Testosterone and the metabolic syndrome

Vakkat Muraleedharan and T. Hugh Jones

Abstract: Metabolic syndrome and testosterone deficiency in men are closely linked. Epidemiological studies have shown that low testosterone levels are associated with obesity, insulin resistance and an adverse lipid profile in men. Conversely in men with metabolic syndrome and type 2 diabetes have a high prevalence of hypogonadism. Metabolic syndrome and low testosterone status are both independently associated with increased all-cause and cardiovascular mortality. Observational and experimental data suggest that physiological replacement of testosterone produces improvement in insulin resistance, obesity, dyslipidaemia and sexual dysfunction along with improved quality of life. However, there are no long-term interventional studies to assess the effect of testosterone replacement on mortality in men with low testosterone levels. This article reviews the observational and interventional clinical data in relation to testosterone and metabolic syndrome.

Keywords: diabetes, insulin resistance, metabolic syndrome, obesity, testosterone deficiency

Introduction

Obesity has reached epidemic proportions globally, with more than 1 billion adults overweight – at least 300 million of them clinically obese [WHO, 2010]. It leads to adverse metabolic effects on blood pressure, lipid and glucose metabolism mediated by insulin resistance. This constellation of cardiovascular risk factors, constitute the metabolic syndrome. The metabolic syndrome is associated with significant increase in cardiovascular morbidity and mortality being the most common cause of death in the Western world. Men are at increased risk of developing coronary artery disease earlier in life compared with women. The reason for this bias toward males is still poorly understood.

The metabolic syndrome was first described in 1923 by Kylin, a Swedish physician, as a clinical association between hypertension and gout [Kylin, 1923]. In 1947, it was modified to include upper body adiposity [Vague, 1947], however it was Reaven in 1988 who emphasized the importance of metabolic syndrome [Reaven, 1988]. He described ‘Syndrome X’ as a constellation of insulin resistance, hyperglycaemia, hypertension, low high-density lipoprotein (HDL) cholesterol (HDL-C) and increased very-low-density lipoprotein (VLDL) and triglyceride (TG) levels. Since then it has evolved as a major risk factor for coronary artery disease.

The metabolic syndrome is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function [Olufadi and Byrne, 2008]. It is a risk factor for coronary heart disease (CHD), as well as diabetes, fatty liver, and several cancers. The clinical manifestations of this syndrome as described above may include hypertension, hyperglycaemia, hypertriglyceridaemia, reduced HDL-C and abdominal obesity.

A new joint statement from a number of professional organizations has identified specific criteria for the clinical diagnosis of the metabolic syndrome. Patients with three of the five criteria (elevated waist circumference, elevated TGs, reduced HDL-C levels, elevated blood pressure and elevated fasting glucose levels) are considered to have the syndrome. The joint statement includes the participation of the International Diabetes Federation (IDF), the National Heart, Lung, and Blood Institute (NHLBI), the World Heart Federation, the International Atherosclerosis Society and the American Heart Association (AHA) [Alberti *et al.* 2009].

Adipose tissue is metabolically active and produces cytokines, the adipocytokines, that link the various components of metabolic syndrome and their cardiovascular effects. Central

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obesity, as measured by waist circumference or waist–hip ratio, strongly correlates independently with insulin resistance and cardiovascular disease. Visceral adipocytes are metabolically more active than subcutaneous adipocytes. Visceral fat is a major source of free fatty acids and adipocytokines to the liver which stimulates gluconeogenesis and inhibits hepatic insulin binding.

Although clinically easy to measure, waist measurements do not fully correlate with visceral obesity as it also measures the subcutaneous fat around the abdomen and back. Radiological methods such as CT, MRI and dual-energy X-ray absorptiometry (DEXA) scanning are better techniques which allow a greater distinction between the two fat deposits but are not yet widely used in clinical practice.

Role of testosterone in the metabolic syndrome

There is convincing evidence that low testosterone is an independent risk factor for development of metabolic syndrome and type 2 diabetes in men. Furthermore evidence is also accumulating that testosterone deficiency is a cardiovascular risk factor [Jones, 2010]. There are many recent reviews highlighting the important link between hypogonadism, metabolic syndrome, diabetes and cardiovascular disease [Grossmann *et al.* 2010; Jones, 2010; Corona *et al.* 2009; Diaz-Arjonilla *et al.* 2009; Jones and Saad, 2009; Stanworth and Jones, 2009; Traish *et al.* 2009; Zitzmann, 2009; Shabsigh *et al.* 2008; Yassin *et al.* 2008; Makhsida *et al.* 2005].

