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Testosterone Supplementation Therapy in the Treatment of Metabolic Syndrome

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Abstract

Metabolic syndrome (MetS) is a clinical complex of risk factors including increased waist circumference, high triglycerides, low HDL cholesterol, high blood pressure and insulin resistance whose presence increases the likelihood of developing diabetes and cardiovascular disease. With a quarter of the American adult population affected, MetS has been referred to as the most significant public health threat of the 21st century. While lifestyle modification and weight loss are recommended, no specific pharmacological treatment is known. Given that low levels of testosterone have been implicated in the pathogenesis of MetS and an inverse relationship exists between circulating testosterone and the development of MetS, it is tempting to speculate that men with MetS may benefit from testosterone supplementation therapy (TST). As such, this review seeks to examine the role of testosterone and the use of TST as a treatment modality in men with MetS.

Keywords

testosterone supplementation; hypogonadism; sexual dysfunction; erectile dysfunction; prostate cancer; metabolic syndrome; diabetes

INTRODUCTION

Following studies of castration and testicular transplantation in fowl, Arnold Adolph Berthold, in 1849,[1] gave the first hint that androgenic hormones were critical transducers of biological signals. These studies were followed in 1889 by Charles-Edouard Brown-Sequard's self-injection of a "rejuvenating elixir" that was composed of dog and guinea pig testicular extract that transiently "increased feelings of vigor".[2] For the following 40 years, progress towards the isolation of the active substances in these extracts remained slow until the isolation of testosterone [3] and the determination of its molecular structure by Schering [4] in the 1930's.

Independently, Butenandt and Hanisch,[5] along with Ruzickan and Wettstein [6], reported on the synthesis of the testosterone molecule in 1935 resulting in Butenandt and Ruzicka's

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sharing of the Nobel Prize in chemistry in 1939. From these humble beginnings, the "Golden Age of Steroid Chemistry" developed and encompassed the period of the 1930s–1950s. During this time, the synthesis of numerous potent steroid esters permitted the demonstration of testosterone's androgenic and anabolic properties. [7,8]

Recently, testosterone has developed into a type of clinical 'wonder-drug' that has experienced negative connotations when over-dosed in professional athletes [9] and positive advantages in the medically supervised and monitored treatment of male hypogonadism. [10,11] One of the most commonly prescribed medications in the world, the number of available testosterone formulations continues to grow with the number of testosterone prescriptions increasing 170% since 2007 [12] and 500% since 1993. [13] What was previously only available in a single topical or injectable formulation a decade ago has now expanded to include multiple topical, injectable, and implantable testosterone formulations.

Testosterone Supplementation therapy (TST) is used clinically in the treatment of hypogonadism. In men, testosterone levels are known to decrease at a rate of ~1% per year beginning at ~30 years of age. [14] The symptoms of hypogonadism are numerous and non-specific including low libido, erectile dysfunction (ED), cognitive effects including insomnia, memory loss, difficulty concentrating, depression, and fatigue, increased central adiposity, decreased muscle and bone mass, anemia, breast discomfort, gynecomastia, and hot flushes. [15] It has been estimated that 3.1–7.0% of men 30–69 years old, 18.4% of men over 70 years old [16] and up to 38.7% in men over 45 [17] are hypogonadal.

The diagnosis of hypogonadism includes both the presence of symptoms as well as biochemical evidence of low serum testosterone. Making this diagnosis particularly challenging is that normal serum testosterone levels vary between individuals, requiring clinical discretion during diagnosis. [14,18,19] For most men, the average lower limit of serum testosterone levels is ~300 ng/dL, with an increased risk of symptoms occurring below this limit. [18,20–22]

TST has also been shown to improve quality of life as well as body weight and waist circumference. [23,24] In certain situations, the side effects of TST may potentially outweigh its benefits, particularly with regard to prostate cancer; however, these beliefs are currently being aggressively challenged. [25] In summary, claims of testosterone as a "fountain of youth" are not completely accurate and are indeed, over-reaching. At the present time, testosterone levels are linked to a plethora of human disease conditions, many of which manifest as men age, including metabolic syndrome (MetS). [26] This review seeks to examine the role of testosterone and the use of TST as a treatment in men with MetS.

