Review Article

Testosterone and metabolic syndrome: The link

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ABSTRACT

Metabolic syndrome (MetS) or "Syndrome X" which is a constellation of insulin resistance, hyperglycemia, hypertension, low high-density lipoprotein cholesterol (HDL-C), and increased very-low-density lipoprotein (VLDL) and triglyceride (TG) levels. It is one of the main threats for public health in the 21st century with its associated risk of cardiovascular disease. This condition affects a major chunk of mankind. International Diabetes Federation (IDF) estimated that around 20-25% of the adult population of the world has MetS. Several definitions have been put forward by different expert bodies leading to confusion. To overcome this, joint new statement of many expert group have been issued. Serum testosterone (T) has been shown to be associated with MetS. Several studies have shown a higher prevalence of MetS in subjects with low testosterone. There are also several studies showing a significant difference in serum T between those with MetS and those without. Serum T has also been shown to be associated with components of MetS and testosterone replacement therapy (TRT) improves various metabolic and anthropometric parameters in MetS. Patients with androgen deprivation for treatment of various cancers have also been reported to have higher prevalence of MetS. But the evidence of association is not sufficient evidence for the causation of MetS by low testosterone and long-term studies are needed to confirm whether T deficiency is the cause or is a feature of MetS.

Key words: Androgen deprivation, insulin resistance, metabolic syndrome, testosterone, testosterone replacement therapy

Introduction

The metabolic syndrome (MetS) was first described by Kylin, a Swedish physician, in 1923 as a clinical association between hypertension and gout. It was modified in 1947, to include upper body adiposity. In 1988 Reaven emphasized the importance of MetS.[1] He described it as "Syndrome X" which is a constellation of insulin resistance, hyperglycemia, hypertension, low high-density lipoprotein cholesterol (HDL-C), and increased very-low-density lipoprotein (VLDL) and triglyceride (TG) levels.[2]

It is considered the main threat for public health in the 21st century with its associated risk of cardiovascular disease.[3]

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Several definitions for MetS have been put forward by different expert bodies such as World Health Organization (WHO),[4] European Group for Study of Insulin Resistance (EGIR),[5] National Cholesterol Education program (NCEP),[6] American Association of Clinical Endocrinologist (AACE),[7] National Heart, Lung, and Blood Institute/American Heart Association,[8] and International Diabetes Federation (IDF).[9] In 2005 IDF has drafted a singly unifying definition. The main emphasis is on central obesity defined by waist circumference: waist circumference (WC) in Europids ≥94 cm and in Asians >90 cm. And there should be two or more of the following four factors: elevated TG ≥1.7 mmol/l (≥150 mg/dl), reduced HDL-C <1.03 mmol/l (<40 mg/dl), elevated blood pressure (BP) systolic ≥130 mmHg, diastolic ≥85 mmHg (or treatment), and dysglycemia (raised fasting plasma glucose, FBG ≥5.6 mmol/l (≥100 mg/dl) (or type 2 diabetes mellitus, DM).[10] A new joint statement from a number of professional organizations such as IDF, the National Heart, Lung, and Blood Institute (NHLBI), WHO, the International Atherosclerosis Society, and the American Heart Association (AHA) has identified

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specific criteria for the clinical diagnosis of the metabolic syndrome. Patients with three of the five criteria (elevated WC, elevated TGs, reduced HDL-C levels, elevated BP and elevated FBG levels) are considered to have MS.[11]

Prevalence of MetS: It is estimated that around 20-25% of the world's adult population have the metabolic syndrome.[12] In the United States the prevalence of MetS is 34.5% based on the NCEP definition and 39.0% based on IDF definition.[13] Even in children and adolescents it has been reported in up to 9%.[14] In North India the prevalence of MetS was reported to range from 31.6% to 49.2% of the urban population using NCEP ATP III/ modified NCEP ATP III guidelines.[15-18] Two studies from urban North India reported the prevalence of MetS ranging from 35.8% to 38.5% by NCEP ATP III criteria, 45.3% by modified NCEP ATP III criteria and 39.5% to 47.4% by IDF criteria.[19,20] In South India the prevalence has been reported in the range of 18.3-41% using NCEP ATP III guidelines.[21,22] In an urban population of South India the prevalence of MetS ranges from 18.3% by NCEP ATP III criteria, 23.2% by WHO criteria and 25.8% by IDF criteria.[22] Another two studies showed a prevalence of 29.7-41.3% using IDF guidelines.[23,24] Using WHO criteria a higher prevalence of 46.4% was reported from South India.[25] In Mumbai, West India, the prevalence is reported in the range of 19.5-35.2% using different criteria.[26,27] In a rural population of Central India it is seen in around 9% by modified ATP III criteria.[28] In Sub-Himalayan region of Eastern India, MetS ranges from 4% to 50%.[29]