There is a strong inverse correlation between body fat and testosterone levels in men [Kapoor *et al.* 2005]. In men, abdominal obesity has usually been associated with low testosterone levels in cross-sectional [Pasquali *et al.* 1991; Zumoff *et al.* 1990] and longitudinal studies [Gapstur *et al.* 2002; Khaw and Barrett-Connor, 1992]. Waist circumference or waist–hip ratio are also inversely associated with sex hormone-binding globulin (SHBG) levels [Gapstur *et al.* 2002; Khaw and Barrett-Connor, 1992]. Studies which have measured abdominal fat deposits using imaging techniques such as CT or MRI have confirmed that low testosterone concentrations correlate with greater visceral fat accumulation [Tsai *et al.* 2004; Garaulet *et al.* 2000; Haffner *et al.* 1993; Seidell *et al.* 1990]. Central fat deposits have a high aromatase activity thus

converting more testosterone to oestrogen locally [Vermeulen *et al.* 2002]. This partially explains the higher level of oestrogens found in obese healthy men. Testosterone also promotes myocyte and inhibits adipocyte development from pluripotent stem cells, thus increasing muscle mass, whereas a state of testosterone deficiency enhances greater fat mass [Singh *et al.* 2003]. In addition testosterone increases the number of beta-adrenergic receptors which, in turn, promotes lipolysis and reduces fatty acid synthesis [De Pergola, 2000]. Evidence from androgen receptor (AR) knockout mouse models demonstrates that deficiency of androgen action decreases lipolysis and is mainly responsible for the induction of obesity [Yanase *et al.* 2008].

The hypogonadal–obesity cycle hypothesis was originally put forward by Cohen in 1999 [Cohen, 1999]. Testosterone inhibits adipocytes lipoprotein lipase activity, the enzyme which breaks down circulating TG to absorbable free fatty acids which are taken up into the fat cells and converted back to TG for storage. The hypothesis suggests that low testosterone as a result of high aromatase activity leads to a cycle which promotes increasing adipocyte number and fat deposition which gradually leads to a lower testosterone levels. The hypogonadal–obesity–adipocytokine hypothesis explains why the body cannot respond to low testosterone levels by a compensatory production of the hormone. Oestradiol and the adipocytokines tumour necrosis factor α (TNF α), interleukin-6 (IL6) and leptin (human obesity is associated with leptin resistance) are all known to inhibit the hypothalamic–pituitary–testicular axis and hence causing a state of hypogonadotrophic hypogonadism (Figure 1) [Jones, 2007]. Also the excess aromatase activity exhibited by obese men results in the suppression of gonadotrophin-mediated testosterone secretion. This is because the bulk of negative feedback exerted by circulating testosterone on the hypothalamo–pituitary axis is actually mediated via its aromatization (either in peripheral adipose tissue or centrally) to oestradiol [Hayes *et al.* 2001, 2000]. This supports the known association of type 2 diabetes and metabolic syndrome with low gonadotrophins [Dhindsa *et al.* 2004] and various reports of enhanced luteinizing hormone (LH), follicle-stimulating hormone (FSH) and testosterone secretion in (generally obese) men with aromatase inhibitors and selective oestrogen receptor modulators [Hill *et al.* 2009].

Figure 1. The Hypogonadal–obesity–adipocytokine hypothesis. (1) High aromatase activity in adipocytes converts testosterone to oestradiol. Reduced tissue testosterone facilitates triglyceride storage in adipocytes allowing (2) increased lipoprotein lipase activity and stimulating pluripotent stem cells into mature adipocytes. (3) Increased adipocyte mass is associated with greater insulin resistance. (4) Oestradiol and adipocytokines TNF α , IL6 and leptin inhibits the hypothalamic–pituitary–gonadal axis (HPG axis shown in blue shade) response to decreasing androgen levels (blue arrows). Orange shade represents the hypogonadal–obesity cycle. Green arrow, low testosterone promotes the formation of adipocytes from pluripotent stem cells. +ve, positive effect; –ve, negative effect [Jones, 2010]. Some figures were produced using Servier Medical Art- www.servier.com

Testosterone, insulin resistance and diabetes

Insulin resistance and hyperglycaemia are the key characteristics of type 2 diabetes which are often associated with obesity. There is now evidence that low testosterone is closely linked to diabetes and testosterone replacement therapy (TRT)

can improve insulin sensitivity and glycaemic control.