MATERIALS AND METHODS

A PubMed/MEDLINE literature search was conducted for the periods of 1960–2013 in November, 2013. Key search terms included combinations of "Metabolic Syndrome", "testosterone", "hypogonadism", "obesity", "type 2 diabetes mellitus" and "erectile dysfunction". In excess of 2000 manuscripts were screened using title search and abstract summaries. Applicable studies were read in-depth and included in this current review.

DISCUSSION

METABOLIC SYNDROME

MetS, first named “Syndrome X”, consists of a constellation of risk factors that, when found together, increases the likelihood of developing diabetes mellitus (DM) and cardiovascular disease. [27,28] Reaven, [29] in 1998, first brought the clustering of these risk factors to the attention of the modern medical establishment. The World Health Organization (WHO) was the first to propose specific diagnostic criteria for MetS. These criteria included impaired fasting glucose, insulin resistance along with an abnormal waist-to-hip ratio (WHR), high blood pressure, increased urinary albumin and elevated serum levels of: triglycerides, high-density lipoprotein (HDL) and cholesterol. [30] The American Association of Clinical Endocrinologists (AACE) [31] and the National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP III) [32] subsequently modified components of the WHO criteria as more research became available. The most recent, and specific definition has come from the International Diabetes Federation (IDF). Published in 2005, the IDF criteria were constructed in response to the need for a worldwide definition that identified people at risk for DM and/or cardiovascular disease (CVD). [33] This new document de-emphasized the role of insulin resistance and instead focused on waist circumference and triglycerides; both of which display a high correlation with insulin sensitivity and are easily measured. [33,34]

Currently, MetS affects 20–30% of the adult population and is associated with an all cause mortality of 7%. [35] Based on the IDF definition, the prevalence of MetS in the United States is approximately 39%. [36] In children, the rates have been increasing and are currently reported to be around 9%. [37] It is this prevalence of disease, coupled with the fact that MetS is associated with a 2-fold increased risk of developing CVD and a five-fold increase in the risk for Type 2 DM (T2DM), that makes the potential costs to society staggering. [38–40] Indeed, the amount of Americans afflicted with MetS and T2DM is increasing at such alarming rates that it has been referred to as the most significant public health threat of the 21st century. Some estimate that ~15% of Americans older than 60 years of age have DM [41] and this statistic is likely an underestimate given the high rates of undiagnosed disease. [39,42] These numbers are likely to keep growing due to the 23% increase in incidence and the 62% increase in prevalence that occurred between 1994 and 2004. [43]

SERUM TESTOSTERONE, SHBG AND METABOLIC SYNDROME

Low levels of testosterone have been implicated in the pathogenesis of both MetS and T2DM. [44] An inverse relationship between circulating testosterone and MetS has been identified and found to be constant between race and ethnicity. [44] Men with MetS and DM are nearly two times as likely to have low testosterone levels (64%) than they are to have normal testosterone levels (38%), [45] - a finding that was supported by a Finnish study by Laaksonen *et al.*. [46] In that report, the authors found free testosterone levels to be 11% lower in men with MetS. [46] Interestingly, sex hormone binding globulin (SHBG) levels, a testosterone transport protein, were found to be 18% lower in men diagnosed with MetS. [46] These findings were confirmed in a cross-sectional, population based study of 452 elderly Italian men with MetS who were found to have lower levels of both total testosterone and SHBG compared to controls. [47]

Numerous studies have identified an inverse relationship between MetS and serum levels of SHBG, total testosterone and free testosterone.[48] Moreover, in a study by Brand and colleagues, [49] higher SHBG levels were associated with a reduced risk of developing MetS. Given that higher levels of SHBG are associated with lower levels of testosterone, a non-linear relationship between SHBG, MetS and testosterone exists. Genetic evidence has also shown that an alteration in SHBG gene expression directly affects serum levels as well as the overall risks of developing T2DM. [50,51] Recently, insulin therapy has been found to increase SHBG through improved insulin resistance [52] suggesting a relationship between these factors in MetS.

