Hypogonadism and metabolic syndrome: review and update

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Purpose of review
The prevalence of metabolic syndrome and hypogonadism continues to rise in the United States and around the world. These two conditions are inexorably linked, and understanding their relationship with each other is key to treating men with either of these conditions.

Recent findings
Testosterone has been shown to be a key regulator in the maintenance of metabolic homeostasis. A large volume of research has found that testosterone deficiency is closely linked to metabolic syndrome through complex physiologic mechanisms of endothelial dysfunction, inflammation, and glucose metabolism.

Summary
Interventions through lifestyle modification and testosterone replacement in hypogonadal men may reduce the morbidity and mortality risks associated with metabolic syndrome.

Keywords
hypogonadism, metabolic syndrome, testosterone replacement

INTRODUCTION

In the United States, almost 70% of men aged 20 years and older can be classified as overweight [1]. Additionally, the overall prevalence of metabolic syndrome (MetS) in the United States is almost 35%, with greater than 40% of men older than 60 being classified as having MetS [2]. Hypogonadism, also known as testosterone deficiency, similarly impacts a large number of men with approximately 30% of men ages 40–79 years effected [3]. Testosterone has been shown to be a key regulator in the maintenance of metabolic homeostasis. Insight from studies of hypogonadal men undergoing treatment with testosterone replacement therapy (TRT), and additional studies with androgen-deprivation therapy in prostate cancer patients, suggests that testosterone deficiency is closely linked to metabolic syndrome (MetS) through several complex pathways. These pathways include changes in insulin resistance, hyperglycemia, visceral fat accumulation, increases in waist circumference, dyslipidemia, increased synthesis of inflammatory cytokines and endothelial dysfunction; all ultimately leading to cardiovascular disease [4–10]. Hypogonadism itself has been shown to result in significant changes in body composition with decreased lean body mass, increased fat mass (especially visceral fat mass), and decreased bone mineral density. It is through this lens we review the association between hypogonadism and metabolic syndrome [4].

DEFINING METABOLIC SYNDROME

Increased blood pressure, dyslipidemia, elevated fasting blood sugar, and abdominal obesity have been known to be significant risk factors for cardiovascular disease for many decades. Patients with metabolic syndrome compared with those without are two times more likely to develop significant cardiovascular (CVS) disease over 5–10 years [11]. There have been some disagreements as to whether metabolic syndrome is simply a constellation of related diseases and CVS risk factors, or an independent entity. With this in mind, several definitions have been proposed by international medical

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KEY POINTS

- Metabolic syndrome and hypogonadism impact 30–40% of Americans, and are increasing in prevalence in the United States and around the world.
- Metabolic syndrome and hypogonadism have been shown to be closely linked and may have bidirectional causation.
- Lifestyle modification has been shown to resolve metabolic syndrome and improve testosterone levels.
- Testosterone replacement in hypogonadal men has resulted in improvements in the components of metabolic syndrome and may prevent the development metabolic syndrome in certain populations.

societies. The most recent consensus definition was determined through the combination of the International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute in 2009 [12]. The National Cholesterol Education Program Adult Treatment Panel III (ATP III) in 2001 defined MetS as having three of the five factors of abdominal obesity, elevated triglycerides, reduced high-density lipoprotein cholesterol, elevated blood pressure, and elevated fasting glucose [13]. The 2009 consensus definition recommends utilizing country or ethnicity specifications for waist circumference. For the United States, The American Heart Association defines an elevated waist circumference as at least 102 cm (40 in) in men and at least 88 cm (35 in) in women [14]. Additional cut points include triglycerides at least 150 mg/dl, HDL-C less than 40 mg/dl (in men), SBP at least 130 mmHg or DBP at least 85 mmHg, and fasting glucose at least 100 mg/dl [12].

