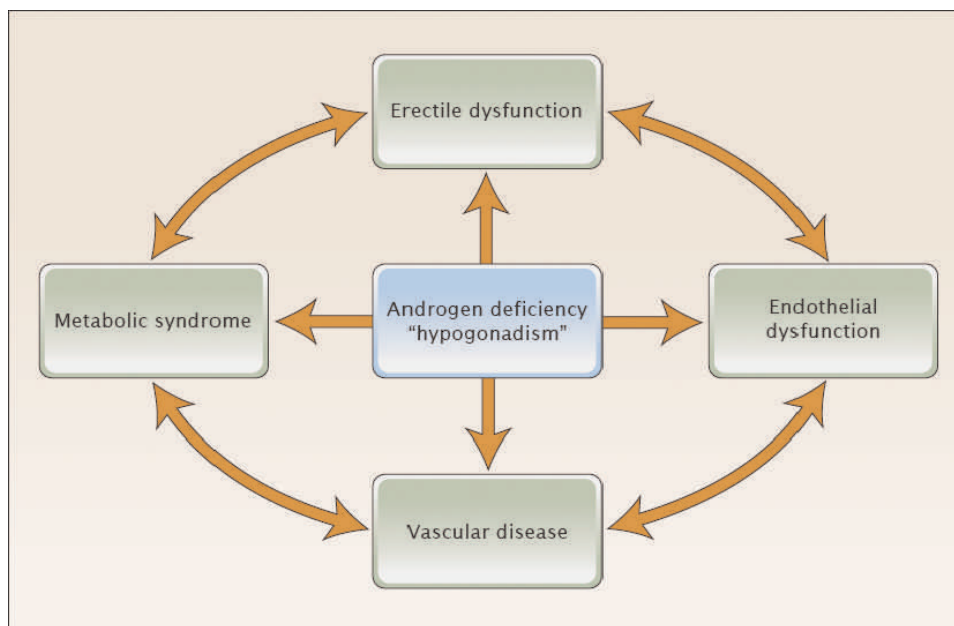


Figure. Interplay among androgen deficiency, metabolic syndrome (MetS), vascular disease, and erectile dysfunction. A conceptual framework of the potential interactions between androgen deficiency (low testosterone and hypogonadism) and MetS components, endothelium dysfunction leading to vascular disease, and in particular erectile dysfunction (penile vascular insufficiency). Color figure available online at [www.andrologyjournal.org](http://www.andrologyjournal.org).

Visceral obesity can lead to endocrinologic imbalances and has been positively associated with an increase in insulin, glucose, and C-peptide levels and negatively associated with T levels (Seidell et al, 1990), and may also be a risk factor for prostate cancer (von Hafe et al, 2004). The association of obesity with CV risks has been shown to be independent of other components of MetS, in particular hyperlipidemia and blood pressure (Rogers et al, 2007). Meigs et al (2007) found that MetS increased the risk of diabetes regardless of insulin resistance, although the simultaneous presence of both MetS and insulin resistance identifies an especially high-risk population.

Central or abdominal obesity, measured as WC, is a classical feature of MetS and is associated with reduced total T levels (Pasquali et al, 1997; Svartberg et al, 2004a,b, 2007; Osuna et al, 2006). Svartberg et al (2004a,b) showed free T and SHBG levels in 1548 community-dwelling men (age 25–84) to be inversely related to WC. These authors suggested that WC, as compared with BMI and waist-hip ratio (WHR), should be the preferred anthropometric measurement to predict endogenous T concentration. Other studies have confirmed the significant inverse correlation between total T and obesity (Pasquali et al, 1991; Laaksonen et al, 2003; Kalyani and Dobs, 2007). A plausible mechanism that may account for this inverse relationship involves elevated serum leptin levels in individuals with large fat reserves. In obese individuals, it has been hypothesized that elevated leptin levels

interfere with LH/hCG-stimulated androgen production, suppressing androgenic hormone formation (Isidori et al, 1999). In addition, it has been shown that patients with excess cortisol secretion have an increased BMI, WC, and WHR, potentially mediated through the suppression of T production via the hypothalamic-pituitary axis (Rosmond et al, 2003). Other possible mechanisms found in obesity include decreased SHBG, increased aromatization of T to estradiol in fat cells, or cytokine-mediated inhibition of testicular steroid production (Kalyani and Dobs 2007). In addition, the increased aromatase activity in visceral adipose tissue leads to higher circulating levels of estradiol, which suppresses T production by negative feedback. Therefore, men with visceral obesity are in a vicious cycle as T deficiency leads to reduced lipolysis, reduced metabolic rate, visceral fat deposition, and IR.