Men with MetS have also been found to be at increased risk of developing hypogonadism. [53] In a population-based cohort study of 651 Finnish men, those with MetS had a 2.6 fold increased risk of developing hypogonadism at an 11-year follow-up. [53] To further understand the relationship between MetS, SHBG and DM, Laaksonen *et al.* [54] followed 702 middle aged (mean age 51.3±6.7 years old) Finnish men for 11 years. The authors found that those men with testosterone and SHBG levels in the lower fourth of the cohort (<15.6 and <28.4 nmol/L respectively) had an increased risk of developing MetS (1.7–2.8 times) and DM (1.7–4.3 fold). [54] Furthermore, these rates were specific to those hormones since adjustment for CVD, smoking, alcohol and socioeconomic status did not alter the association. [54]

Two detailed meta-analyses have recently been conducted in an attempt to collate the known data and determine the exact nature of the relationship between testosterone and MetS [40,49]. In one of these meta-analyses by Brand *et al.,* [49] the authors identified 52 studies involving 22043 men and 7839 women. After appropriate exclusions, 32 articles on men were selected as part of the analysis [49] with a correlation being drawn between MetS and lower levels of endogenous total testosterone, free testosterone and SHBG. These findings were correlated to the fact that men with higher total testosterone levels had lower risks for developing MetS. [49] In a separate meta-analysis, Corona and colleagues [40] identified 13 cross-sectional, 3 longitudinal and 4 randomized control trials dealing with the relationship between testosterone and MetS. Consistent with the meta-analysis by Brand *et al.*, [49] Corona found that serum testosterone levels in patients with MetS were significantly lower compared to healthy individuals. [40] Furthermore, patients with T2DM had even greater declines in testosterone and the presence of DM and MetS both independently predicted low levels of testosterone. These findings suggest an independent association between MetS and hypogonadism. [40]

While the association between MetS and testosterone is strong, several factors must be considered when examining the relationship. Firstly, it is important to consider the absolute value of testosterone that is being reported. In spite of the fact that testosterone is regularly lower in patients with MetS, do the observed levels classify the patient as hypogonadal? Are the patients identified symptomatic? Should they be treated? For example, in the study by Maggio *et al.*, [47] control patients had a mean testosterone of 433±129 ng/dL while those with MetS had a level of 399±139 ng/dL. [47] Thus, while it is true that the testosterone was significantly lower in patients with MetS - is this finding clinically relevant?

Other factors that bring doubt to the MetS and testosterone relationship is that while a natural, age-related decline in testosterone occurs in men as they age, the ability to control for these changes is very challenging. Moreover, treatment decisions are not only based on abnormal levels of testosterone (normal range=300–1000 ng/dL), but also on hypogonadal symptomology. Lastly, the different biochemical tests used to measure testosterone can vary from laboratory to laboratory. This variability is compounded by the fact that as testosterone levels decrease, so does the accuracy of the test. [55] Therefore, while there is strong evidence of an association between men with MetS and low serum levels of testosterone, the relationship has not yet fully been developed.

THE INFLUENCE OF OBESITY ON SERUM TESTOSTERONE

An inverse relationship between testosterone and body fat exists in men. [48] Elevated levels of abdominal obesity and visceral fat have been associated in numerous studies with low levels of testosterone. [48,56] One reason for this phenomenon is that the aromatase within the fat converts testosterone to estrogen. Thus, the presence of increased visceral obesity contributes to a greater conversion to estrogen. Furthermore, aromatase levels are increased in visceral, compared to subcutaneous fat suggesting that the type and quantity of fat may also contribute to this finding. [57,58] The fact that testosterone inhibits adipocyte development and promotes lipolysis creates a feedback loop in hypogonadal men that propagates a worsening of this condition. [48,59]