In a study of 1292 healthy nondiabetic men there was an inverse correlation between total testosterone and insulin levels independent of age and

obesity [Simon *et al.* 1992]. In the San Antonio Heart Study the researchers found an inverse relation between total and free testosterone with insulin levels [Haffner *et al.* 1994]. A meta-analysis of 21 clinical reports which included data from 3825 men confirms that there is a high prevalence of low testosterone levels in men with diabetes and/or metabolic syndrome [Ding *et al.* 2006]. Conversely men with higher testosterone levels had a 42% lower risk of type 2 diabetes. There are also studies which suggest that low testosterone may in fact be a precursor of development of diabetes or insulin resistance [Kupelian *et al.* 2006; Laaksonen *et al.* 2004; Oh *et al.* 2002; Stellato *et al.* 2000; Haffner *et al.* 1996]. The third National Health and Nutrition Survey (NHANESIII) found that men in the lowest tertile of free or bioavailable (free + albumen bound – the biologically active fraction) testosterone are more likely to have diabetes when compared with the upper tertile after adjustment for age and obesity [Selvin *et al.* 2007].

Kapoor and colleagues demonstrated in a recent cross-sectional study of 355 men with type 2 diabetes, that overt hypogonadism (defined as the presence of clinical symptoms of hypogonadism and total testosterone <8 nmol/l and/or bioavailable testosterone <2.5 nmol/l) was present in 17% of individuals. Borderline hypogonadism was found in a further 25% of individuals [Kapoor *et al.* 2007a]. Another study investigated the prevalence of hypogonadism in type 2 diabetes by measuring free testosterone by equilibrium dialysis in a cohort of 103 type 2 diabetes patients [Dhindsa *et al.* 2004]. They found that 33% of these men had free testosterone below the normal range consistent with biochemical hypogonadism.

Several longitudinal studies have shown that low testosterone is an independent risk factor for the development of diabetes and metabolic syndrome. Baseline testosterone levels correlate inversely with the accumulation of central fat but not other fat deposits in a cohort of 110 men [Tsai *et al.* 2000]. Three other studies, the Massachusetts Male Aging Study (MMAS) [Stellato *et al.* 2000], the Multiple Risk Factor Intervention Trial (MRFIT) [Haffner *et al.* 1996] and Rancho Bernado [Oh *et al.* 2002], showed an inverse correlation between baseline testosterone and the future development of diabetes. A Finnish study showed that low

baseline testosterone and SHBG predicted metabolic syndrome and diabetes after a 11-year follow up [Laaksonen *et al.* 2004].

The mechanisms linking testosterone with insulin resistance and type 2 diabetes are still not fully understood. Although testosterone deficiency leads to increased fat deposition and this would result in increasing insulin resistance, it may not explain the total action on insulin sensitivity. For example, one study which assessed insulin resistance by hyperinsulinaemic/euglycaemic clamps in 60 men with a range of glucose tolerance from normal to diabetic levels [Pitteloud *et al.* 2005]. Their findings confirmed an inverse relation between total testosterone and insulin resistance. From muscle biopsies they showed that low testosterone impairs mitochondrial oxidative phosphorylation. As up to 70% of the body's insulin sensitivity can be accounted for by muscle this tissue may develop reduced insulin sensitivity in the hypogonadal state sufficient to contribute in part to the overall state of insulin resistance.

Testosterone and metabolic syndrome

Low testosterone as explained above is closely linked to the metabolic syndrome. Hypogonadal men exhibit an increased body fat mass. For example, in a study of 57 men aged between 70 and 80 years, testosterone levels were negatively correlated with percentage body fat [Vermeulen *et al.* 1999]. There are a number of epidemiological studies linking testosterone and metabolic syndrome. One of them is a Finnish study of 1896 nondiabetic men where they found free and total testosterone levels were significantly lower in those with metabolic syndrome [Laaksonen *et al.* 2003]. Similarly the Quebec Family study found higher levels of testosterone reduced the risk of metabolic syndrome and increased insulin sensitivity [Blouin *et al.* 2005]. Conversely a study of 803 men showed that hypogonadism is common in those with metabolic syndrome [Corona *et al.* 2006].

The data from the Baltimore Longitudinal Study of Aging looking at 618 community-dwelling healthy adult men with a mean age of 63 years reported that age alone did not predict the development of the metabolic syndrome. Total testosterone and SHBG were inversely related to the development of the metabolic syndrome over a mean follow-up period of 5.8 years and the free

testosterone index and body mass index were positively related to the incidence of the metabolic syndrome [Rodriguez *et al.* 2007]. Another important report analysing 950 men without metabolic syndrome from the Massachusetts Male Aging Study has demonstrated that low testosterone levels in a nonobese population were found to predict the later onset of the metabolic syndrome [Kupelian *et al.* 2006].

Data from the Finnish study noted above also reported that men with metabolic syndrome at baseline are at an increased risk of developing hypogonadism based on an 11-year follow up [Laaksonen *et al.* 2005]. A recent cross-sectional study from Australia involving 2502 community-dwelling men aged ≥ 70 years without known diabetes reported that men with hypogonadotropic hypogonadism have a high prevalence of metabolic syndrome [Chubb *et al.* 2008].

