Androgens Insulin Resistance and Vascular Disease in Men

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Summary and Introduction

Summary

Type 2 diabetes mellitus is increasing globally and is an established risk factor for the development of atherosclerotic vascular disease. Insulin resistance is the hallmark feature of type 2 diabetes and is also an important component of the metabolic syndrome. There is evidence to suggest that testosterone is an important regulator of insulin sensitivity in men. Observational studies have shown that testosterone levels are low in men with diabetes, visceral obesity (which is strongly associated with insulin resistance), coronary artery disease and metabolic syndrome. Short-term interventional studies have also demonstrated that testosterone replacement therapy produces an improvement in insulin sensitivity in men. Thus hypotestosteronaemia may have a role in the pathogenesis of insulin-resistant states and androgen replacement therapy could be a potential treatment that could be offered for improvements in glycaemic control and reduction in cardiovascular risk, particularly in diabetic men.

Introduction

The prevalence of the metabolic syndrome and type 2 diabetes is increasing dramatically in the Western world. The consequences of this are an increased morbidity and mortality from vascular disease. The primary pathological feature of these conditions is insulin resistance. Initially compensatory hyperinsulinaemia allows maintenance of normal glucose tolerance but as the degree of insulin resistance deteriorates, impaired glucose tolerance occurs and eventually diabetes develops. There is a broad range of insulin sensitivity in apparently healthy individuals. Up to 25% of the population have unrecognized insulin resistance to a similar degree to patients with known glucose intolerance and type 2 diabetes. The clinical significance of this insulin resistance is uncertain.[1] The commonest described state of insulin resistance is the metabolic syndrome (Syndrome X, Reaven's syndrome), which is now recognized by the World Health Organization. Metabolic syndrome is defined as a state of glucose intolerance associated with at least two of the following factors: hypertension, dyslipidaemia or visceral obesity.[2] This syndrome is strongly associated with an increased risk of coronary heart disease.

Interaction of sex hormones and insulin has been described extensively in women. Hormone replacement therapy improves insulin resistance in type 2 diabetic women.[3] Hyperandrogenicity, on the other hand, is well known to correlate with insulin resistance in women with polycystic ovarian syndrome and in nondiabetic women with abdominal obesity. In female rats, moderate increases of testosterone concentration are followed by a marked decrease in whole-body insulin sensitivity.[4] The mechanisms involved are uncertain. It is generally believed that high insulin levels found in insulin-resistant states stimulate the ovary to secrete androgens either through binding to the insulin receptor or to the insulin-like growth factor-1 receptor through a phenomenon known as specificity spillover.[5] Insulin sensitivity generally improves when the hyperandrogenism is corrected.

Further evidence for sex hormone-associated insulin resistance comes from studies in children that have shown that normal puberty is associated with a reduction in insulin-stimulated glucose uptake in peripheral tissues.[6] As serum levels of sex hormones rise considerably during puberty,

elevated levels of androgens and oestrogens could contribute to the insulin resistance observed, although variations in growth hormone levels could also be relevant.

Little attention has been paid to the role of testosterone in the pathogenesis of insulin-resistant states in men. Type 2 diabetes is more prevalent in men than in women[7] – a conceivable explanation being the differences in endogenous sex hormones. Low androgen levels are associated with various components of the metabolic syndrome including coronary artery disease, dyslipidaemia, visceral obesity, hypertension and pro-thrombotic state.[8] The aim of this article is to provide an overview of the relationship between testosterone, insulin resistance and vascular disease in men and to understand the role androgens may play in the male predisposition to diabetes.

Measurement of Testosterone

Testosterone has a diurnal rhythm, with peak blood levels in the morning (06:00–08:00 h) and a nadir in the evening (18:00–20:00 h). Testosterone also has a circannual rhythm, with higher levels in late summer and early autumn and lower levels in late winter and early spring. Within the circulation, testosterone is present in three major fractions: SHBG-bound testosterone, albumin-bound testosterone and free testosterone (Fig. 1). Non-SHBG-bound testosterone is called 'bioavailable' testosterone because both the free and albumin-bound testosterone fractions are thought to be readily available to the tissues whereas the testosterone bound to SHBG is tightly bound and thus considered to be inactive. Early studies only measured total testosterone and not the free or bioavailable testosterone. Bioavailable and free testosterone measurements provide stronger correlations with parameters such as bone mineral density[9] and muscle strength[10] than total testosterone. Bioavailable testosterone (by ammonium sulfate precipitation) and free testosterone (by equilibrium dialysis) assays are not used routinely as only small numbers of samples can be analysed. Mathematical formulae based on total testosterone and SHBG are available to calculate free testosterone[11] and bioavailable testosterone.[12]

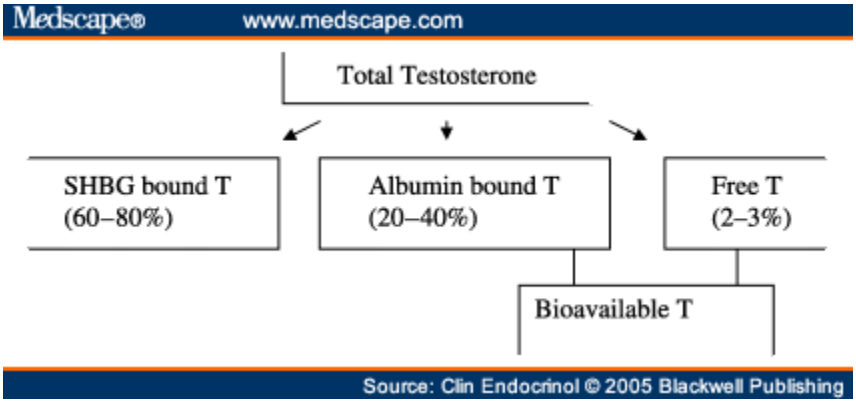

Figure 1.

Fractions of circulating total testosterone in men. Non-SHBG-bound testosterone is called bioavailable testosterone and comprises both albumin-bound testosterone and free testosterone. Bioavailable testosterone is readily available to the tissues and correlates more strongly with bone mineral density and muscle strength than total testosterone.

Assessment of Insulin Resistance

Insulin resistance can be defined as a state in which normal amounts of insulin produce a suboptimal biological response. There are a number of tests used to assess the degree of insulin resistance. All of the investigative techniques have limitations and are not suitable for routine clinical use.[13] The most commonly used tests are the euglycaemic clamp and the homeostatic model assessment (HOMA). The hyperinsulinaemic euglycaemic clamp, which involves simultaneous infusions of insulin and glucose, is regarded as the gold standard. It is based on the principle that if glucose production by the liver is suppressed by an intravenous infusion of insulin then the amount of exogenous glucose required to maintain euglycaemia provides an estimate of the insulin sensitivity of target tissues (mainly skeletal muscle). This test is useful for intensive physiological studies on small numbers of patients. HOMA is a simpler test and is more appropriate for large epidemiological studies. HOMA is a mathematical model by which values of insulin sensitivity can be calculated if simultaneous fasting plasma glucose and fasting insulin concentrations are known. It gives an estimate of basal insulin resistance, unlike other techniques, which measure stimulated insulin resistance.