DEFINING HYPOGONADISM

Although defined definitively by the United States Food and Drug Administration (FDA), there is a lack of age-specific norms and consistency in method of testing of testosterone levels throughout the literature. Furthermore, there is a paucity of data correlating testosterone levels to symptoms typically associated with hypogonadism. The FDA defines 300 ng/dl as the lower limit of normal for serum testosterone levels consistent with the early definition from the Endocrine Society guidelines originally published in 2000. Clinical practice guidelines on testosterone deficiency in men recognize that the condition is both a biochemical and clinical state, suspected on the basis of symptoms but confirmed by laboratory findings. Furthermore, they all recommend that testosterone levels should be checked in the morning, with a confirmatory test if the level is low. The American Urologic Association guideline on the evaluation and management of testosterone deficiency sets the threshold for low as at least two serum total testosterone levels early in the morning below 300 ng/day [15]. Symptoms of low testosterone include reduced energy, reduced endurance, diminished work and/or physical performance, fatigue, visual field changes, anosmia, depression, reduced motivation, poor concentration, impaired memory, irritability, infertility, reduced sex drive, and changes in erectile function. The Endocrine Society set the lower limit of normal testosterone to 264 ng/dl [16]. The European Urologic Association and British Society for Sexual Medicine also includes a threshold for free testosterone at 7–6.49 ng/dl, respectively [17,18]. The British Society for Sexual Medicine, the International Society for Sexual Medicine, and International Society for the Study of the Aging Male all use 350 ng/dl as a cutoff for normal [18–20].

ASSOCIATIONS BETWEEN HYPOGONADISM AND METABOLIC SYNDROME

Testosterone levels in men appear to be inversely related to the presence of comorbid medical conditions that accompany obesity: type 2 diabetes; obstructive sleep apnea; pulmonary hypertension; dyslipidemia, and coronary artery disease. Androgen deprivation therapy, used in the treatment of advanced prostate cancer, causes profound testosterone deficiency and is associated with negative changes in body composition as well as increased risk of incident diabetes mellitus [20]. Testosterone deficiency is consistently found in men with metabolic syndrome. It appears that hypogonadism predisposes men to insulin resistance, obesity, abnormal lipid profiles, and borderline or overt hypertension [21]. Studies have consistently demonstrated that MetS is more prevalent in men with low concentrations of testosterone [22].

The American Association of Clinical Endocrinologists recommend screening for hypogonadism in all men with an elevated waist circumference, BMI greater than 30, and type II diabetes [23]. The American Diabetes Association notes the very high prevalence of hypogonadism in patients with type II diabetes, and recommends checking testosterone levels in diabetic men who may be symptomatic [24].

A comprehensive review found that the link between MetS and hypogonadism is so strong that hypogonadism should be considered a diagnostic

parameter of metabolic syndrome [25]. New-onset hypogonadism has been found to be 5.7–7.4 times more common among men with metabolic syndrome at baseline [26]. Further, meta-analysis has demonstrated that having MetS independently predicts low testosterone level, and baseline testosterone levels are two times lower in men with MetS compared with controls [27].

A cross-sectional study was performed in Korea on 6967 adult men who attended a health screening [28]. Men were screened for MetS using the National Cholesterol Education Program Adult Treatment Panel III criteria. They found an approximate 13% reduction in the risk of MetS per 1 ng/ml increase in serum testosterone levels. Furthermore, they found that testosterone levels were inversely correlated with hyperglycemia, triglyceride levels, decreased high-density lipoprotein cholesterol (HLD) levels, and blood pressure.

In a study of Finish patients, men in the lowest tertial of testosterone were 2.7 times more likely to have MetS, and 1.7 time more likely to have MetS after adjusting for BMI. This demonstrated that testosterone deficiency was independently associated with MetS and not only the components of MetS [29]. Another cross sectional survey, this of Japanese men, found in regression analysis close correlations between testosterone level and waist circumference, HTN, dyslipidemia, HLD, and insulin resistance based on fasting plasma glucose levels [30].