We postulate that androgen deficiency contributes to the components of MetS and that the latter produces pathologic states that contribute to androgen deficiency. The relative odds that an individual will present with a specific component of MetS, or MetS itself, are dependent on the measure of adiposity used for analysis. Using a 1-standard-deviation increase in measures of adiposity in 2924 men with no history of diabetes or CVD, Wannamethee et al (2005) determined the relative odds of the presence of individual components of MetS and found that both BMI and WC had the strongest association with these components, whereas percentage



body fat had the weakest association. BMI and WC measurements also predicted the highest relative odds of the presence of MetS itself. In contrast, Svartberg et al (2004a,b) suggested that WC was superior to BMI in correlating with the components of MetS. Additionally, it was found that approximately 25% of obese individuals (BMI > 30) had MetS. With other measures of adiposity, the maximum prevalence of MetS clustered around 21%, suggesting that different measures of adiposity in the same study will yield different MetS prevalence values. Guize et al (2007) demonstrated that no matter which definition was used for MetS, WC was always of central importance for predicting all-cause mortality in men.

Corona et al (2006a,b, 2007a,b) found that men with MetS had significantly higher prevalence of hypogonadism, with WC and hyperglycemia most strongly predicting this condition. There is a strong link between MetS and diabetes because one of the criteria in most definitions is abnormal blood sugar or frank diabetes. Selvin et al (2007), reporting on the Third National Health and Nutrition Examination Survey study, found not only that low free and bioavailable T concentrations were related to diabetes, but that this association was independent of adiposity. A large study (Selvin et al, 2007) confirmed that low androgen levels may be a risk factor for diabetes.

#### *IV. Changes in Body Composition in Men Undergoing Androgen Deprivation Therapy*

The studies discussed above linking low endogenous androgen levels in aging men with increased risk of developing MetS are similar in concept to studies that have assessed the prevalence of MetS in patients who have undergone androgen deprivation therapy (ADT) for advanced prostate cancer.

Chen et al (2002) investigated the effect of androgen deprivation on total body fat mass after 1–5 years of treatment in 62 men with prostate cancer. There was a significant increase in total body fat mass and reduction in lean body mass. Smith et al (2002, 2006) compared the changes in body composition of men at baseline and after ADT for prostate cancer for a period of 12 to 48 weeks. The authors observed a significant decrease in lean body mass, and an increased fat mass, BMI, and total body weight, after androgen deprivation in reference to baseline. Similarly, Haider et al (2007) and Saad et al (2008a,b) show changes in these parameters with T treatment, suggesting a marked increase in body weight in diabetic patients. Stoch et al (2001) further demonstrated that in patients with prostate cancer who were treated with gonadotropin-releasing hormone agonist (n = 19) or

untreated (n = 41) for 6 months, total lean mass decreased and fat mass increased in men deprived of androgens when compared with men who were eugonadal.

Patients with prostate cancer undergoing ADT become hypogonadal and are at increased risk for developing MetS and CV risks (D'Amico et al, 2007). ADT induces a hypogonadal state and many studies have taken advantage of this to measure the prevalence of MetS in individuals receiving ADT. Braga-Basaria et al (2006) investigated the prevalence of MetS and its components in men with prostate cancer who were either treated with ADT (n = 20) or untreated (non-ADT, n = 18), and compared these changes with those of healthy controls (n = 20). The data suggest that MetS is more prevalent in men with ADT (55%), as compared with the non-ADT (22%) and control groups (20%). Specifically, BMI, triglycerides (TGs), and fasting glucose levels in men receiving ADT were all significantly elevated with respect to healthy controls. Lage et al (2007) found that the incident risk ratio (RR) of diabetes after ADT was 1.36, even after controlling for older age, poorer health, prior statin use, and comorbid conditions.