Testosterone and Insulin Resistance

Epidemiological Studies in Healthy Population

Studies in healthy men have shown an inverse correlation between testosterone and insulin levels (Table 1). The Telecom study involving 1292 healthy adult men demonstrated a significant inverse relationship between levels of plasma total testosterone and insulin independent of age, alcohol consumption, cigarette smoking and plasma glucose.[14] Even though the association was reduced to some extent by obesity, it still persisted after adjustment for body mass index (BMI) and subscapular skinfold thickness. Another large prospective population-based study of 1009 men, who were followed-up for 12 years, also demonstrated similar inverse correlations between total testosterone levels and fasting blood glucose and BMI.[15]

Epidemiological Studies in Diabetic Men

In diabetic men, an early case–control study showed that androgen levels were lower than in normal men.[16] Subsequently in a larger cross-sectional study of 985 men from the Rancho Bernardo community in California, of whom 110 were diabetic, testosterone levels were found to be lower in diabetic men, although the association was not as great after controlling for age and BMI.[17] Of the diabetic men, 21% were hypogonadal compared to 13% of nondiabetic men, and the testosterone levels were related to the degree of glycaemia as assessed by fasting plasma glucose concentrations.

Another case–control study by the same group measured plasma androgen levels in 44 men with type 2 diabetes and compared them with 88 age-matched men with normal glucose tolerance.[18] Men with diabetes were found to have significantly lower levels of both total and bioavailable testosterone, as well as dehydroepiandrosterone sulfate (DHEAS), than controls, even when these associations were adjusted for obesity and fat distribution. As both testicular and adrenal androgens were reduced, a selective effect of diabetes on the testicular Leydig cells was thought to be unlikely.

A larger German study comparing 155 male type 2 diabetic patients with 155 healthy controls showed that free testosterone levels were lower in type 2 diabetic men and inversely correlated with BMI.[19] However, no correlation was found between testosterone and serum levels of C-peptide. A recent study in 103 type 2 diabetic men showed the prevalence of hypogonadism to be 33% based on assessment of free testosterone by the equilibrium dialysis method.[20] Furthermore, men with impaired glucose tolerance and not diabetes were also found to have low total testosterone levels.[21]

Studies in Hypogonadal Men

The association between hypogonadism and insulin levels in men has also been reported in studies on patients undergoing treatment for prostate carcinoma. Androgen ablation has been the mainstay treatment for metastatic disease as the growth of cancer cells in the prostate is stimulated by testosterone. Hormonal therapy consists of either surgical or medical castration induced by GnRH agonists, antiandrogens, or a combination of both. Dockery *et al.*[22] showed that fasting insulin levels increased after 3 months in 16 men with prostate cancer under treatment with GnRH agonists as compared to age-matched controls. Arterial stiffness also increased in these men but there was no significant change in BMI or serum glucose. Smith *et al.*[23] also found an increase in serum insulin levels and arterial stiffness, after 3 months, in 22 men in this group. These men also had an increase in fat mass and a decrease in lean mass. Similarly, in another study, 30 men who underwent surgical castration for primary prostate limited adenocarcinoma had an increase in both fasting and postprandial glucose as well as postprandial insulin, 1 month after surgery.[24]

Effect of Ageing

Ageing in males is accompanied by a progressive decline of gonadal function manifested by a fall in total, bioavailable and free plasma testosterone levels. Free and bioavailable testosterone levels decline more steeply than total testosterone levels because of the age-associated increase in SHBG level. Ageing is also associated with an increasing prevalence of type 2 diabetes. The European Group for the Study of Insulin Resistance showed that insulin action declines with ageing.[25] Another study also demonstrated an age-related impairment in glucose handling.[26]

The Massachusetts Male Ageing Study is a large population-based study of 1156 men aged 40–70 years who were followed up for 7 to 10 years. In this study the mean baseline total and free testosterone and SHBG levels were significantly lower among men who later developed diabetes.[27] Similarly, another retrospective analysis from participants enrolled in the Multiple Risk Factor Intervention Trial (MRFIT) showed that the nondiabetic men who subsequently developed diabetes during 5 years' follow-up also had significantly lower levels of free testosterone and SHBG than those who did not.[28] Further evidence that there is a prospective association between low endogenous testosterone levels and future onset of type 2 diabetes was found in older men taking part in the Rancho Bernardo study. This study reported a significant inverse relationship between low baseline total testosterone levels and follow-up levels (8 years later) of fasting and postchallenge glucose and insulin levels, as well as HOMA in men.[29] Another study in 659 elderly men found that total and free testosterone and SHBG levels were negatively correlated with glucose and insulin values.[30]

Further insight into the potential role of male hormones in the future development of insulin resistance and diabetes is provided by a study performed in relatives of diabetic patients. It is well established that first-degree relatives of type 2 diabetic patients have a higher risk of developing diabetes. Jansson *et al.*[31] compared 33 healthy first-degree relatives of type 2 diabetic patients with 33 age-matched controls. Relatives showed decreased insulin sensitivity as measured by the euglycaemic hyperglycaemic clamp method and this difference was significant for males only. Male relatives of the diabetic patients had lower plasma total testosterone levels as compared to the male controls and the total testosterone levels observed in these relatives were positively associated with insulin sensitivity. As SHBG levels were similar between groups, it was postulated that the alterations in total testosterone levels would reflect the free hormone levels as well. Thus it would seem likely that dysregulation of androgen levels could contribute to the development of insulin resistance in male subjects who have a higher genetic predisposition for type 2 diabetes.

In summary, these studies suggest that low testosterone levels in men may potentially be a contributory factor to the development of insulin resistance and the subsequent progression to type 2 diabetes.

Contribution of SHBG

SHBG is the circulating steroid-binding protein produced by the liver that binds testosterone with high affinity. It is an important regulator of androgen homeostasis and functions as a modulator of androgen delivery to the tissues. SHBG concentration falls during puberty in both boys and girls. Serum SHBG levels are primarily regulated by sex steroids and thyroxine.

It has been suggested that the link between total testosterone and insulin resistance is due to the negative relationship between SHBG and insulin, with low SHBG leading to low total testosterone. Birkeland *et al.*,[32] using the insulinglucose clamp technique, demonstrated an inverse correlation between insulin resistance and serum SHBG levels in 23 type 2 diabetic men that was independent of serum insulin or C-peptide level as well as being independent of obesity and abdominal fat accumulation. In the Telecom study, healthy men with lower total testosterone levels had significantly higher insulin levels and markedly reduced levels of SHBG.[33] Bioavailable testosterone levels, however, were not significantly different in the two groups, implying that the link between total testosterone and plasma insulin could be explained by the negative association between SHBG and plasma insulin. Similarly, Andersson *et al.*[34] found that total testosterone and SHBG levels were significantly lower in diabetic men than nondiabetic control subjects and had a negative correlation with insulin values. There was no difference in free testosterone levels between the groups, again demonstrating that low total testosterone levels were secondary to the low SHBG. Even in relatives of hypertensive men, an inverse relationship was found between low total testosterone and SHBG concentrations and lower insulin sensitivity, with no change in free testosterone levels.[35]

Insulin is an important regulator of SHBG production by the liver. *In vitro* studies have shown that insulin in physiological concentrations was a potent inhibitor of SHBG production by cultured hepatoma cells.[36] Peiris *et al.*[37] also showed a significant association between SHBG levels and the insulin secretory pulse interval but not with peripheral insulin sensitivity in 10 nondiabetic men. Furthermore, Pasquali *et al.*[38] demonstrated that inhibition of insulin secretion by giving diazoxide to normal weight and obese men led to increased SHBG levels. Acute hyperinsulinaemia has also been found to result in a small but significant reduction in SHBG concentration in healthy men.[39] Nestler has thus suggested that lower SHBG levels may be a marker for hyperinsulinaemia and insulin resistance.[40] Men with low SHBG concentrations have an increased risk of developing the metabolic syndrome.[41] Therefore, the available data, in men, suggest that insulin resistance maybe a determinant of SHBG levels.