Testosterone and Metabolic Syndrome Mechanism

There is a strong inverse relationship between T and body fat in men.[30] Abdominal obesity has been associated with low T in both cross-sectional[31] and longitudinal studies,[32] and low T concentration correlates with greater visceral fat accumulation.[33] Central fat depots have high aromatase activity converting T to estradiol (E2).[34] Testosterone normally inhibit adipocyte development but in states of low T there is greater fat mass.[35] Testosterone promotes lipolysis and reduces fatty acid synthesis.[36] An animal model has shown that T deficiency decreases lipolysis.[37] Visceral obesity causes increased inflow of free fatty acids into the liver and perturbs metabolism. Liver fat is correlated with all components of MetS.[38]

Obesity is associated with increased inflammatory cytokine production, as well as increased aromatization of T to estradiol in peripheral fat tissue. Both of these factors then decrease the pituitary production of gonadotropins, which, in turn, decreases testicular production of T.[39,40] The increased level of leptin in obese individuals may interfere with luteinizing hormone/human chorionic gonadotropin stimulation of androgen production, thereby decreasing T levels.[41]

Testosterone deficiency leads to increased fat deposition resulting in insulin resistance. In states of low T muscle biopsy showed impaired mitochondrial oxidative phosphorylation. And as up to 70% of the body's insulin sensitivity is accounted by muscle, low T leads to insulin resistance.[42]

Hyperinsulinemia, as encountered in insulin resistance, might impair T secretion by the Leydig cell may be directly since there are insulin receptors on the Leydig cell.[43] It has also been found in obese men that there is an attenuated pulse amplitude of luteinizing hormone (LH) while the LH pulse frequency is unaffected, thus producing a less strong stimulation of testicular T production.[44]

Testosterone and Metabolic Syndrome

There are a number of epidemiological studies linking T and MetS. Although there are a number of publications showing the association of T and MetS in females,[45-56] in this review we will restrict to the association in males.

The frequency of MetS is increased with declining tertiles of total T (TT).[57] And an inverse relationship for circulating T,[58] bioavailable T, sex-hormone binding globulin (SHBG), and dehydroepiandrosterone sulphate (DHEA-S) is also seen with MetS.[59] The Quebec Family study found higher levels of T reduced the risk of metabolic syndrome and increased insulin sensitivity.[60]

In a Finnish study of 1896 nondiabetic middle-aged men, free T and SHBG were 11% and 18% lower in men with MetS.[40] Men with metabolic syndrome at baseline are at an increased risk of developing hypogonadism based on an 11-year follow-up.[61] In another Finish study of 702 middle-aged men who had neither diabetes nor the metabolic syndrome, after 11 years of follow-up 147 men developed MetS using NCEP ATP III criteria and 57 men developed diabetes. After adjustment for age men with total T, calculated FT, and SHBG levels in the lower fourth had a severalfold increased risk of developing the metabolic syndrome and diabetes.[62]

In a population-based sample of 462 older Italian men with mean age of 75 years, participants with MetS had lower levels of TT and SHBG. After adjusting for multiple confounders, including age, smoking, alcohol intake, and

physical activity, TT was found to be negatively associated with MetS.[63]

The Massachusetts Male Aging Study has demonstrated that low T levels in a nonobese population were found to predict the later onset of the metabolic syndrome particularly among men with a BMI < 25 kg/m^2.[64]

In the Baltimore Longitudinal Study of Aging of 618 healthy Caucasian adult men with a mean age of 63 years alone did not predict the development of MetS. Total T and SHBG were inversely related to the development of MetS over a mean follow-up period of 5.8 years.[65]

A cross-sectional study from Australia involving 2502 community dwelling men aged 50-70 years without known diabetes reported that men with hypogonadotrophic hypogonadism have a high prevalence of metabolic syndrome. The risk of metabolic syndrome increased for total T<20 nmol/l, SHBG<50 nmol/l, and free T<300 pmol/l.[66]