In an interesting study of monozygotic twins, testosterone levels were inversely correlated with waist circumference [31]. Similarly, in a study of 864 men, mean testosterone levels were 150–300 ng/dl lower in obese and severely obese men with metabolic syndrome compared with aging lean men [32]. They also found that diabetes and elevated fasting serum glucose had significant impacts on the level of testosterone.

Men with Kleinfelter's syndrome have been found to be at significantly higher risk for having metabolic syndrome when compared with eugonadal men. Kleinfelter's patients are known to have truncal obesity and decreased muscle mass, driven by their lack of endogenous testosterone production. One cross-sectional study of Kleinfelter's patients found a 44% prevalence of MetS [33].

DIABETES AND HYPOGONADISM

Hypogonadism and insulin resistance go hand-in-hand. The prevalence of hypogonadism in diabetic men has been found to range from 20 to 64% [34–37]. In cross sectional studies, men with type II diabetes have, on average, significantly lower concentrations of testosterone than men with normal fasting glucose [38].

Furthermore, hypogonadism can be a risk factor for the development of diabetes and the metabolic syndrome. In a study of Finish men in the Kiopio Ischemic Heart Disease risk factor study, a prospective population-based study investigating risk factors for chronic disease, nondiabetic men were approximately four times more likely to develop metabolic syndrome if they were hypogonadal and over two times more likely to develop diabetes or metabolic syndrome if there were in the lower quartile for testosterone levels [28,29]. Furthermore, if men had MetS at baseline, they were 2.9 times more likely to develop hypogonadism [39].

Insulin resistance in hypogonadal men may be because of changes in body composition and inhibition of lipoporotein lipase, and decreased circulating free fatty acids [40]. Data from 1226 men from the Third National Health and Nutrition Examination Survey (NHANES III) found that lower concentrations of total testosterone, SHBG, free testosterone, and bioavailable testosterone were significantly associated with higher levels fasting serum insulin and markers of insulin resistance [41].

In one of the largest studies, 5250 Danish men were followed for up to 29 years. Through linear Cox proportional hazards models, they found T quartiles had a significant negative association with the risk of type II diabetes. Through analysis of other gonadotropins, they determined that hypogonadism can be considered to be a screening marker for type II diabetes [42].

TESTOSTERONE DEFICIENCY AND METABOLIC SYNDROME: INFLUENCE MORBIDITY AND MORTALITY

A wealth of evidence indicates that low levels of testosterone are associated with poor cardiovascular health and known risk factors for cardiovascular disease, such as obesity, diabetes, and metabolic syndrome. This association has been demonstrated repeatedly in long-term studies and metanalyses. There is particular risk of cardiovascular death likely related to the frequent concomitant impact of MetS. Metabolic syndrome is associated with two times increased risk of cardiovascular disease and five times risk of developing type II diabetes [43,44].

Observational studies have identified significant associations between testosterone deficiency and all-cause and cardiovascular death in general populations of men aged older than 40 years. In general, the population of men presenting with hypogonadism may have up to twice the mortality risk when compared with men with normal testosterone levels

[45]. In one study examining men admitted to the hospital with acute myocardial infarction, low testosterone levels on admission were independently related to higher mortality after 30 days [46]. A database study of United States veterans identified 858 men who had repeated testosterone levels over an approximately 4-year period. The mortality was 34.9% in the low testosterone group, significantly higher than the 20.1 and 24.6% in the normal or equivocal group testosterone group [47].

The European prospective investigation into cancer in Norfolk (EPIC-Norfolk) nested case–control study followed 11 606 men for up to 10 years. They found that testosterone concentrations at baseline were inversely related to mortality because of all causes, cardiovascular disease and cancer [48]. They also found that every 173 ng/dl increase in serum testosterone was associated with a 21% lower risk of all cause death.

In the Rancho Bernardo study, 794 men were followed on average 11.8 years up to 20 years. They found that testosterone levels were inversely related to the risk of death and men in the lowest quartile of testosterone levels were 44% more likely to die during the follow-up period compared with those in the highest quartile. This was independent of age, BMI, and waist-to-hip ratio [49,50].