Yannucci et al (2006) discussed the differential effect of multiple types of ADT on metabolic parameters in patients. These authors suggested that depending on whether a GnRH agonist or antagonist is used, it may be possible to observe differing trends in HDL levels during the course of a patient's treatment. The mechanism may be an increase in IR induced by hypogonadism, and IR is thought to be the cornerstone of MetS as well as a very common accompaniment of obesity (Pitteloud, 2005a,b). Yialamas et al (2007) found that acute withdrawal of T therapy in men with hypogonadotropic hypogonadism—in as little as 2 weeks—reduced insulin sensitivity without any change in leptin or BMI; the mechanism may be related to an increase in selected inflammatory cytokines. Lee et al (2007) found that the prevalence of the individual components of MetS increases with decreasing insulin sensitivity even in youths of various ethnic origins. Greenfield et al (2007) found that a certain percentage of young cancer survivors had frankly low total T levels and that this was associated with increased fat mass and increased insulin levels, so the relationship of insulin resistance to hypogonadism even extends to young men as well as to an older population. This may indicate an increased risk of CVD at a young age. Bonora et al (2007) reported on the Bruneck study of nearly 1000 men aged 40–79 years, and found that homeostatic model assessment (HOMA<sub>IR</sub>)-estimated insulin resistance was associated with subsequent symptomatic CVD in a general population, and that this was independent of classical risk factors.

### V. Central Obesity and WC in Men Undergoing T Therapy for Hypogonadism

Several studies have investigated the hypothesis that androgen treatment may ameliorate MetS in men without prostate cancer and in those who have been free of cancer. Page et al (2005) investigated 70 men over the age of 65 with serum T levels under 350 ng/dL and assigned them to 1 of 3 treatment groups for 36 months: 1) T only; 2) T + Finasteride (F); and 3) placebo. The authors showed a significant reduction in total body fat percentage in the T and T + F groups when comparing the 6-, 12-, and 36-month follow-up visits to baseline. Compared with the placebo group, the T and T + F groups also showed a significant increase in lean body mass, decrease in total fat mass, and decrease in leptin levels from baseline. Cholesterol, LDL, and TGs were reduced significantly over the course of 36 months, whereas HDL and fasting insulin did not show significant changes in response to treatment. Katznelson et al (1996) found a similar result in 36 men, between the ages of 22 and 69, who had acquired hypogonadism. These hypogonadal men were given 100 mg/wk of T enanthate therapy over the course of 18 months and were compared with 44 age-matched eugonadal controls. T therapy led to a significant reduction in the percentage of body fat with an increase in lean muscle mass over the course of treatment. In contrast to these favorable changes in body composition, there was no significant change in total and LDL cholesterol, a result that differs from the significant decline in total cholesterol and atherogenic fraction of LDL observed by Zgliczynski et al (1996). These 2 studies highlight an important consideration in which T treatment may produce conflicting results with regard to changes in metabolic parameters, especially if the dosage regimen and baseline characteristics of study subjects are very different between studies. Although one might have predicted a favorable effect of T in raising HDL levels in the study by Katznelson et al (1996), the observed decline may be accounted for via an androgenic effect on hepatic lipase activity (Tan et al, 1998). It is possible that the observed decline in HDL level might have been because of supraphysiological levels of T often seen with intramuscular depot long-acting T esters (Isidori et al, 2000, 2005).

Bojesen et al (2006) found that in patients with Klinefelter syndrome, who present with hypogonadism, T treatment did not result in a favorable change in body composition in comparison to untreated Klinefelter patient controls. Additionally, only LDL cholesterol was significantly reduced, whereas the other components of MetS were not. The authors account for these results by suggesting that the dosage of T given may

have been inadequate. It is also possible that other unidentified genetic abnormalities that affect metabolism, lipid, and hormonal profiles are present in patients with Klinefelter syndrome.

Interestingly, Pagotto et al (2003) showed a highly significant correlation between ghrelin levels and both free and total T, the latter having a stronger correlation. Ghrelin is considered to be the hormonal counterpart to leptin and is produced in the stomach and acts as a satiety signal. An interesting hypothesis involving T administration to hypogonadal men might involve ghrelin mediating the body fat reduction that is often seen in these patients with this type of treatment. Investigative studies are needed that control for ghrelin levels while evaluating the relationship between T administration, hypogonadism, and body fat mass, which might shed more light on ghrelin's role in fat metabolism.

A double-blind, placebo-controlled, crossover study in 13 men (57–76 years) who were given 100 mg T enanthate per week, as compared with placebo, over the course of 3 months showed a significant increase in body weight (fat-free mass) and a significant reduction in fat mass (Tenover, 1992). A similar trend was found with the same dosage of T, given to hypogonadal men, over the course of 18 months (Katznelson et al, 1996) and with T gel treatment for 6 months (Swerdloff et al, 2003) and 42 months (Wang et al, 2004).