In Study of Health in Pomerania (SHIP), which is a population-based prospective cohort of adults aged 20-79 years without baseline MetS, after a median follow-up time of 5.0 years 47.8% developed MetS. With increasing number of MetS components T levels decreased. Testosterone in the lowest quartile predicted MetS particularly among men aged 20-39 years.[67]

Data from the Third National Health and Nutrition Examination Survey showed that after adjustment for age, race/ethnicity, smoking status, alcohol intake, physical activity level, LDL -C, CRP, and insulin resistance, men with lower total testosterone were more likely to have metabolic syndrome than men with higher T (P<0.001 for linear trend). Similarly, men with lower SHBG were more likely to have metabolic syndrome than men with higher SHBG (P=0.02 for linear trend).[68]

In a study of 63 males with MetS total and calculated FT and SHBG were significantly lower in cases with MetS than controls. Hypogonadism was seen in 30% cases with MetS compared to 3.1% in controls[69] [Table 1].

In a meta-analysis of 20 studies, patients with MetS showed significantly lower T compared to healthy individuals. Separate analysis of subjects with and without erectile dysfunction yielded similar results. Comparison of data using NCEP ATP III criteria and other MetS classifications

Table 1: The various studies which reported the difference in the serum testosterone level in normal subjects and those with MetS

Source (reference)	Place	Number of subjects	Mean age (in years)	Criteria used to diagnose MetS	Prevalence of MetS (in %)	Testosterone in normal subject (ng/dl)	Testosterone in MetS subjects (ng/dl)	*P* value
Laaksonen *et al*.[43]	Finland	1896	52.5 ± 5.7 in normal	WHO	18.2	622.7 ± 213.3	507.4 ± 196	<0.001
Laaksonen *et al*.[62]	Finland	854	51.2	ATP	20.9 After 11 years follow-up	588.1 ± 198.9	527.6 ± 184.5	<0.001
Yong *et al*.[57]	China	307	39.1 ± 8.1 years with FH of DM 43.8 ± 8.5 years without FH of DM	WHO	32.6% overall 39.1% 23.4%	527.6	461.3	<0.001
Maggio *et al*.[63]	Italy	452	75	ATP III	15.8%	433 ± 129	399 ± 139	0.03
Rodriguez *et al*.[65]	USA	618	63.3	ATP III	4:20–39 21:40-59 21:60-79, 18:80-94 years	368.7 ± 6.2	430.5 ± 3.5	<0.01
Laughlin *et al*.[70]	California, USA	794	73.8 (median)	ATP III	18	244	311	<0.001
Chubb *et al*.[67]	Australia	2502	76	ATP III	24.1	481.5 ± 164.6	403.6 ± 141.3	<0.001
Haring *et al*.[66]	Germany	1004	48.7	ATP III	47.8 After median follow-up for 5 years	510.3	446.9	<0.05
Katabami *et al*.[71]	Japan	274	46	ATP III	25.5	337.3 ±115.3	423.8 ± 132.6	<0.0001

ATP: Adult treatment panel National Cholesterol Education Program, WHO: World Health Organization, FH: family history, DM: diabetes mellitus

reveals the same. Lower baseline T was demonstrated among patients with incident MetS compared to controls in longitudinal studies.[72]

In another meta-analysis of 52 observational studies comprising 22,043 men and 7839 women, endogenous TT and FT levels were lower in men with MetS and higher in women with MetS. Similarly, men with higher TT levels had a lower MetS risk whereas higher TT levels increased the risk of MetS in women. In both sexes, higher SHBG levels were associated with a reduced risk.[73]

Although various studies have shown that lower T levels may be associated with MetS and type 2 DM, both conditions associated with cardiovascular disease, reverse causation has to be considered, as systemic illness may result in reduced T levels. Thus, the strength of these associations and the likely direction of causation need to be carefully considered.[74]

Testosterone and Components of MetS

In the Telecom Study, there appeared to be an association of T and cardiovascular risk factors in healthy, nondiseased adult men. Serum TG, TC, LDL-C, apolipoprotein B, fasting, and 2-hour plasma insulin were higher and serum HDL-C was lower in men with lower serum T levels.[75]