Studies in obese men have identified decreased levels of SHBG as a result of hyper-insulinemia. [28] Given that SHBG functions to bind testosterone, this situation would lead to a net increased amount of testosterone available for conversion to estrogen in fatty tissue. [28] Increased estrogens can then feedback and inhibit the hypothalamic-gonadotropin-pituitary axis, resulting in decreased secretion of gonadotropins and lower testosterone levels. [28] Furthermore, testosterone release may also be inhibited in obese men by the elevated circulating levels of leptin. [60] Leptin functions to interfere with androgen production (via the LH-hCG pathway) thus acting to decrease testosterone levels. [60] The fact that Leydig cells have insulin receptors and are sensitive to the hyper-insulinemia seen in metabolic syndrome, could lead to another direct point of interaction between testosterone production and secretion. [61]

THE USE OF TESTOSTERONE SUPPLEMENTATION THERAPY (TST) IN METABOLIC SYNDROME

Given the known relationship between obesity and low levels of testosterone, preventative measures are the first line of defense for those individuals at risk of developing MetS. [33] Lifestyle modifications, coupled with weight loss and increased physical activity is extremely beneficial and should be recommended to all patients presenting with hypogonadism, regardless of the presence of MetS or T2DM. [33] Unfortunately, no specific pharmacological treatments have been identified for patients with MetS. However, many recent studies have begun to identify the benefits of TST in treating men with hypogonadism, MetS and/or T2DM.

Intervention with TST in hypogonadal men with MetS has shown both improvements in the individual risk factors comprising MetS as well as complete resolution of the condition. [23,62] In a study by Haider *et al.*,[23] a cohort of 117 hypogonadal men aged 34–69 years were treated with testosterone undecanoate (TU). Improvement in body weight, BMI, waist circumference and lipid profiles were observed. [23] These gains resulted in lowering the number of men with MetS from 63% (prior to treatment) to 36% (following one year of TU treatment alone). [23] Similarly, in another single blinded, 52-week randomized clinical trial, the effects of diet and exercise along with transdermal testosterone were assessed. Only hypogonadal men diagnosed as having a testosterone <12 nmol/L with MetS or newly diagnosed T2DM were included. [62] Addition of TST to a regiment of diet and exercise, significantly improved glycosylated hemoglobin, fasting plasma glucose, cholesterol and lipid blood values as well as waist circumference. [62] The plan of diet, exercise and TST was so effective that it actually reversed MetS after 52 weeks of treatment. [62]

Several other randomized clinical studies have been conducted to determine the effects of TST on MetS. [63–66] A recent meta-analysis found a significant reduction of fasting plasma glucose, triglycerides and waist circumference regardless of the formulation and dose of TST used. [40] One randomized, double blind trial was conducted by Aversa *et al.* [65] and found that intramuscular TU for 12 months improved MetS parameters, waist circumference and fat mass. La Vignera *et al.* [66] also performed a 12-month, longitudinal study on 60 men finding that the group who receive transdermal testosterone improved their MetS to greater degrees than controls. Another study examined the effects of TST on obese patients with MetS with respect to the effects on bone mineral density. [63] Sixty men with low testosterone (<320 ng/ml) and MetS were randomized to get intramuscular TU four times per year for 36 months. The effects on BMD on age-matched men with MetS found that TU evoked significant improvements in bone mass after 36 months. [63] TU, given at 1000 mg for 12 weeks to 50 patients with MetS, improved carotid intima media thickness and C-reactive protein values, suggesting a reduction in cardiovascular risk factors following TST. [64] Moreover, Bhattacharya *et al.* [67] analyzed results from a 12-month multi-center, prospective, observational registry of 849 hypogonadal men who were given Testim (1% testosterone gel). Those patients with MetS at baseline had significantly lower SHBG and testosterone levels than those without MetS. [67] Patients in the lowest quartile of total testosterone levels (<206 ng/dL) had a significantly increased risk of being classified as having MetS. After 12 months of treatment, MetS patients demonstrated significant decreases in waist circumference, fasting blood glucose levels and blood pressure. [67]