Impact of Obesity

Obesity is the most common cause of insulin resistance. BMI is traditionally used as an indicator of overall obesity. However, certain patterns of fat distribution are more closely related to increased incidence of diabetes and cardiovascular disease. Abdominal or central obesity, as assessed by waist/hip ratio, is an essential component of metabolic syndrome and more strongly linked to the development of impaired glucose tolerance. Visceral fat, which constitutes a significant proportion of the intra-abdominal fat, has certain characteristic metabolic and anatomical features.[42] Visceral adipose tissue is more highly metabolically active than any other adipose tissue in the body. Furthermore, the visceral fat is drained through the portal vein to the liver, in contrast to the peripheral fat, which is drained by the systemic circulation. The above two processes result in the liver being exposed to higher concentrations of free fatty acids produced by the adipocytes than in any other organ. Free fatty acids decrease hepatic insulin binding and extraction, increase hepatic gluconeogenesis and increase hepatic insulin resistance. These effects ultimately lead to peripheral hyperinsulinaemia and systemic insulin resistance (Fig. 2).

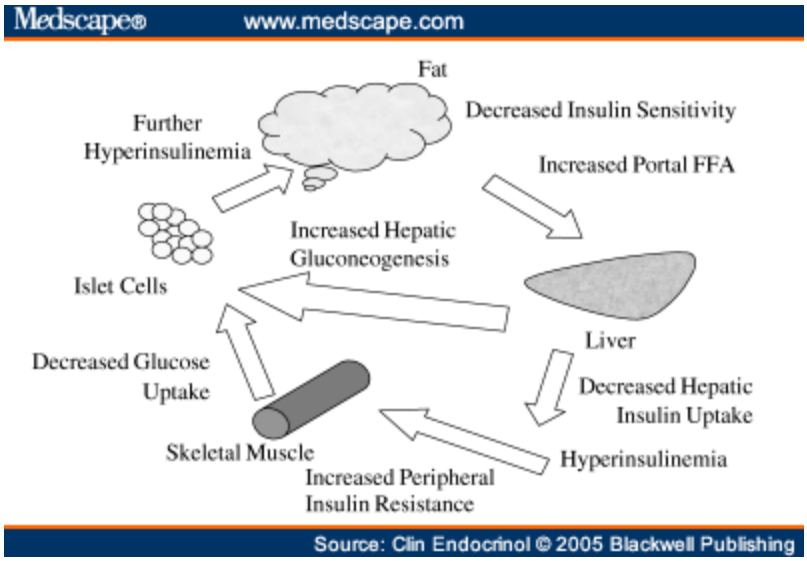

Figure 2.

Role of visceral fat in peripheral hyperinsulinaemia and systemic insulin resistance. Increasing abdominal fat leads to liver being exposed to higher concentrations of free fatty acids. The free fatty acids increase hepatic glucose production and decrease hepatic insulin uptake. This Results in systemic hyperinsulinaemia and skeletal muscle insulin resistance, which in turn causes further release of insulin by the islet cells.

Unlike the situation in women, in men there is an inverse relationship between serum testosterone levels and visceral fat mass. The visceral obesity in men is associated with relative hypogonadism. Obesity itself is one of the several conditions that can result in a low SHBG level.[43] In the HERITAGE Family Study, increasing total body fat content and visceral adiposity were associated with decreased plasma levels of SHBG.[44] As a result, total testosterone is frequently low but the free testosterone is normal, suggesting that this not a true clinical hypogonadism.[43] This is generally seen in moderate obesity.

By contrast, other studies have shown that free testosterone levels are low in obese individuals (Table 2) and the relative hypogonadism is proportional to the degree of obesity.[45] Abdominal or upper body obesity is more strongly related to free testosterone levels than other forms of obesity. Haffner *et al.*[46] found, in a population of 178 men recruited to the San Antonio Heart Study, that BMI was inversely related to total and free testosterone as well as SHBG level. Waist/hip ratio was also strongly inversely related to total and free testosterone. Similarly, Abate *et al.*[47] showed that subcutaneous fat accumulation in the truncal area is highly predictive of low plasma concentrations of free testosterone. Studies by Seidell *et al.*[48] and Phillips[49] have also reported that waist/hip ratio in men was significantly inversely correlated with total testosterone, free testosterone and SHBG levels. Pasquali *et al.*,[50] on the other hand, found a significant inverse relationship between BMI and both total and free testosterone and SHBG but no association between waist/hip ratio and any sex hormone or binding protein.

The prevalence of obesity in ageing men has increased and is a strong predictor of the testosterone deficiency seen in ageing males. Hypogonadal men also have a reduced lean body mass and an increased fat mass. Vermeulen *et al.*[51] reported in a study of 57 men between 70 and 80 years that testosterone levels correlated negatively with percentage of body fat, abdominal fat and insulin levels. Chang *et al.*[52] also showed that elderly men with type 2 diabetes had higher BMI, waist/hip ratio and lower serum testosterone levels than elderly men without type

2 diabetes. Testosterone levels correlated negatively with BMI, waist/hip ratio and skinfold thickness.

The changes in total and free testosterone concentrations are reversible with weight loss. Strain *et al.*[53] assessed the effect of weight loss on sex hormones in 11 healthy obese men. Weight loss of between 26 and 129 kg over 5–39 months produced significant increases in mean plasma total and free testosterone and SHBG levels. The increases in plasma free and total testosterone and SHBG levels were also proportional to the degree of weight loss. Similar Results have also been reported in other smaller studies.[54]

The underlying mechanisms responsible for the reduced testosterone levels in obese men are unknown. The reduction in free testosterone seen in massive obesity is not accompanied by a reciprocal increase in LH, suggesting a form of hypogonadotrophic hypogonadism.[54] One hypothesis postulated for the decreased free testosterone in massively obese individuals is functional alterations at the hypothalamicpituitary level of the testicular axis characterized by decreased amplitude of the LH pulses.[43] Some rare hypothalamic syndromes, such as Prader–Willi syndrome, are associated with both obesity and hypogonadotrophic hypogonadism.

Another possible mechanism to explain the aetiology of low testosterone levels and the subsequent insulin resistance in obese men is hyperoestrogenemia. Earlier studies found increased serum levels of oestradiol and oestrone in obese men.[55] This primarily occurs as a result of increased peripheral conversion of androgens to oestrogens through the action of the enzyme aromatase, which is present in higher levels in the adipose tissue as compared to other tissues. This increase in serum oestrogen concentration is, however, not accompanied by overt signs of feminization. It is thus possible that the increased oestradiol levels contribute to the insulin resistance in obese men. Phillips *et al.*[56] found in 80 adult men that both total and free testosterone correlated inversely, and the ratio of oestradiol to testosterone directly, with insulin levels. However, after controlling for visceral adipose tissue, only the oestradiol to testosterone ratio and insulin concentration remained significant. Similarly, another study found higher oestradiol levels in diabetic subjects compared to the nondiabetic ones.[57] A small study of six obese men treated with the aromatase inhibitor testolactone showed a decrease in oestradiol and an increase in testosterone levels.[58] However, others have found no relationship between oestradiol concentrations and glucose or insulin levels or insulin resistance.[59] Administration of ethinyl oestradiol to normal men has been reported to induce insulin resistance.[60] There are case reports of two men, one with oestrogen resistance caused by a mutation of the oestrogen receptor alpha gene[61] and another with low oestradiol and elevated testosterone levels as a result of a mutation in the aromatase gene.[62] These men had glucose intolerance and insulin resistance.