Dyslipidaemia and hypertension

HDL-C and TG levels comprise two central components of the metabolic syndrome whereas total and low-density lipoprotein (LDL) cholesterol (LDL-C) are not. Raised total cholesterol, LDL-C and TG confer risk for future cardiovascular events whilst HDL-C is protective against atherosclerosis and low levels are associated with increased cardiovascular risk. HDL-C presents a complicated picture and the effect seems to be gender specific [Fan and Dwyer, 2007]. Low HDL correlates with CHD more in men than women [Johnsen *et al.* 2005]. In both healthy and diabetic men, testosterone correlates positively with HDL level [Stanworth *et al.* 2007; Van Pottelbergh *et al.* 2003].

In the context of cardiovascular disease and the fact that elevated total cholesterol and LDL-C is common in type 2 diabetes, the management of this hyperlipidaemia in type 2 diabetes is vital for the prevention of cardiovascular events.

Derangements in lipid metabolism play a pivotal role in the formation of atherosclerotic plaque. High total cholesterol and LDL-C are proatherogenic whereas high HDL seems to be protective against atherosclerosis [Maron, 2000; Simons *et al.* 1998]. The same pathogenic process is also implicated in the development of metabolic syndrome and type 2 diabetes although elevated total cholesterol and LDL-C are not part of the definition of the metabolic syndrome.

Declining levels of testosterone with age is associated with a relative increase in oestrogen levels through the increased aromatase activity [Cohen, 2008, 2001]. The increased oestrogen levels are associated with increased circulating cholesterol and more atherogenic lipoprotein particles [Tomaszewski *et al.* 2009; Vaidya *et al.* 2008; Yasui *et al.* 2008].

A number of studies have shown a negative correlation between testosterone levels and total cholesterol and LDL-C [Simon *et al.* 1997; Haffner *et al.* 1993; Barrettconnor, 1992]. A meta-analysis of 19 clinical trials in hypogonadal men reports that significant reductions in total cholesterol and LDL-C is associated with intramuscular TRT [Whitsel *et al.* 2001].

Studies have shown that low testosterone levels are associated with known hypertension [Bocchi *et al.* 2008; Kapoor *et al.* 2007b; Svartberg *et al.* 2004; Khaw and Barrettconnor, 1988; Messerli *et al.* 1987]. Conversely men with anabolic steroid abuse are known to have an increased risk of developing hypertension [Maravelias *et al.* 2005; Mottram and George, 2000; Sullivan *et al.* 1998].

Effect of androgen suppression on obesity and diabetes

There are studies from special groups of patients where hypogonadism is a feature, either due to genetic defects or due to pharmacotherapy, which strengthens opinion that testosterone deficiency is a risk factor for the development of the metabolic syndrome and type 2 diabetes, and is an independent cardiovascular risk factor.

A longitudinal study followed a large population of 73,196 men with loco-regional prostate cancer followed for a median of 4.55 years (mean age of 74.2 years at diagnosis) [Keating *et al.* 2006]. Those treated with androgen suppression therapy were more likely to have a higher hazard ratio of developing diabetes, ischaemic heart disease, myocardial infarction and sudden death from cardiovascular disease compared with those patients untreated or treated with other modalities. Similarly a study of 396 men with prostate cancer undergoing androgen-deprivation therapy showed worsening glycaemic control with an increase in HbA1c and an increased incidence of new onset of diabetes [Derweesh *et al.* 2007]. A smaller study showed that initiation of GnRH agonist or anti-androgen therapy in 22 men with

prostate cancer led to increases in serum insulin, arterial stiffness and fat mass over the subsequent 3-month period [Smith *et al.* 2001].

Men with Klinefelter's syndrome, the most common classical form of hypogonadism, have an increased risk of death from diabetes, cancer, cardiovascular and respiratory diseases [Bojesen *et al.* 2006]. This again supports an association of testosterone deficiency states with these major causes of mortality.

Acute withdrawal of testosterone replacement from men with idiopathic hypogonadotropic hypogonadism caused significant rises in fasting insulin, HOMA-IR (Homeostatic Model Assessment Insulin Resistance), IL6 and TNF α . This occurred after just 2 weeks of suspension of treatment [Yialamas *et al.* 2007].

Testosterone and atherosclerosis

Several studies have demonstrated that low testosterone is associated with the presence of atherosclerosis [Jones and Saad, 2009]. The degree of atherosclerosis in the carotid artery as assessed by intimal media thickness (IMT) and plaque scores is correlated with low testosterone [Svartberg *et al.* 2006; Demirbag *et al.* 2005; Muller *et al.* 2004; Fukui *et al.* 2003]. A 4-year follow-up study demonstrated that low testosterone led to increased deterioration of the IMT [Muller *et al.* 2004]. This provides evidence to support the hypothesis that testosterone deficiency promotes the pathogenesis of atherosclerosis. Low testosterone also correlates with the degree of aortic atherosclerosis [Hak *et al.* 2002].