LIFESTYLE MODIFICATION IN THE TREATMENT OF METABOLIC SYNDROME AND TESTOSTERONE DEFICIENCY

Many interventions around the treatment of metabolic syndrome have centered around lifestyle modification, which includes diet, weight loss, and regular exercise programs. Attempts have been made to correlate exercise with testosterone levels. There is some literature to suggest men with better aerobic exercise potential have higher levels of testosterone [51].

If men were able to resolve their metabolic syndrome, they had no increased risk of low testosterone [26]. When given a prescribed diet, weight loss and weight maintenance can result in sustained increases in free testosterone [26].

Weight loss does appear to have some impact on testosterone levels in patients with MetS. A randomized study of obese men with MetS, 48% with concurrent hypogonadism, were placed on a very low-calorie diet. At the end of the study, participants on average lost about 16 kg, which resulted in only 9% of the men having testosterone levels indicative of hypogonadism. In the weight maintenance period, study participants gained approximately 2 kg resulting in 21% being hypogonadal [52]. Testosterone replacement in hypogonadal men with MetS has also demonstrated significant improvements in insulin sensitivity, fasting glucose, high-density lipoprotein (HDL) [53].

In a randomized placebo-controlled clinical trial of symptomatic obese men, men in the testosterone replacement group had significant improvements in skeletal muscle and fat-free mass, while decreasing fat mass, with relative decreases in cholesterol levels [54].

Another randomized double-blind placebo-controlled crossover study of 24 diabetic men with hypogonadism treated with testosterone found significant improvements in insulin sensitivity, HbA1c, and fasting blood glucose [55].

In a prospective cohort study of 31 abdominally obese men with type II diabetes were given either a meal replacement-based low-calorie diet or a low-fat, high-protein, reduced-carbohydrate diet. Over 8 weeks, there was a 10% reduction in waist circumference with the low-calorie diet, and 5% with the low-fat, high-protein, reduced carbohydrate diet. Men on the diet also saw improvements in fasting plasma glucose low-density lipoprotein (LDL) levels, and sexual function [56].

Ninety men with abdominal obesity and sedentary lifestyle were randomized to a low-calorie diet with low-volume or high-volume moderate-intensity exercise. The high-volume exercise group saw greater average improvements over the low-volume exercise group in sexual function, testosterone levels, and waist circumference [57].

In one study that was a metanalysis of available trials found a diet-induced weight loss of 9.8% was associated with a significant increase in total testosterone of 2.8 nmol/l [58]. Another more recent metanalysis, which included a total of 567 patients, found that for each 5 kg of weight reduction testosterone increases by 1 nmol/l [59▪].

Kumagai *et al.* conducted a study in which 16 normal-weight men and 28 overweight or obese men were prescribed a 12-week aerobic exercise program. Each patient had testosterone levels measured before and after the exercise intervention program as well as a number of other anthropometric, blood biochemistry measures. Serum total testosterone, free testosterone, and bioavailable testosterone levels significantly increased in overweight/obese men ($P < 0.01$) as well as significant improvements in weight, BMI, and lipids [60▪].

TESTOSTERONE THERAPY IMPACT ON METABOLIC SYNDROME

A number of studies have investigated the effects of testosterone replacement therapy on MetS and its components. Testosterone therapy in hypogonadal

men has been shown to decrease body weight, improve the waist-to-hip ratio, improve glycemic control, insulin resistance, and lipid profile [52,61,62]. Testosterone therapy produces improvement in lean muscle mass and muscle strength [63]. Though broad improvements are often seen, testosterone therapy does not resolve or reverse metabolic syndrome completely. It has been challenging to perform meta analyses or compare studies on this as the delivery mechanism of testosterone therapy has been variable as well as the goals for normalization, and outcome measures chosen. In one metanalysis of RCTs, testosterone was found to significantly reduce fasting plasma glucose, triglycerides, and waist circumference while increasing high-density lipoprotein [27].