Total and FT and SHBG were inversely associated with concentrations of insulin, glucose, TG, C-reactive protein (CRP), and CRP-adjusted ferritin and positively associated with HDL-C. Low TT and FT levels were associated with high levels of insulin, glucose, and TG and low levels of HDL-C.[40]

In the Tromso Study, T levels were inversely associated with anthropometrical measurements with the lowest levels of total and free T found in men with the most pronounced central obesity. Total T was inversely associated with systolic blood pressure, and also men with hypertension had lower levels of both total and free T. Furthermore, men with DM had lower T levels compared to men without a history of DM, and an inverse association between T levels and HbA1c was found.[76]

A strong association of MetS with sex hormones was observed for TG higher than 150 mg/dl and WC more than 102 cm and a modest with hypertension. Total T and FT were associated with dysglycemia, but SHBG was not. Increased odds of low HDL-C <40 mg/dl were observed with lower TT levels and SHBG but not with FT. Further adjusting for BMI, observed associations of sex hormones and MetS were attenuated but remained statistically significant with the exception of the associations observed with hypertension.[64] Total T was positively associated with HDL-C but not with other components of MetS. Log SHBG is positively associated with HDL-C, negatively associated with TG and WC, but not associated either way with BP or BG levels.[63] Total T was significantly associated with abdominal obesity and high concentrations of TG. SHBG was also significantly associated with abdominal obesity and a high concentration of TG. Free T was not significantly associated with any MetS components. Bioavailable T was significantly associated with abdominal obesity and marginally associated with high blood pressure. TT was also shown to be associated with all except hypertension, and free T was associated only with WC and TG.[67]

In a study of middle-aged Japanese men, T was significantly related to the MetS parameters of obesity (WC and BMI), hypertension, dyslipidemia, insulin resistance, and adiponectin.[77]

Androgen Suppression and Metabolic Syndrome

There are studies from special groups of patients where hypogonadism is a feature due to pharmacotherapy, which strengthens opinion that T deficiency is a risk factor for the development of MetS and type 2 DM, and is an independent cardiovascular risk factor.

A small study showed that initiation of GnRH agonist or antiandrogen therapy in 22 men with prostate cancer led to increases in serum insulin, arterial stiffness, and fat mass over the subsequent 3-month period.[78]

Braga-Basaria *et al.* evaluated 58 men, including 20 with prostate carcinoma undergoing androgen deprivation therapy for at least 12 months. The prevalence of MetS was higher in the androgen deprivation group compared with the nonandrogen deprivation group and control groups. Men in the androgen deprivation group had a higher prevalence of abdominal obesity and hyperglycemia. Androgen-deprived men also had elevated TG compared with controls but the prevalence of hypertension and low HDL levels were similar.[79]

A longitudinal study followed a large population of 73,196 men with loco-regional prostate cancer followed for a median of 4.55 years. Those treated with androgen suppression therapy were more likely to develop diabetes, ischemic heart disease, myocardial infarction, and sudden death from cardiovascular disease compared with those patients untreated or treated with other modalities.[80]

Similarly, a study of 396 men with prostate cancer undergoing

androgen-deprivation therapy showed worsening glycemic control with an increase in HbA1c and an increased incidence of new onset of diabetes.[81]

Another study has shown increased risk of MetS with chemotherapy compared with radiotherapy for testicular cancer. Metabolic syndrome was positively associated with cumulative cisplatin, bleomycin, and etoposide doses but not with cumulative vinblastine dose. Logistic regression using a backward stepwise model with all four chemotherapy agents and age included, revealed cumulative cisplatin dose as significant variables.[82]

Effect of testosterone replacement on components of metabolic syndrome

One of the earliest studies reporting the effect of TRT on obesity was by Rebuffescrive *et al.* in 1991 in a small group of 11 men where it was found that waist-hip ratio decreased in 9 out of 11 men after 6 weeks of testosterone replacement.[83] Recently, there have been a number of studies published investigating the effect of TRT in men primarily with type 2 DM and MetS.