In one of the first studies to investigate the effects of testosterone treatment on T2DM (the late stage end-point of MetS), Boyanov *et al.* [68] studied 48 men of mean age 57.5 years. These men were recently given a diagnosis of T2DM and had hypogonadal levels of testosterone (<15.1 nmol/L); they were treated with TST for three months. Those who received oral TU exhibited reductions in weight, waist-to-hip ratio and percentage body fat with concurrent decreases in glycosylated haemoglobin (by 1.8%) and fasting blood sugars. [68] In another series, Kapoor *et al.* [69] enrolled 24 patients with T2DM and a total testosterone of <12 nmol/L. A double blind, placebo controlled study was conducted with TST given intramuscular every 2 weeks vs. placebo. In those patients receiving insulin, treatment resulted in a reduction of 7 units/day on average and improvements in fasting

blood glucose levels. [69] Recently, several studies have found that TST significantly improved multiple factors in men with DM and/or MetS including: hemoglobin A1c levels, total cholesterol, liver function tests, C-reactive protein, body mass index and waist circumference. [70–72] Therefore, while currently the clinical research suggests men with MetS benefit from TST; however, the optimal dose and frequency remains controversial.

SERUM TESTOSTERONE AND ERECTILE DYSFUNCITON IN PATIENTS WITH METABOLIC SYNDROME

One of the main complaints from men with MetS is erectile dysfunction (ED). While this is due to the fact that MetS is a disease with microvascular implications, the presence of decreased testosterone/hypogonadism in these patients may also contribute to their ED. Indeed, low libido and ED are two of the most common symptoms of hypogonadism, and testosterone levels are significantly associated with sexual function. In cross-sectional studies of aging urologic patients [18,73] and men with ED, [73–75] low testosterone levels were associated with both decrements in sexual desire as well as and increased incidence of ED. Interestingly, in one study, the association between testosterone levels and sexual desire was only significant in men aged 17–42. [76] While no doubt other factors influence desire, other randomized controlled trials have also noted improvements in sexual desire in most men on TST, suggesting further benefit to its use in men on TST. [77,78]

The prevalence of ED in men with MetS is known to increase in conjunction with the number of MetS components (described above). Indeed, men with three MetS components had a 20% incidence of ED while those with 5 MetS components noted a 35% incidence of ED. [79] In another study of 2,371 men with a mean age of 46.1 years, MetS was found to be independently associated with ED as captured by the International Index of Erectile Function. [80] In those men older than 50 years, MetS was associated with a higher proportion of men with moderate to severe ED. [80] Given that TST restores erectile function in young men with organic ED, with the magnitude of the effect of TST being inversely related to baseline serum testosterone level, [81] it is highly likely that the use of TST in hypogonadal MetS patients will result in restoration of at least some form of erectile function.

Several theories have been put forward to explain the relationship between low testosterone and ED (reviewed in [82,83]). Regulation of nitric oxide synthase and phosphodiesterase activity and expression as well as influence over penile smooth muscle metabolism and connective tissue synthesis and deposition have all been suggested as possible mechanisms. [82,83] Further work needs to be conducted in order to more clearly identify the affects of hypogonadism on ED in men with MetS.

CONCLUSION

In summary, the rising prevalence of MetS and T2DM within our population is creating a health epidemic. The results of clinical research studies suggest that men with MetS benefit from TST. While the methods, doses and frequency of administration are still unknown; the observed improvements in fasting blood glucose, glycosylated haemoglobin, cholesterol levels and triglyceride blood values are not disputed. Recent studies have highlighted cardiovascular adverse events in elderly men with multiple co-morbidities on TST. [84,85]

Moreover, work by Yeap and colleagues [86] illustrates a U-shaped association between serum testosterone levels and cardiovascular mortality in which ‘moderate’ levels of testosterone appear to be protective. As such, while further work continues to be conducted, at the present time, TST constitutes a valid therapeutic option for men with hypogonadism and MetS.

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Abbreviations

MetS	Metabolic Syndrome
DM	Diabetes Mellitus
T2DM	Type 2 DM
TST	testosterone supplementation therapy
SHBG	sex hormone binding globin

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