A year-long trial of 32 men diagnosed with hypogonadism and newly diagnosed diabetes were given a supervised diet and exercise and randomized to with and without transdermal testosterone. Patients were confirmed to have MetS through the ATP III definition. Patients were contacted twice a week to confirm adherence to the exercise and diet regimen. After 1 year, all patients had improvements in HbA1c, fasting glucose, HDL levels, triglycerides, and waist circumference. The group who received testosterone had significant improvements over the placebo group. Hundred percent of patients in the testosterone treatment group met the HbA1c goal. Furthermore, 81% of patients receiving testosterone no longer met the criterial for MetS compared with only 31% of the diet and exercise along group [64].

In the largest double-blind randomized placebo-controlled trial to date, the T4DM study, 1007 men in Australia with metabolic syndrome, hypogonadism, and impaired glucose tolerance were randomized to testosterone therapy or placebo and enrolled in the lifestyle diet program. The authors hypothesized that treating men with testosterone might prevent or reverse early type II diabetes greater than a lifestyle program alone. Men were treated and followed for 2 years. The men treated with testosterone had significant improvements in the primary outcome of oral glucose tolerance threshold for diabetes. Twelve percent of men in the testosterone group had elevated oral glucose challenge test versus 21% in placebo group. The testosterone group also gained greater amounts of lean muscle mass, had improvements in sexual function, and had a greater decrease in fasting blood sugar than the placebo group [65▪▪].

Another smaller randomized controlled trial of obese men with hypogonadism and type II diabetes were treated with testosterone for 2 years. Over the course of the study, the participants had improvements in fasting plasma glucose, HbA1c, lipid profile, and endothelial function parameters [66▪].

Testosterone treatment provides not only transient improvements but also likely has sustained effects. A long-term 5-year observational study of 261 men with hypogonadism and erectile dysfunction treated with long-acting testosterone undecanoate found improved overall body weight, waist circumference, BMI, lowered total cholesterol, LDL cholesterol, triglycerides, fasting blood glucose, HbA1c, and blood pressure. These improvements were seen in year 1 of the study and then sustained throughout the 5-year study period [67]. In a longer cohort registry study, over an 8-year study period, 316 men with prediabetes and hypogonadism, were treated with testosterone undecanoate. Compared with an untreated group, men treated had significant improvements in all anthropometric, glycemic control, lipids, and blood pressure parameters. In the testosterone-treated group, 100% of patients were able to achieve an HbA1c <6.5, and 90% achieved HbA1c of <5.7, compared with only 1% of the untreated group [68▪]. Another registry study followed 823 hypogonadal men for 11 years. Four hundred and twenty-eight men were treated with testosterone undecanoate and were compared with 395 untreated men. Regardless of baseline weight, men in the treated group had significant improvements in body weight, waist circumference, and BMI. Weight loss was progressive throughout the study period while weight gain was observed in all untreated groups. There was also significant improvement in glycemic control, blood pressure, and lipid profiles. The greatest improvement was seen in men with the least favorable cardiometabolic risk profiles at baseline [69▪].

CONCLUSION

The associations of hypogonadism and metabolic syndrome is strong, though bidirectional causality has not been clearly established. The abundance of evidence suggests that hypogonadism and concurrent MetS put men at significant risk for morbidity, specifically diabetes and also significant risk of mortality. The impact of both hypogonadism and MetS crosses many medical specialties and is ripe for collaborative treatment and future research endeavors. Most evidence points to testosterone therapy as safe and potentially helpful in reducing morbidity and mortality risks in men with MetS. This is most effective when combined with lifestyle modifications, most importantly regular aerobic exercise. Although testosterone replacement is clearly not a panacea, it can be a helpful adjunct to help enhance

a patient's path to a healthier lifestyle and improved cardiovascular risk.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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