The major modifiable cardiovascular risk factors are smoking, hypertension, elevated LDL-C, diet, lack of exercise, abdominal obesity and diabetes [Yusuf *et al.* 2004]. Whilst not constituting a formal diagnostic criterion for the metabolic syndrome, the condition and type 2 diabetes are both recognized to be pro-inflammatory states, with a number of cytokines and adipokines being proposed to be involved in the pathophysiology of insulin resistance. Furthermore, pro-inflammatory cytokines are also intimately involved in the atherosclerotic process, and both type 2 diabetes and the metabolic syndrome are strong risk factors for, and often coexist with, CHD. Evidence suggests that pro-inflammatory cytokines play crucial role in the development of atherosclerosis [Jones and Saad, 2009]. *In vitro* studies suggest that testosterone has immunomodulatory properties [Jones and

Saad, 2009]. Testosterone has been shown to suppress the expression of IL6, IL1 β and TNF α in human cell lines [Hatakeyama *et al.* 2002; D'Agostino *et al.* 1999; Gornstein *et al.* 1999; Hofbauer *et al.* 1999; Li *et al.* 1993] and stimulating production of anti-inflammatory IL10 [Liva and Voskuhl, 2001]. In a detailed study of the relation between testosterone and inflammatory cytokines in men with low testosterone and stable coronary artery disease, serum IL1 β inversely correlated with testosterone [Nettleship *et al.* 2007b; Malkin *et al.* 2004a]. In men with type 2 diabetes highly sensitive C-reactive protein (CRP) and IL6 also are inversely correlated with testosterone [Kapoor *et al.* 2007c].

Adiponectin is well known to have an atheroprotective action. In two studies, one with hypogonadal men and the second with hypogonadal men with type 2 diabetes, both found that testosterone replacement reduced serum adiponectin. There is no clear explanation for this but may be proportional to reduction in fat cell mass and further investigation is needed [Kapoor *et al.* 2007c; Lanfranco *et al.* 2004].

Animal models have demonstrated that androgen-deficient states including orchidectomy or lack of an active androgen receptor develop lipid streak formation on high cholesterol diets whereas testosterone replete littermate controls do not [Nettleship *et al.* 2007a; Alexandersen *et al.* 1999].

Role of the androgen receptor in diabetes, obesity and metabolic syndrome

The biological function of testosterone (androgenicity) is a function both of testosterone level and of the efficiency of transcriptional activity mediated by the interaction of testosterone with the androgen receptor. Serum total (or even free) testosterone level is only a surrogate marker for the functions testosterone. The androgen receptor (AR) gene contains a polymorphic CAG repeat sequence in exon 1 which encodes a variable length polyglutamine stretch AR CAG. The length of this sequence correlates with the transcriptional activity of AR with longer AR CAG sequences associated with reduced transcriptional activity. Longer AR CAG was associated with increased body fat and leptin levels in a study of 106 healthy men [Zitzmann and Nieschlag, 2003] and in a study of 233 men with type 2 diabetes [Stanworth *et al.* 2008]. The latter study demonstrated that increased

central adiposity as measured by waist circumference was greater in association with a less sensitive AR. Longer AR CAG sequences are also associated with higher serum insulin levels in healthy men [Zitzmann and Nieschlag, 2003] but did not correlate with HbA1c in diabetic men [Stanworth *et al.* 2008].

Men with Kennedy's syndrome, which is a neurological disease caused by abnormally long AR CAG (CAG > 37 repeats), are reported to be more likely to develop diabetes. This might suggest that AR CAG may have a potential role in the pathogenesis of diabetes in this context; however, the distribution of CAG repeat numbers in diabetic men is similar to a healthy population.

AR CAG length also correlates positively with HDL-C levels in diabetic men [Zitzmann *et al.* 2001]. As mentioned previously serum testosterone also positively correlates with HDL-C. This implies that the effect of testosterone on HDL-C may be mediated independently of the AR. Animal work suggests that this action of testosterone may be mediated by its conversion to oestradiol [Nettlehip *et al.* 2007a].

Testosterone and mortality

The metabolic syndrome is associated with a significant increase in morbidity and mortality. This is mainly attributed to cardiovascular disease but there is also increased mortality due to cancer [Hanefeld *et al.* 2007; Zitzmann and Nieschlag, 2003]. Over the last 3 years there have been many epidemiological studies [Laughlin *et al.* 2008; Khaw *et al.* 2007; Shores *et al.* 2006] which have demonstrated that low testosterone status is associated with increased mortality. Most of these studies have reported an increase in all-cause and cardiovascular mortality. On the other hand, there are at least two major studies which showed a weak association or no significant association between testosterone levels and mortality [Araujo *et al.* 2007; Smith *et al.* 2005b]. Results of major epidemiological studies are shown in Table 1.