It has also been observed that the percentage body fat reduction by T administration displays a dose-dependent response. In one study, the effect of the T patch (5 mg T) was much less compared with the 100-mg T gel application over the course of 3 months (Wang et al, 2000). In a subsequent study, the authors demonstrated a similar dose-response relationship, regarding change in lean body mass and fat body mass, with a T gel over the course of 30 months (Wang and Swerdloff, 2002). Although T gel significantly reduced WC and hip circumference, 5- $\alpha$  dihydrotestosterone (5  $\alpha$ -DHT) gel did not (Marin et al, 1993).

Although T supplementation clearly has a positive impact on hypogonadal individuals, Marin et al (1992) found 160 mg of T per day for 8 months to have a positive impact on eugonadal, obese men (age > 45). Total adipose tissue, visceral adipose tissue, and sagittal abdominal diameter significantly decreased, whereas subcutaneous adipose tissue did not (Marin et al, 1993). Boyanov et al (2003) showed that in diabetic men, 120 mg of T per day for 3 months significantly reduced weight, WHR, body fat, and percentage of body fat. In addition, Kapoor et al (2006) demonstrated that WC declined significantly in a group of diabetic patients treated with T. Allan et al (2008) further showed that transdermal T therapy for 1 year selectively lessened

Table 2. Incidence of metabolic syndrome and insulin resistance in men with erectile dysfunction ( $n = 154$ )

Severity of ED	Metabolic Syndrome, %	Insulin Resistance, %	FBS 110, %
Mild (SHIM 17–21)	14.5	14.8	19.1
Moderate (SHIM 11–16)	35.5	32.8	25.5
Severe (SHIM 1–10)	50.0	44.2	46.8

Abbreviations: ED, erectile dysfunction; FBS, fasting blood sugar; SHIM, Sexual Health Inventory for Men (Bansal et al, 2005).

visceral fat accumulation, which is the fat component that best correlates with CV risk.

Allan et al (2007) recently reviewed T therapy in aging men and suggested that, with respect to body composition and specifically fat mass, men were likely to notice improvement with T treatment, but only if the baseline levels were low. They further reported (Allan et al, 2008) the  $\Delta$  in visceral fat to be inversely correlated with the  $\Delta$  in T levels. They also noted that obesity was a more important determinant than age in influencing the decline of T levels in aging men. They further suggested that, given the association of obesity with MetS and excess CV morbidity and mortality, the question as to whether T therapy in older men with low T levels will modify metabolic and CV risk is a pertinent one and deserves to be investigated.

It is interesting that T therapy might ameliorate components of MetS and decrease cardiac risk because for many years T was thought to be the factor that produced earlier cardiac disease in men versus women. A recent meta-analysis by Haddad et al (2007) confirmed that T therapy does not carry any increased risks of CV events. In fact, there is evidence to suggest that low T levels are associated with coronary artery disease (Rosano et al, 2007). There is no consensus that T therapy will correct the components of MetS. Basu et al (2007) treated elderly men with T for 24 months, and did not observe any improvement in carbohydrate metabolism or insulin secretion and/or action. Given the standard definition for hypogonadism in most studies is a total T level below 300 ng/dL, the concern with this study is that the men who were treated with T are not hypogonadal, because the baseline total T levels varied from 370 ng/dL to 390 ng/dL. The lesson to be learned here is that men have to be truly hypogonadal before any benefits from T therapy can be expected. Most of the clinical data suggest that responses to T therapy may be observed as early as 3 months, but may need 6 or more months to obtain the full biological effect.

## VI. Role of Cytokines in the Pathology of MetS

MetS and obesity, in particular, are affected by a variety of biochemical substances related to satiety and/or fat metabolism. It is interesting that even in young healthy men, plasma adiponectin levels may predict endothelial dysfunction, even before any evidence of vascular damage (Torigoe et al, 2007). A similar suggestion was made by Bocchio et al (2004), who found that cytokines were elevated in men with ED without known vascular cofactors who appear to have normal blood flow as assessed by corpus duplex ultrasound. Recently a link has been found to exist between some of these cytokines and T levels. Leptin has been shown to be involved in the regulation of testicular function (Tena-Sempere et al, 1999). Ghrelin has also been observed to inhibit the stimulation for T secretion in vitro (Tena-Sempere et al, 2002). Ishikawa et al (2007) have shown that ghrelin expression by Leydig cells in the testis was inversely correlated with the serum T level. These observations suggest a complex relationship between T and the biochemical factors involved in obesity, MetS, and CVD.