At the cellular level, adipocytes express androgen receptors.[63] Testosterone inhibits the activity of lipoprotein lipase, the main enzymatic regulator of triglyceride uptake in adipose tissue.[64] This Results in inhibition of triglyceride uptake, increase in lipid mobilization and a subsequent decrease in visceral adipose tissue mass (Fig. 3). In the ageing male the natural diminution in testosterone is contributory to visceral adiposity. Furthermore, the relative hypogonadism produced in abdominally obese men also contributes to an increase in fat mass. Tsai *et al.*[65] reported that a low baseline total testosterone level in Japanese-American men predisposed to an increase in visceral adiposity.

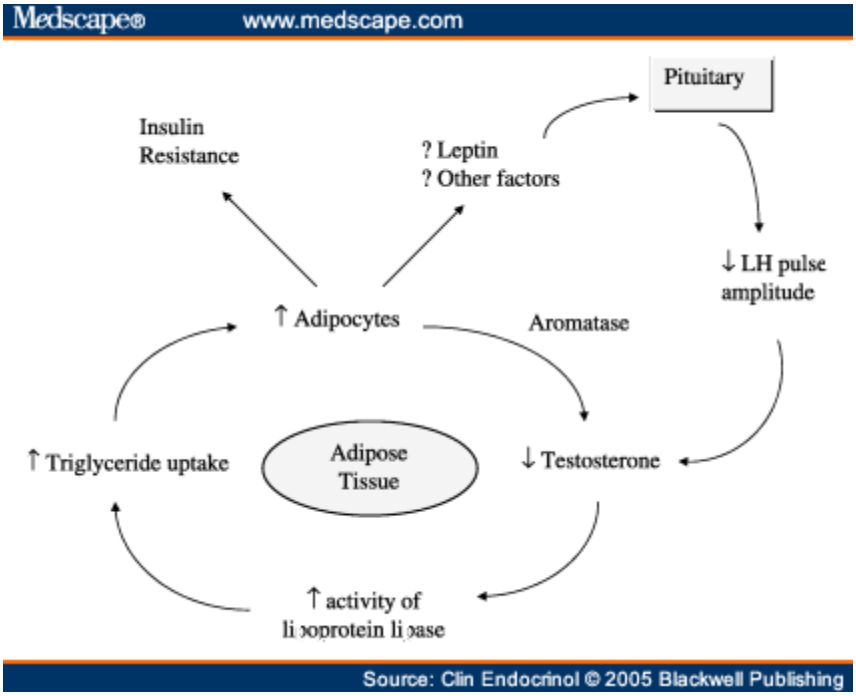

Figure 3.

Interaction between adipose tissue, testosterone and insulin resistance. The enzyme aromatase, present in high concentrations in adipose tissue, converts testosterone to oestrogen. Increasing abdominal fat leads to an increased aromatase activity. The resulting low testosterone increases lipoprotein lipase activity and triglyceride uptake leading to an increased visceral adiposity and insulin resistance. This in turn causes further hypogonadism and abdominal fat deposition. Furthermore, with increasing visceral fat, LH pulse amplitude is reduced, probably through the action of certain factors such as leptin at the pituitary level, leading to further reduction in testosterone levels.

Cohen[66] has described the hypogonadal–obesity cycle. During the hypogonadal state, there is an increase in deposition of abdominal adipose tissue. This Results in increased aromatase activity leading to a greater formation of oestradiol from testosterone. This will then lead to a further reduction in serum and tissue testosterone concentrations, increased deposition of abdominal fat and progressive hypogonadism.

Leptin is the adipocyte-secreted protein product of the ob gene. It is strongly linked to obesity and regulates weight and adipose tissue mass. Serum leptin levels correlate positively with age, BMI, serum insulin and fat mass and inversely with testosterone.[67] Leptin levels are higher in ageing males with lower testosterone and testosterone replacement therapy corrects this. The mechanism is unclear but is likely to be related to a combination of reduction in adipose tissue mass and a direct suppressive effect on ob gene expression.[68] As total body fat mass increases with low testosterone, hormone resistance develops for leptin and insulin. Increasing leptin fails to prevent weight gain and the hypogonadal–obesity cycle ensues, causing further visceral obesity and insulin resistance.[69] Although the mechanisms responsible for the hypogonadism in obesity are varied, testosterone therapy in obese men reduces visceral fat mass.[70] In elderly men, studies have demonstrated that testosterone decreases body fat mass and increases the lean mass. There is a variability in the responsiveness of the body fat to testosterone administration that depends on the duration of therapy, although other factors such as pretreatment body composition and the age of the subjects also play a role.[69]

Effect of Testosterone Replacement on Insulin Sensitivity

Animal Models

The effects of androgens on insulin sensitivity have been studied in animal models and the Results of these concur with those observed in men. Castrated male rats exposed to supraphysiological doses of testosterone have increased insulin resistance but, conversely, physiological testosterone replacement improves insulin sensitivity.[71] This implies that testosterone has a major role as a regulator of insulin sensitivity.

The effects of long-term administration of testosterone enanthate on glucose metabolism in rhesus monkeys were studied by Tyagi *et al.*[72] Nine adult male rhesus monkeys were given 50 mg of testosterone enanthate bimonthly for 32 months and glycaemic control was compared with placebo-treated animals. Significant changes in the glucose tolerance test were not observed in animals treated with testosterone throughout this period. However, serum insulin levels decreased significantly between 27 and 32 months in the testosterone-treated group and returned to baseline values within 3 months of stopping the treatment.

Centol *et al.*[73] compared serum androgen levels in streptozotocin-induced diabetic rats with controls. The diabetic state produced a marked reduction in serum androgen levels between 10 and 15 days after streptozotocin administration. Further studies with streptozotocin-induced diabetic rats have also shown a similar decrease in testosterone levels, which have been shown to occur as a combination of impaired gonadotrophin secretion at the pituitary level[74] and reduced function of the LH receptor in the testes.[75] Moreover, insulin administration in these diabetic rats partially restored the circulating androgen levels by stimulating testicular 3-beta-hydroxysteroid dehydrogenase activity,[74] thereby enhancing testosterone synthesis as well as receptor binding capacity.