A 7-year follow-up study of 930 men with CHD proven by angiography has shown that a low testosterone is a major risk factor for all-cause (hazard ratio [HR] 2.25) and cardiovascular mortality only surpassed by reduced left-ventricular function at baseline for all-cause mortality (HR 3.85) [Malkin *et al.* 2010]. More recently, in a

6-year follow-up study involving 587 men with type 2 diabetes from Barnsley, United Kingdom, the researchers found that low baseline testosterone levels were also associated with increased all-cause and cardiovascular mortality [Muraleedharan *et al.* 2010].

Effect of testosterone replacement on components of metabolic syndrome

One of the earliest studies reporting effect of TRT on obesity was by Rebuffescribe and co-workers in 1991. In a small group of 11 men it was found that waist-hip ratio decreased in 9 out of 11 men after 6 weeks of testosterone replacement. This finding has been confirmed in subsequent larger studies [Rebuffescribe *et al.* 1991]. Recently, however, there have been a number of studies published investigating the effect of testosterone replacement in men primarily in men with type 2 diabetes and with metabolic syndrome.

Boyanov and colleagues reported a study of 48 type 2 diabetic men with symptoms of androgen deficiency [Boyanov *et al.* 2003]. It was an open-label, randomized, nontreatment, (nonplacebo-)controlled study undertaken over 3 months. Patients received 120 mg oral testosterone undecanoate daily, in divided doses of 80 mg at breakfast and 40 mg at the evening meal ($n=24$) or no treatment ($n=24$). Compared with the nontreatment group, testosterone treatment resulted in significant reductions in weight, waist-hip ratio and percentage body fat. Fasting blood glucose (FBG) and postprandial blood glucose levels were reduced significantly, and HbA1c fell by 1.8% ($p<0.05$). No significant effects on lipid parameters were observed. The limitations of this study are that there was no placebo group and that more intensive clinic visits itself might have had a beneficial effect on glycaemic control. However, this study provided the first evidence that testosterone treatment may offer clinical benefit to men with type 2 diabetes.

The first double-blind placebo-controlled study was published by Kapoor and colleagues which enrolled 24 patients with type 2 diabetes with a clinical diagnosis of hypogonadism [Kapoor *et al.* 2007c]. This study was a double-blind placebo-controlled crossover design, with patients randomized to treatment with either testosterone first or placebo first by a computer-generated system; each treatment phase was of 3 months

Table 1. Major epidemiological studies on testosterone levels and mortality in men.

Study	Population	N	Follow up (years)	Age group (years)	Major outcome
Laughlin <i>et al.</i> [2008] (Rancho Bernado)	Community dwelling	794	11.8	50–91	Low TT ↑ all-cause (HR 1.88) CV (HR 1.38) and respiratory (HR 2.29)
Shores <i>et al.</i> [2006] (Veterans)	Male veterans, hospital based	858	4.3	>40	Low TT ↑ all-cause mortality (HR 1.88)
Khaw <i>et al.</i> [2007] (EPIC-Norfolk)	Community, nested case–control	11,600	7	40–79	Low TT ↑ all-cause mortality (OR 0.59), CV (OR 0.62) and cancer (0.59)
Haring <i>et al.</i> [2010] (Pomerania)	Community dwelling	1954	7.2	20–79	Low TT ↑ all-cause mortality (HR 2.32), CV (2.56) and cancer (HR 3.46)
Vikan <i>et al.</i> [2009] (Tromso)	Community dwelling	1568	10	59 ± 10.2	Low free TT ↑ all-cause mortality Vikan <i>et al.</i> [2009] (HR 1.24)
Tivesten <i>et al.</i> [2009] (Swedish MrOS)	Community dwelling	3014	4.5	69–80	Low TT ↑ all-cause mortality (HR 1.65)
Smith <i>et al.</i> [2005b] (Caerphilly)	Community dwelling	2512	16.5	45–59	Low TT ↔ all-cause and CV mortality
Araujo <i>et al.</i> [2007] (MMAS)	Community dwelling	1709	15.3	40–70	Low TT ↔ all-cause and CV mortality

↑ Increased; ↔ No significant relations.
TT, total testosterone; CV, cardiovascular; HR, hazard ratio.