## VII. Is There a Link Between MetS and ED?

Men with MetS have a higher risk for ED (Esposito, 2005). Because MetS increases CV risk, it is not surprising that ED may also be a predictor of subsequent CVD. Thompson et al (2007) studied over 9000 men in the Prostate Cancer Prevention Trial and the hazard ratio of men with new ED for CV events over 5 years was 1.45. This is consistent with evidence presented by Corona et al (2006a,b), in that 96.5% of their subjects with MetS exhibited ED, and Bansal et al (2005), who reported that in 154 men with organic ED, 43% had MetS and the percentage of individuals expressing MetS increased with increasing ED severity. Interestingly, Paick et al (2007a,b) did not find a significant relationship between ED severity and MetS parameters, except hypertension, in impotent men, suggesting that the relationship between MetS and ED severity may not be clear-cut, or may be selective for certain components. Similar findings were made by Bansal et al (2005), where the severity of ED was positively associated with MetS and IR (Table 2). Because ED is a peripheral vascular disease (PVD), it is significant that Wang et al (2007) showed that MetS correlated with PVD, especially when diabetes and microalbuminuria was present.

The prevalence of ED among men with MetS increases with the number of MetS components (Esposito et al, 2004), with approximately 20%, 30%, and 35% of patients with ED having 3, 4, or 5 components of MetS, respectively. This is consistent



with the finding that MetS is an independent risk factor for ED (Heidler et al, 2007), and the more specific risk factor of WC (Demir et al, 2006) is also an independent predictor.

Shabsigh et al (2005) further assessed the relationship between the prevalence of comorbidities by ED severity in a cross-national survey on men's health (ages 20–75). Hypertension and high cholesterol were the most prevalent comorbidities for each degree of ED severity. The authors also found that men between the ages of 70 and 75 were 14 times as likely to develop ED as compared with men between the ages of 20 and 29. This finding is consistent with the observation that androgen levels decline, with concomitant increase in the prevalence of MetS with aging. Bansal et al (2005) also reported that of 154 men with organic ED, 43% displayed MetS (general population, 24%), 79.2% displayed insulin resistance (general population, 25%) and 90.9% displayed both insulin resistance and MetS. Clearly, ED represents a risk factor and may be a warning signal for MetS and insulin resistance, both being clear risk factors of CVD. Interestingly, the largest jump in expression of MetS occurred between men with moderate ED and men with severe ED (21.7%–70%). The authors also demonstrate that the prevalence of fasting blood sugar >110 mg/dL, a component of MetS, increases with severity of ED.

A recent study by Zhody et al (2007) elegantly tied together androgen deficiency with ED and MetS by analyzing BMI measurements in 158 obese men. These authors found a significant statistical association between increasing BMI and the following parameters: systolic blood pressure, serum T, penile duplex parameters, TGs, HDL, and LDL. With increasing BMI, the frequency of hypogonadism and ED increased, whereas total serum T showed a strong negative correlation. To assess the effect of BMI on vasculogenic ED, the authors examined this relationship in the absence of other risk factors and found that for a BMI <25, 3 out of 13 men (23.1%) had vasculogenic ED, as compared with 32 out of 54 men (59.3%) with a BMI ≥25. Although Zhody et al (2007) put forth convincing data, this result may be at odds with a study done by Kupelian et al (2006a,b), who suggest that having ED is a better predictor of MetS in men with a BMI of less than 25, although Kupelian et al (2006a,b) did not limit their results to vascular ED.

All of the metabolic factors comprising MetS affect blood flow, and if circulation is impaired, then the oxygen saturation of the tissues is also impaired. Padmanabhan and McCullough (2007) found that men with ED had significantly lower corporal penile oxygen saturation than did men without ED. Although several recent studies have investigated the relationship between

ED and MetS, 3 major issues have yet to be adequately addressed. These are: 1) sexual dysfunction as it relates to MetS in men and women, 2) the effect of diet on ED in patients with MetS, and 3) whether different definitions of MetS applied to the same study population will yield significantly different ED prevalence statistics. Esposito and colleagues (2005, 2006) demonstrated that diet improved ED in subjects with MetS (Esposito et al, 2006). The “Mediterranean Diet” was utilized and contained a higher percentage of olive oil, fruits, vegetables, nuts, legumes, and omega-3 fatty acids than the control diet. Over the course of 2 years, individuals on this diet showed a significant reduction in plasma glucose, serum insulin, LDL, TGs, and systolic blood pressure, and a significant increase in HDL levels. Men on this diet also showed a significant increase in International Index of Erectile Function (IIEF) score, a measure of improvement of erectile function.