Effect of Anabolic Steroids

Early literature revealed that anabolic steroids lowered fasting blood sugar and reduced glycosuria.[76] The cause for this effect was unknown, although methandienone was reported to enhance insulin secretion.[77] Subsequent research, however, has shown that anabolic steroids adversely affect glucose metabolism. Godsland *et al.*[78] found that when anabolic steroid methandrostenolone was given to underweight men, insulin action was impaired. Similar Results were also seen when oxymethalone led to impaired glucose intolerance and hyperinsulinaemia in children with idiopathic acquired aplastic anaemia or Fanconi's anaemia.[79] Cohen and Hickman[80] found that powerlifters who ingested anabolic steroids had insulin resistance compared to the nonsteroid-using powerlifters, obese men or nonobese sedentary men. Further evidence of impaired insulin action with high-dose testosterone comes from a study of a transsexual population that included women who chose to become men.[60] The women were treated with high doses of testosterone that resulted in impaired glucose uptake. Thus it would seem that excess androgen and anabolic steroid use reduces insulin sensitivity and impairs glucose tolerance. However, a study in healthy men has shown that nandrolone improved glucose metabolism by enhancing noninsulin-mediated glucose disposal.[81]

Effect of Testosterone Replacement in Hypogonadal Men

No adverse effects of testosterone therapy on insulin secretion or glucose tolerance have been demonstrated in normal men with pharmacologically-induced hypogonadism.[82] Sixty-one eugonadal men between 18 and 35 years of age were randomly assigned to receive monthly injections of long-acting GnRH agonist, to suppress endogenous testosterone secretion, and then given weekly doses of 25, 50, 125, 300 or 600 mg of testosterone enanthate for 20 weeks. In this study no significant effect of testosterone on insulin sensitivity was observed, even though the

higher doses of testosterone produced an increase in fat free mass and muscle size. Friedl *et al.*[83] also demonstrated that pharmacological doses of testosterone and 19-nortestosterone given for 6 weeks to normal men did not impair glucose tolerance.

Testosterone replacement therapy in adult men with hypogonadism improves insulin sensitivity. Simon *et al.*[84] randomized 18 men to one of three treatment groups – testosterone, dihydrotestosterone and placebo, administered in the form of gel. At the end of 3 months, men receiving androgens had a significantly lower fasting plasma insulin, fasting plasma insulin/fasting plasma glucose ratio, HOMA index and leptin levels. However, in another study of 10 men with idiopathic hypogonadotrophic hypogonadism treated with testosterone, no decrease in insulin sensitivity was observed using the hyperglycaemic euglycaemic clamp method.[85]

A beneficial effect of testosterone treatment on insulin resistance has also been seen in a study in HIV-infected men.[86] Reduced circulating testosterone levels are commonly found in patients with HIV infection and these levels correlate with weight loss and generalized muscle wasting. Sattler *et al.*[86] compared the effects of nandrolone decanoate and resistance training in 30 HIV-infected men over a 3-month period. Those patients who received both treatments had significantly lower fasting insulin and glucose levels and HOMA index. However, these changes were transient, with the metabolic effects returning to baseline 2 months after treatment was withdrawn.

Effect of Testosterone Treatment in Obese Men

Intra-abdominal fat may be a part of the pathway through which lower testosterone level is related to insulin resistance. Marin *et al.*[70] examined the effects of testosterone administration in middle-aged obese men. Reduced glucose tolerance was observed 1 week following intramuscular injection of 500 mg testosterone (producing supraphysiological plasma levels of testosterone). However, following treatment with doses achieving plasma levels high in the physiological range, plasma levels of insulin were reduced and insulin sensitivity increased. The greatest effect was observed in menwith lower baseline testosterone levels. In another study by the same group, 23 middle-aged abdominally obese men were randomized to 8 months of treatment with testosterone and placebo.[87] Testosterone treatment led to reduced insulin resistance. These changes could be due either to the effects of testosterone on visceral fat or to a direct effect on muscle insulin sensitivity.

Effect of Testosterone Replacement in Diabetic Men

Men with type 2 diabetes have a higher prevalence of hypogonadism, as mentioned earlier. Testosterone is an important modulator of insulin sensitivity and the consequences of improved insulin sensitivity in diabetic subjects is better glycaemic control. There are, however, few interventional studies that have been performed in this group of patients. Boyanov *et al.*[88] assessed the effects of oral testosterone supplementation in 48 type 2 diabetic men with mild androgen deficiency. Twenty-four men received testosterone and the other 24 men were given placebo. Oral treatment with testosterone resulted in a significant reduction in body weight, body fat, blood glucose and mean glycated haemoglobin (from 10·4% to 8·6%). Even though this was a nonblinded study and oral testosterone was used, favourable effects of testosterone treatment on the metabolic parameters in type 2 diabetic men were observed. However, although Corrales *et al.*[89] also found a high prevalence of hypogonadism in type 2 diabetic men, a neutral effect on glycaemic control with intramuscular testosterone replacement therapy was observed in 10 type 2 diabetic men with partial androgen deficiency.

DHEA and Insulin Resistance

Dehydroepiandrosterone and its sulfated form (DHEA-S) are produced primarily in the adrenal cortex and are the most abundantly circulating adrenal steroids in the blood. These adrenal

androgens show a progressive age-related decline in men from the third decade onwards.[90] This age-related decline has led to the suggestion that DHEA supplementation in the elderly may be beneficial in the prevention of a variety of disorders including type 2 diabetes and coronary heart disease.

Hyperinsulinaemia has been associated with lower adrenal androgen levels in ageing men. The fall in DHEA can be explained by the insulin-induced inhibition of 17, 20-adrenal lyase activity,[91] which is a key enzymatic step involved in adrenal androgen synthesis. Ageing-associated hyperinsulinaemia may explain the lower DHEA levels seen with age. Lower levels of DHEAS have been reported in diabetic men.[18] Haffner *et al.*[46] also showed an inverse relationship between DHEAS levels and waist/hip ratio. Other studies have found no such association with either obesity or insulin levels.[49] However, weight reduction by diet in obese men leads to an increase in DHEAS levels.[92] A cross-sectional study in elderly Italian men suggested that low DHEAS levels are a nonspecific indicator of ageing and health status, rather than a risk indicator of specific disease.[93]

Few studies have examined the effects of DHEA on insulin action in humans. Usisken *et al.*[94] treated six obese men with DHEA 1600 mg/day for 28 days. Neither insulin action nor glucose effectiveness, measured with the minimal model, were found to be altered in this study. Similarly, no change in insulin sensitivity with DHEA treatment has been found in normal men[95] or in men with dyslipidaemia.[96] A recent double-blind cross-over placebo-controlled study of 12 men, who were treated with DHEA 50 mg/day or placebo for 3 months, reported no significant changes in either serum insulin and glucose levels or body fat composition.[97] It would thus appear that DHEA replacement has no effect on insulin sensitivity,[98] although all the above studies involved small group of subjects and for short durations. Any potential benefits of DHEA replacement in preventing diabetes in men can only be determined by larger, long-term studies.

Insulin Resistance, Vascular Disease and Testosterone in Men

Diabetes mellitus is a well-known risk factor for the development of atherosclerotic vascular disease. It has been suggested that insulin resistance is the major cause for this rather than diabetes *per se*.[99] Ruige *et al.*[100] demonstrated that hyperinsulinaemia (an early marker of insulin resistance) was associated with an increased risk of cardiovascular disease.