duration separated by a 1-month washout period. Testosterone treatment was with 200 mg testosterone esters administered as a deep intramuscular injection once every 2 weeks. The final assessment of clinical parameters was made 12–14 days after the final injection. Testosterone treatment resulted in a significant improvement in the HOMA-IR index in those patients not receiving insulin therapy ($n=14$) and resulted in a reduction in insulin dose by an average of 7 units per day in those patients on insulin therapy ($n=10$). In the entire patient population statistically significant reductions in both FBG (-1.58 mmol/l) and fasting insulin were observed, with HbA1c falling by 0.4% ($p=0.03$). In addition to improvement in blood glucose parameters, testosterone treatment also resulted in statistically significant improvement in waist circumference, waist–hip ratio and total cholesterol (-0.4 mmol/l) although no significant

effect was observed on HDL-C, LDL-C, TGs or blood pressure

Another important study is by Heufelder and colleagues investigating the effects of TRT in men with type 2 diabetes [Heufelder *et al.* 2009]. This was undertaken over a 52-week treatment period, and therefore representing the first longer-term investigation. The study enrolled 32 hypogonadal men with newly diagnosed, treatment-naïve type 2 diabetes but with the added criteria of also having metabolic syndrome. All patients were also abdominally obese in addition to having hypogonadism and type 2 diabetes. The study was a single-blind, randomized design and was not placebo controlled, with patients either receiving diet and exercise advice alone, or diet and exercise advice in conjunction with 50 mg testosterone gel once daily. Compared with diet and exercise

alone, testosterone 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 $<6.5\%$ markedly more than in the diet and exercise alone arm. This was combined with a statistically significant reduction in the HOMA-IR index, although the observed treatment-mediated reduction in FPG (-0.3 mmol/l) narrowly failed to achieve statistical significance ($p = 0.06$). In addition, a significant improvement in waist circumference was observed. Testosterone treatment was also associated with a statistically significant reduction in serum levels of TGs and a statistically significant increase in serum levels of HDL-C.

A large multicentre, randomized, double-blind, placebo-controlled study was recently undertaken in eight European countries, providing suitable statistical power to test this hypothesis formally (currently only published in abstract form) [Jones *et al.* 2010]. The TIMES2 (Testosterone replacement In men with Metabolic Syndrome or type 2 diabetes) study recruited 220 hypogonadal men (aged ≥ 40 years) diagnosed with either type 2 diabetes and/or the metabolic syndrome (defined according to the IDF criteria) with either a total serum testosterone <11 nmol/l or calculated free serum testosterone <255 pmol/l, and/or at least two symptoms of hypogonadism with no TRT within the previous 6 months. Patients were stratified according to disease status (type 2 diabetes and/or metabolic syndrome) and were randomized to receive TRT initially as a 60 mg/day transdermal gel, which was subsequently dose adjusted to 20–80 mg/day to achieve serum testosterone levels >17 nmol/l with dummy dose adjustment in the placebo group. Insulin resistance as assessed by HOMA-IR improved after 6 and 12 months of therapy. TRT was also associated improvement in the sexual function, reductions in percentage of body fat, total cholesterol and LDL-C and lipoprotein a after 6 months but no significant effects on HDL-C or TGs. HbA1c was 0.58% lower compared with placebo after 9 months treatment but no differences prior to this timepoint.

Other studies have similarly demonstrated an improvement in waist circumference [Saad *et al.* 2008, 2007] and fat mass [Agledahl *et al.* 2008; Kenny *et al.* 2001] with testosterone replacement. One of the links between visceral adiposity

and type 2 diabetes is thought to occur through the exposure of the liver to free fatty acids derived from central adipocytes. Testosterone decreases visceral fat mass which reduces the waist circumference. It also reduces insulin resistance by decreasing the exposure of free fatty acids to the liver. It is also noted that testosterone reduces lipoprotein lipase activity a key enzyme involved in the uptake of TGs into adipocytes. [Marin *et al.* 1995; Rebuffescribe *et al.* 1991].

Physiological replacement of testosterone has been shown to decrease total cholesterol and LDL-C [Muraleedharan, 2010; Fan and Dwyer, 2007; Malkin *et al.* 2004a, 2004b]. Studies on the effect of testosterone replacement on HDL-C have yielded differing and confounding results with either a decrease [Bagatell *et al.* 1994; Thompson *et al.* 1989], no change [Kapoor *et al.* 2006; Malkin *et al.* 2004b; Uyanik *et al.* 1997; Zgliczynski *et al.* 1996] or some reporting an increase in the HDL concentration [Saad *et al.* 2007; Zitzmann and Nieschlag, 2007]. It has been postulated that testosterone increases the shuttling of cholesterol back to the liver from peripheral tissues resulting in an initial lowering of HDL-C before stabilization of levels. Higher testosterone and/or oestradiol levels may increase HDL-C over a longer duration as is the case in statin therapy. Apart from one published study in elderly men [Saad *et al.* 2008] with late-onset hypogonadism where testosterone replacement reduced TGs, other studies have found no change.