Central obesity is a predictor of ED. Riedner et al (2006) found that different anthropometric measurements better predicted the odds of developing ED than others. The authors calculated that a WC of greater than 102 cm has an adjusted odds ratio of 19.37, a number that outranks the 11.72 and 8.56 odds ratios for a maximum abdominal circumference of greater than 106 cm and a WHR of greater than 0.91, respectively.

The degree to which an individual suffers from ED is often measured by a numerical score (IIEF scale), with a low score representing increased ED severity. This was carried out with 110 obese, sedentary men (BMI ≥30, <1 hr/wk physical activity), and correlated with various measurements of obesity, such as BMI or WHR (Esposito et al, 2004). The authors found that for both BMI and WHR, significant age-adjusted negative correlation coefficients existed. The lower IIEF score (greater severity of ED), the stronger the correlation with a high BMI ( $r \approx -0.35$ ) and WHR ( $r \approx -0.5$ ) value.

### Summary

The relationship among hypogonadism, MetS, diabetes, CVD, and ED is very complex. The most important aspect of this working hypothesis is recognizing that individuals identified as having MetS (age-adjusted prevalence in US adults is 23.7%) are at high risk for developing hypogonadism, type 2 diabetes, CVD, and ED. Although only some definitions of MetS use insulin resistance as one of the criteria for diagnosis, the importance of insulin resistance should not be ignored. Insulin resistance contributes to the onset of MetS and is a risk factor for both diabetes and CVD. Clinical consequences of insulin resistance include dyslipidemia (Ginsberg, 2000), hyperglycemia (Haffner et al, 2000),



hypertension and abnormal vascular behavior (Reaven et al, 1996), and vascular inflammation and risk of thrombotic inflammation (Sobel, 1999; Calles-Escandon et al, 1998; Calles-Escandon and Cipolla, 2001; Gustafson et al, 2007). The relationship between androgen deficiency, type 2 diabetes, and insulin resistance will be addressed in a separate review. Endothelial dysfunction is also associated with dyslipidemia, obesity, and diabetes (McVeigh and Cohn, 2003), which are linked to ED (Guay, 2005, 2007; Guay and Jacobson, 2007). Clearly, there may be a link between insulin resistance and endothelial dysfunction, both of which are also implicated in MetS, ED, and diabetes. Hypogonadism has been shown to be an independent determinant of endothelial dysfunction, thus contributing to vascular pathology, including ED (Akishita et al, 2007). Androgen deficiency contributes to MetS pathologies that adversely affect the endothelium, resulting in multiple vascular sequelae. Androgen deficiency may be viewed as a common denominator of the various pathologies affecting the endothelium and a central factor in the development of MetS (Shabsigh et al, 2008).

The emerging evidence linking androgen deficiency to multiple risk factors, including obesity, diabetes, hypertension, and altered lipid profiles, suggests that androgens play an important role in the regulation of homeostasis and that androgen deficiency contributes to many risk factors and pathologies associated with MetS and CVD. New clinical information is emerging linking T deficiency to the development of the pathology of MetS, diabetes, and vascular disease. T therapy has significantly improved lipid profiles in men, reduced body fat percentage, increased lean muscle mass percentage, lowered blood pressure, and decreased fasting glucose levels. This is in line with evidence suggesting that decline of androgens with aging, hypogonadism, and ADT are significantly associated with an increased risk for developing MetS, vascular disease, and ED. In addition, lifestyle modifications with regard to diet and exercise may also play a positive role in reducing the risk for MetS. Therefore, T treatment as well as lifestyle modifications may synergistically slow or halt the progression of MetS, type 2 diabetes, CVD, and ED.

The data from studies of androgen deprivation therapy for prostate cancer, and of androgen treatment in hypogonadal men, have provided a new paradigm for a role of T in MetS, diabetes, and vascular diseases. These pathologies are all associated with higher prevalence of ED. We suggest that T deficiency is linked to multiple causes of MetS as well as ED and may be a central factor in the pathology of MetS and ED.

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