Coronary artery disease is more prevalent in men than women, although the gender gap does narrow with age.[101] There is increasing evidence to suggest that a relative testosterone deficiency in men is responsible for this male preponderance. There have been several cross-sectional and some longitudinal studies that have either shown a neutral or a negative correlation with serum testosterone levels.[102,103]

A study using men with normal coronary angiogram as controls showed that men with coronary artery disease have significantly lower levels of bioavailable and free testosterone.[104] In a recent study by our group in men with angiographically proven coronary disease, 23·4% had overt hypogonadism (total testosterone < 7·5 nmol/l and/or bioavailable testosterone < 2·5 nmol/l) and a further 29·2% had borderline levels of testosterone (total testosterone 7·5–12 nmol/l and/or bioavailable testosterone 2·5–4 nmol/l). This represents a greater prevalence of hypogonadism than could be explained by ageing alone.[105]

Insulin resistance also plays a role in the development of atherosclerosis and hypertension.[99] Higher levels of plasminogen activator inhibitor-1 (PAI-1) and increased fibrinogen levels are related to insulin resistance. Dyslipidaemia with increased low density lipoprotein (LDL) cholesterol and reduced high density lipoprotein (HDL) cholesterol are also found in insulin-resistant states. Again, lower levels of testosterone in men have been associated with a proatherogenic lipid profile (high total and LDL cholesterol), hypertension, higher levels of

fibrinogen, a prothrombotic profile[8] and a proinflammatory state.[106] Serum testosterone level is an important independent predictor of HDL cholesterol, with higher levels being positively correlated with this hormone.[107]

Interventional studies have demonstrated a beneficial effect of testosterone on the above cardiovascular risk factors. Anderson *et al.*[108] demonstrated that administration of high-dose testosterone can reduce fibrinogen levels. Physiological testosterone replacement in hypogonadal men has been shown to reduce total and LDL cholesterol, with no change in HDL cholesterol,[85] and also to lower total cholesterol in patients already treated with statin therapy for coronary artery disease.[106] Alexandersen *et al.*[109] reported that androgens ameliorated atherosclerosis in castrated male rabbits. Testosterone replacement has been shown to suppress proinflammatory cytokines interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α) and to increase levels of IL-10, which has an antiatherogenic action.[106] Testosterone replacement also produced a modest reduction in diastolic blood pressure of about 5 mmHg in one study.[110]

Testosterone is a coronary vasodilator[111] and can improve ischaemia in men with chronic stable angina.[112] Testosterone acts by a rapid nongenomic mechanism directly on vascular smooth muscle cells.[113] Although research has shown that this is a direct effect of testosterone, additional effect of oestrogens through conversion from testosterone cannot be excluded. The mechanism has been further elucidated to identify that testosterone is an L-channel calcium blocker acting directly at the level of the ion pore in a similar manner to the commonly used dihydropyridine drugs, such as nifedepine, for angina and hypertension.[114] Testosterone has also been reported to act as a systemic vasodilator, acutely improving cardiac index[115] and functional capacity in men with chronic heart failure.[116]

It is thus clear that testosterone has a beneficial effect on several cardiovascular risk factors. Various mechanisms for these effects have been described, and testosterone-mediated improvement in insulin sensitivity could be the major contributory factor.

Conclusions

Clinical observations and experimental data suggest that hypotestosteronaemia is associated with insulin resistance in men. Testosterone treatment inhibits the hyperinsulinaemia and thus may delay the onset of diabetes mellitus in men or even improve glycaemic control. Furthermore, reduction in insulin resistance by testosterone could theoretically reduce cardiovascular events in this group.

There is a link between low levels of androgens and hyperinsulinaemia, but which of the two is the primary event is uncertain. In the human model of Klinefelter's syndrome, where hypogonadism is often associated with impaired glucose tolerance, hypotestosteronaemia is the primary modification followed by hyperinsulinaemia. Lower levels of androgens were found to be associated with increasing levels of waist/hip ratio several years later in men of the Rancho Bernardo survey, suggesting that the lower testosterone levels promoted abdominal obesity. A study in men with metabolic syndrome found that those men with free testosterone in the lower third were 1·72·8 times more likely to have metabolic syndrome.[41] Thus derangements in sex hormones in men could contribute to the prediabetic state that eventually leads to the development of type 2 diabetes.

However, insulin has been known to diminish SHBG production in cultured hepatoma cell lines. Additionally, poorly controlled diabetic men have significantly lower free testosterone levels compared to those with good metabolic status.[117] It is possible that insulin resistance with hyperinsulinaemia may be the primary event followed by decrease in SHBG, which in turn influences testosterone concentration.

Another important factor to consider is the influence of obesity. Many of the previous reported findings of low plasma testosterone concentrations and increased risk of type 2 diabetes are in fact the result of an association between low plasma testosterone and obesity. Tchernof *et al*.[118] found that the relationship between total testosterone and insulin resistance is mediated by obesity and visceral adiposity in nondiabetic men.

Whatever the mechanisms underlying the relationship between androgens and insulin resistance, there is little doubt that further studies in this field are indicated. The prevalence of type 2 diabetes is increasing globally and rises with age. Further research into the role of androgens in insulin resistance is thus important because of the therapeutic implications for men with type 2 diabetes, where insulin resistance is a phenomenon that hampers therapy.

Table 1. Association Between Testosterone and Insulin Levels in Healthy and Diabetic Men

Study	Population	Number	Androgen assayed	Outcome
Simon *et al.*[14] (Telecom study)	Healthy	1292	TT	Inverse relationship between TT and insulin
Barrett-Connor and Khaw[15]	Healthy (12 years follow-up)	1009	TT	Inverse relationship between TT and fasting glucose
Stellato *et al.*[27] (Massachusetts Male Ageing Study)	Healthy (7–10 years follow-up)	1156	TT Free T	↓FT predict type 2 diabetes
Haffner *et al.*[28] (MRFIT)	Healthy who developed diabetes Controls (5 years follow-up)	176 352	TT Free T	New diabetes associated with ↓TT and ↓FT
Oh *et al.*[29] (Rancho Bernardo Study)	Healthy (8 years follow-up)	294	TT Bio T	TT inversely related to fasting/post GTT insulin/glucose ↓TT predict onset of type 2 diabetes
Tibblin *et al.*[30]	Healthy	659	TT Free T	TT/FT inversely correlated with insulin and glucose. ↓TT predict onset of diabetes
Goodman-Gruen and Barrett-Connor[21]	Healthy	775	TT Bio T	↓TT in men with impaired glucose tolerance
Ando *et al.*[16]	Diabetic Healthy	41 47	TT	↓TT in diabetic men
Barrett-Connor *et al.* 1990	Diabetic Healthy	110 875	TT	↓TT in diabetic men. 21% diabetics vs. 13% normal were hypogonadal
Barrett-Connor[18]	Diabetic Healthy	44 88	TT, Bio T DHEAS	↓TT, Bio T and DHEAS in diabetic men
Zietz *et al.*[19]	Diabetic Healthy	155 155	FT	↓FT in diabetic men
Andersson *et al.*[34]	Diabetic Healthy	46 11	TT	↓TT in diabetic men
Dhindsa *et al.*[20]	Diabetic	103	TT FT	33% hypogonadal

DHEAS, dehydroepiandrosterone sulfate; TT, total testosterone; FT, free testosterone; Bio T, bioavailable testosterone.