Animal studies have shown that in young orchidectomized hypertensive rats, testosterone replacement exacerbates systolic hypertension [Reckelhoff *et al.* 1998]. Testosterone increases tubular sodium and water reabsorption [Reckelhoff *et al.* 2005]. One clinical study showed testosterone replacement in men with hypopituitarism increases extracellular water and decreases aldosterone levels, but the plasma rennin and atrial natriuretic peptide levels are unaffected. Systolic and diastolic blood pressures remained unchanged in this study [Johannsson *et al.* 2005]. Physiological replacement might have a beneficial effect on blood pressure. There are reports of significant reduction in diastolic and systolic blood pressure [Zitzmann and Nieschlag, 2007; Anderson *et al.* 1996; Marin *et al.* 1993] after TRT. 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, TGs and total cholesterol. Zitzmann and colleagues in a study of 66 hypogonadal men (mean age 38 ± 9.9 years), reported that testosterone substitution resulted in a significant decrease in serum levels of LDL-C, resting diastolic and systolic blood pressure and heart rate. Another important study by Anderson and colleagues (Anderson *et al.* 1996) in men with osteoporosis intramuscular testosterone for 6 months showed significant reduction in diastolic blood pressure along with total cholesterol, TGs and HDL-C.

Several clinical studies have reported that TRT in hypogonadal individuals results in a reduction in the *ex vivo* production [Corrales *et al.* 2006] or the circulating concentration [Agarwal and Oefelein, 2005; Malkin *et al.* 2004a, 2004b] of a number of pro-inflammatory cytokines. A study of hypogonadal men where the majority of subjects had CHD demonstrated that TRT suppressed TNF α and increased the anti-atherogenic cytokine IL10. Although testosterone treatment of men with type 2 diabetes did not result in any significant immunomodulatory effect, the baseline levels of both IL6 and CRP, but not TNF α , were significantly inversely correlated with total and bioavailable amounts of circulating testosterone confirming that low testosterone is associated with inflammation [Kapoor *et al.* 2007c].

No adverse effects on clotting have been identified. In a study of testosterone replacement in men with chronic stable angina there were no changes in tissue activity of either tissue plasminogen activator (tpa) or plasminogen activator inhibitor type 2 (PAI-1), or fibrinogen levels [Smith *et al.* 2005a].

None of these studies or others [Fernandez-Balsells *et al.* 2010; Haddad *et al.* 2007; Calof *et al.* 2005] have reported increases in adverse effects of testosterone replacement on cardiovascular endpoints apart from a recent study published in the *New England Journal of Medicine* [Basaria *et al.* 2010]. This study was unusual and does not reflect common clinical practice. The study was designed to increase muscle strength in frail elderly men. Testosterone gel was administered at a dose which was twice the recommended starting dose in a group of elderly men with a high level of comorbidities including hypertension and diabetes. These men had an

increased incidence attributed potentially to cardiovascular events including oedema and self-reported syncope. The study was not powered to assess this aspect and although the results are of interest, they clearly require further investigation especially as other studies have not reported such effects in men treated within guidelines of common clinical practice.

Summary

There is strong evidence that a low testosterone level and clinical hypogonadism have a high prevalence in men with metabolic syndrome and/or type 2 diabetes. Many components of metabolic syndrome are adversely affected especially in relation to cardiovascular risk in the presence of hypogonadism. Testosterone deficiency is a risk factor in itself for the subsequent development of the metabolic syndrome and type 2 diabetes.

Early interventional studies have shown that TRT in hypogonadal men with type 2 diabetes and/or metabolic syndrome has beneficial effects. These benefits have not only found that hypogonadal symptoms such as sexual function improve, but key metabolic markers also improve. It is important to recognize that these include central adiposity, insulin resistance and glycaemic control, all components of the metabolic syndrome and cardiovascular risk factors. No significant beneficial effects have been consistently identified on blood pressure, TGs 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. Taken into context that there is increasing evidence that low testosterone is associated with increased mortality, then it may be conceivable that physiological testosterone replacement potentially could enhance survival in these men. It is important that the diagnostic criteria for hypogonadism are confirmed before considering testosterone replacement according to international criteria [Bhasin *et al.* 2010; Wang *et al.* 2008]. We do not however know whether low testosterone is just a biomarker of the degree of illness or a contributory factor to the progression of atherosclerosis. Accumulating evidence now suggests that testosterone 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 clear need for a longer-term interventional study, ideally of 5-year duration, to examine the effect of testosterone on cardiovascular disease in men with metabolic syndrome and/or type 2 diabetes. The increasing evidence as reviewed here is becoming too strong to be ignored. It must also not be forgotten that TRT in hypogonadal men with or without metabolic syndrome or diabetes can have a major impact on the patient's quality of life and well-being.

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