Marin and colleagues were the first to report a significant reduction in diastolic blood pressure after TRT in obese middle-aged men, along with a reduction in visceral fat, FBG, TG, and total cholesterol. In a study of 122 men receiving treatment with parenteral T undecanoate over 15 months, both systolic and diastolic blood pressure decreased. A single-blind randomized study of T administration to men with MetS and recent onset of DM established also beneficial effects of testosterone on blood pressure over and above the effects of diet and exercise.[84] In men with osteoporosis intramuscular T for 6 months showed significant reduction in diastolic blood pressure along with total cholesterol, TGs, and HDL-C.[85]

Boyanov *et al.* reported a study of 48 type 2 diabetic men with symptoms of androgen deficiency in an open-label, randomized treatment undertaken over 3 months. Testosterone treatment resulted in significant reductions in weight, WHR, and percentage body fat compared with no treatment. Fasting blood glucose and postprandial blood glucose levels were also reduced significantly, and HbA1c fell by 1.8% ($P<0.05$). No significant effects on lipid parameters were observed. This study provides the first evidence that testosterone treatment may offer clinical benefit to men with type 2 diabetes.[86]

In the first double-blind placebo-controlled study by Kapoor *et al.* with 24 patients of type 2 DM and clinical diagnosis of hypogonadism, T treatment resulted in a significant improvement in the HOMA-IR index in those patients not on insulin therapy and resulted in insulin dose reduction by an average of 7 units per day in those patients recieving insulin. Statistically significant reductions in both FBG (−28.4mg/dl) and fasting insulin were observed, with HbA1c falling by 0.4% ($P=0.03$). Testosterone treatment also resulted in statistically significant improvement in WC, WHR, and total cholesterol although there was no significant effect on HDL-C, LDL-C, TGs, or blood pressure.[87]

Heufelder *et al.* investigated the effects of TRT in 32 hypogonadal men with newly diagnosed, treatment-naive type 2 DM with MetS in a 52-week single-blind, randomized but not placebo-controlled study, with either diet and exercise advice alone, or diet and exercise advice in conjunction with 50 mg T gel once daily. Compared with diet and exercise alone, T treatment resulted in a statistically significant improvement in HbA1c of −0.8% ($P<0.001$), with all patients attaining an HbA1c of <7.0% and 87.5% of patients attaining an HbA1c <6.5%. There was also a statistically significant reduction in the HOMA-IR index, although the observed treatment-mediated reduction in FPG (−5.4 mg/dl) narrowly failed to achieve statistical significance ($P=0.06$). Significant improvement in WC was also observed. Testosterone treatment was associated with a statistically significant reduction in serum TG and a statistically significant increase in serum HDL-C.[88]

In another study, waist circumferences declined significantly over the first 9 months of T replacement. There were declines in plasma total cholesterol, LDL-C, and TG, whereas plasma HDL-C showed an increase. [89]

A large multicenter, randomized, double-blind, placebo-controlled study undertaken in eight European countries, the TIMES2 (Testosterone replacement In men with Metabolic Syndrome or type 2 diabetes), recruited 220 hypogonadal men diagnosed with either type 2 DM and/or MetS (defined according to the IDF criteria) with no TRT within the previous 6 months. Insulin resistance (HOMA-IR) improved after 6 and 12 months of therapy. Testosterone therapy was also associated with reductions in the percentage of body fat, TC, and LDL-C and lipoprotein (a) after 6 months but there was no significant effect on HDL-C or TG. HbA1c was 0.58% lower compared with placebo after 9 months treatment but not earlier.[90]

Summary

There is a strong evidence of a high prevalence of MetS in patients with a low T level. Many components of MetS are adversely affected in the presence of hypogonadism. There are reports of high prevalence of T deficiency in patients with type 2 DM.

Early interventional studies have shown that TRT in hypogonadal men with MetS has beneficial effects on central adiposity, insulin resistance, and glycemic control. There are consistent data regarding beneficial effect on blood pressure, TG, or HDL-C. Furthermore testosterone replacement in several studies has been shown to have a small but significant effect in reducing cholesterol and LDL-C, also important cardiovascular risk factors. Whether low T is just a biomarker of the degree of illness or a contributory factor to the progression of atherosclerosis is unclear. Accumulating evidence now suggests that T deficiency is a risk factor for cardiovascular disease and intervention may ameliorate the process. Active systemic inflammatory disorders including chronic infections may accelerate atherosclerotic progression and destabilize plaques. There is a need for long-term interventional study to examine the effect of T on cardiovascular disease in men with MetS and/or type 2 DM.

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