Table 2. Testosterone Levels in Obese Men

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Study	Population	Number	Measurements	Effect on testosterone
Zumoff *et al.*[45]	Healthy	48	BMI and total body fat	↓ FT and TT
Haffner *et al.*[46]	Healthy	178	BMI, WHR and conicity index	↓ FT and TT
Abate *et al.*[47]	Healthy	24	Total fat, truncal and peripheral	FT correlated with truncal and peripheral
	Mild type 2 diabetes	33	skinfold thickness, WHR	skinfold thickness in nondiabetic men
Seidell *et al.*[48]	Healthy	23	WHR and visceral fat	↓ FT and TT
Phillips[49]	Obese	55	BMI and WHR	↓ FT and TT
Pasquali *et al.*[50]	Obese	52	BMI and WHR	↓ FT and TT with ↑ BMI
	Controls	20		No effect on WHR
Chang *et al.*[52]	Elderly healthy	40	BMI, WHR and skinfold thickness	↓ TT
	Elderly diabetic	20		
	Controls	30		

BMI, body mass index; TT, total testosterone; FT, free testosterone; WHR, waist/hip ratio.

References

1. Reaven, G.M. (1988) Role of insulin resistance in human disease. Diabetes, 37, 1595–1607.
2. Alberti, K.G. & Zimmet, P.Z. (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabetic Medicine, 15, 539–553.
3. Borissova, A.M., Tankova, T., Kamenova, P., Dakovska, L., Kovacheva, R., Kirilov, G., Genov, N., Milcheva, B. & Koev, D. (2002) Effect of hormone replacement therapy on insulin secretion and insulin sensitivity in postmenopausal diabetic women. Gynecological Endocrinology, 16, 67–74.
4. Holmang, A., Larsson, B.M., Brzezinska, Z. & Bjorntorp, P. (1992) The effects of short term testosterone exposure on insulin sensitivity in female rats. American Journal of Physiology, 262, E851–E855.
5. Poretsky, L. & Kalin, M.F. (1987) The gonadotropic function of insulin. Endocrine Reviews, 8, 132–141.
6. Amiel, S.A., Sherwin, R.S., Simonson, D.C., Lauritano, A.A. & Tamborlane, W.V. (1986) Impaired insulin action in puberty: a contributing factor to poor glycemic control in adolescents with diabetes. New England Journal of Medicine, 315, 215–219.
7. UK Prospective Diabetes Study, IV. (1988) Characteristics of newly presenting type 2 diabetic patients. Diabetic Medicine, 5, 154–159.
8. Malkin, C.J., Pugh, P.J., Jones, T.H. & Channer, K.S. (2003) Testosterone for secondary prevention in men with ischaemic heart disease. Quarterly Journal of Medicine, 96, 521–529.
9. Van den Beld, A.W., de Jong, F.H., Grobbee, D.E., Pols, H.A. & Lamberts, S.W. (2000) Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density and body composition in elderly men. Journal of Clinical Endocrinology and Metabolism, 85, 3276–3282.
10. Iannuzzi-Sucich, M., Prestwood, K.M. & Kenny, A.M. (2003) Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 57, M772–M777.
11. Vermeulen, A., Verdonck, L. & Kaufman, J.M. (1999) A critical evaluation of simple

Methods for the estimation of free testosterone in serum. Journal of Clinical Endocrinology and Metabolism, 84, 3666– 3672.
12. Morris, P.D., Malkin, C.J., Channer, K.S. & Jones. T.H. (2004) A mathematical comparison of techniques to predict biologically available testosterone in a cohort of 1072 men. European Journal of Endocrinology, 151, 241–249.
13. Matthews, D.R. & Wallace, T.M. (2002) The assessment of insulin resistance in man. Diabetic Medicine, 19, 527–534.
14. Simon, D., Preziosi, P., Barrett-Connor, E., Roger, M., Saint-Paul, M., Nahoul, K. & Papoz, L. (1992) Interrelation between plasma testosterone and plasma insulin in healthy adult men: the Telecom Study. Diabetologia, 35, 173–177.
15. Barrett-Connor, E. & Khaw, K.T. (1988) Endogenous sex hormones and cardiovascular disease in men. A prospective population-based study. Circulation, 78, 539–545.
16. Ando, S., Rubens, R. & Rottiers, R. (1984) Androgen plasma levels in male diabetics. Journal of Endocrinological Investigation, 7, 21–24.
17. Barrett-Connor, E., Khaw, K.T. & Yen, S.S. (1990) Endogenous sex hormone levels in older men with diabetes mellitus. American Journal of Epidemiology, 132, 895–901.
18. Barrett-Connor, E. (1992) Lower endogenous androgen levels and dyslipidemia in men with non insulin-dependent diabetes mellitus. Annals of Internal Medicine, 117, 807–811.
19. Zietz, B., Cuk, A., Hugl, S., Buttner, R., Straub, R.H., Bauer, B., Daffner, P., Scholmerich, J. & Palitzsch, K. (2000) Association of increased C-peptide serum levels and testosterone in type 2 diabetes. European Journal of Internal Medicine, 11, 322–328.
20. Dhindsa, S., Prabhakar, S., Sethi, M., Bandyopadhyay, A., Chaudhuri, A. & Dandona, P. (2004) Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. Journal of Clinical Endocrinology and Metabolism, 89, 5462–5468.
21. Goodman-Gruen, D. & Barrett-Connor, E. (2000) Sex differences in the association of endogenous sex hormone levels and glucose tolerance status in older men and women. Diabetes Care, 23, 912– 918.
22. Dockery, F., Bulpitt, C.J., Agarwal, S., Donaldson, M. & Rajkumar, C. (2003) Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia. Clinical Science, 104, 195–201.
23. Smith, J.C., Bennett, S., Evans, L.M., Kynaston, H.G., Parmar, M., Mason, M.D., Cockcroft, J.R., Scanlon, M.F. & Davies, J.S. (2001) The effects of induced hypogonadism on arterial stiffness, body composition and metabolic parameters in males with prostate cancer. Journal of Clinical Endocrinology and Metabolism, 86, 4261– 4267.
24. Xu, T., Wang, X., Hou, S., Zhu, J., Zhang, X. & Huang, X. (2002) Effect of surgical castration on risk factors for arteriosclerosis of patients with prostate cancer. Chinese Medical Journal, 115, 1336– 1340.
25. Ferrannini, E., Vichi, S., Beck Nielson, H., Laakso, M., Paolisso, G. & Smith, U. (1996) Insulin action and age. Diabetes, 54, 947–956.
26. Paolisso, G., Scheen, A.S. & Lefebvre, P.J. (1995) Glucose handling, diabetes and aging. Hormone Research, 34, 52–57.
27. Stellato, R.K., Feldman, H.A., Hamdy, O., Horton, E.S. & McKinlay, J.B. (2000) Testosterone, sex hormone binding globulin and the development of type 2 diabetes in middle aged men. Diabetes Care, 23, 490–494.
28. Haffner, S.M., Shaten, J., Stern, M.P., Smith, G.D. & Kuller, L. (1996) Low levels of sex hormone binding globulin and testosterone predict the development of non insulin dependent diabetes mellitus in men. American Journal of Epidemiology, 143, 889–897.
29. Oh, J.Y., Barrett-Connor, E., Wedick, N.M. & Wingard, D.L. (2002) Endogenous sex hormones and the development of type 2 diabetes in older men and women. Diabetes Care, 25, 55–60.
30. Tibblin, G., Adlerberth, A., Lindstedt, G. & Bjorntorp, P. (1996) The pituitary–gonadal axis and health in elderly men: a study of men born in 1913. Diabetes, 45, 1605–1609.
31. Jansson, P.A., Eliasson, B., Lindmark, S. & Eriksson, J.W. (2002) Endocrine abnormalities in healthy first-degree relatives of type 2 diabetes patients – potential role of steroid hormones and leptin in the development of insulin resistance. European

Journal of Clinical Investigation, 32, 172–180.
32. Birkeland, K.I., Hanssen, K.F., Torjesen, P.A. & Vaaler, S. (1993) Level of sex hormone binding globulin is positively correlated with insulin sensitivity in men with type 2 diabetes. Journal of Clinical Endocrinology and Metabolism, 76, 275–278.
33. Simon, D., Charles, M.A., Nahoul, K., Orssaud, G., Kremski, J., Hully, V., Joubert, E., Papoz, L. & Eschwege, E. (1997) Association between plasma total testosterone and cardiovascular risk factors in healthy adult men: The Telecom Study. Journal of Clinical Endocrinology and Metabolism, 82, 682–685.
34. Andersson, B., Marin, P., Lissner, L., Vermeulen, A. & Bjorntorp, P. (1994) Testosterone concentrations in women and men with NIDDM. Diabetes Care, 17, 405–411.
35. Endre, T., Mattiasson, I., Berglund, G. & Hulthen, U.L. (1996) Low testosterone and insulin resistance in hypertension prone men. Journal of Human Hypertension, 10, 755–761.
36. Plymate, S.R., Matej, L.A., Jones, R.E. & Friedl, K.E. (1988) Inhibition of sex hormone binding globulin production in the human hepatoma (Hep G2) cell line by insulin and prolactin. Journal of Clinical Endocrinology and Metabolism, 67, 460–464.
37. Peiris, A.N., Stagner, J.I., Plymate, S.R., Vogel, R.L., Heck, M. & Samols, E. (1993) Relationship of insulin secretory pulses to sex hormone binding globulin in normal men. Journal of Clinical Endocrinology and Metabolism, 76, 279–282.
38. Pasquali, R., Casimirri, F., Iasio, R.D., Mesini, P., Boschi, S., Chierici, R., Flamia, R., Biscotti, M. & Vicennati, V. (1995) Insulin regulates testosterone and sex hormone-binding globulin concentrations in adult normal weight and obese men. Journal of Clinical Endocrinology and Metabolism, 80, 654–658.
39. Ebeling, P., Stenman, U.H., Seppala, M. & Koivisto, V.A. (1995) Acute hyperinsulinaemia, androgen homeostasis and insulin sensitivity in healthy men. Journal of Endocrinology, 146, 63–69.
40. Nestler, J.E. (1993) Sex hormone-binding globulin: a marker for hyperinsulinemia and/or insulin resistance? Journal of Clinical Endocrinology and Metabolism, 76, 273–274.
41. Laaksonen, D.E., Niskanen, L., Punnonen, K., Nyyssonen, K., Tuomainen, T.P., Salonen, R., Rauramaa, R. & Salonen, J.T. (2003) Sex hormones, inflammation and the metabolic syndrome. European Journal of Endocrinology, 149, 601–608.
42. Marin, P. & Arver, S. (1998) Androgens and abdominal obesity. Bailliere's Clinical Endocrinology and Metabolism, 12, 441–451.
43. Vermeulen, A. (1996) Decreased androgen levels and obesity. Annals of Medicine, 28, 13–15.
44. Couillard, C., Gagnon, J., Bergeron, J., Leon, A.S., Rao, D.C., Skinner, J.S., Wilmore, J.H., Despres, J.P. & Bouchard, C. (2000) Contribution of body fatness and adipose tissue distribution to the age variation in plasma steroid hormone concentrations in men: the HERITAGE Family Study. Journal of Clinical Endocrinology and Metabolism, 85, 1026–1031.
45. Zumoff, B., Strain, G.W., Miller, L.K., Rosner, W., Senie, R., Seres, D.S. & Rosenfeld, R.S. (1990) Plasma free and non sex-hormonebinding- globulin-bound testosterone are decreased in obese men in proportion to their degree of obesity. Journal of Clinical Endocrinology and Metabolism, 71, 929–931.
46. Haffner, S.M., Valdez, R.A., Stern, M.P. & Katz, M.S. (1993) Obesity, body fat distribution and sex hormones in men. International Journal of Obesity, 17, 643–649.
47. Abate, N., Haffner, S.M., Garg, A., Peshock, R.M. & Grundy, S.M. (2002) Sex steroid hormones, upper body obesity and insulin resistance. Journal of Clinical Endocrinology and Metabolism, 87, 4522–4527.
48. Seidell, J.C., Bjorntorp, P., Sjostrom, L., Kvist, H. & Sannerstedt, R. (1990) Visceral fat accumulation in men is positively associated with insulin, glucose and C-peptide levels but negatively with testosterone levels. Metabolism, 39, 897–901.
49. Phillips, G.B. (1993) Relationship between serum sex hormones and the glucose–insulin–lipid defect in men with obesity. Metabolism, 42, 116–120.
50. Pasquali, R., Casimirri, F., Cantobelli, S., Melchionda, N., Morselli Labate, A.M., Fabbri,

R., Capelli, M. & Bortoluzzi, L. (1991) Effect of obesity and body fat distribution on sex hormones and insulin in men. Metabolism, 40, 101–104.
51. Vermeulen, A., Goemaere, S. & Kaufman, J.M. (1999) Testosterone, body composition and aging. Journal of Clinical Investigation, 22, 110–116.
52. Chang, T.C., Tung, C.C. & Hsiao, Y.L. (1994) Hormonal changes in elderly men with non insulin dependent diabetes mellitus and the hormonal relationships to abdominal adiposity. Gerontology, 40, 260–267.
53. Strain, G.W., Zumoff, B., Miller, L.K., Rosner, W., Levit, C., Kalin, M., Hershcopf, R.J. & Rosenfeld, R.S. (1988) Effect of massive weight loss on hypothalamic–pituitary–gonadal function in obese men. Journal of Clinical Endocrinology and Metabolism, 66, 1019–1023.
54. Zumoff, B. (1988) Hormonal abnormalities in obesity. Acta Medica Scandinavica, 723, 153–160.
55. Schneider, G., Kirschner, M.A., Berkowitz, R. & Ertel, N.H. (1979) Increased estrogen production in obese men. Journal of Clinical Endocrinology and Metabolism, 48, 633–638.
56. Phillips, G.B., Jing, T. & Heymsfield, S.B. (2003) Relationships in men of sex hormones, insulin, adiposity and risk factors for myocardial infarction. Metabolism, 52, 784–790.
57. Small, M., MacRury, S., Beastall, G.H. & MacCuish, A.C. (1987) Oestradiol levels in diabetic men with and without previous myocardial infarction. Quarterly Journal of Medicine, 64, 617– 623.
58. Zumoff, B., Miller, L.K. & Strain, G.W. (2003) Reversal of the hypogonadotropic hypogonadism of obese men by administration of the aromatase inhibitor testolactone. Metabolism, 52, 1126–1128.
59. Haffner, S.M., Karhapaa, P., Mykkanen, L. & Laakso, M. (1994) Insulin resistance, body fat distribution and sex hormones in men. Diabetes, 43, 212–219.
60. Polderman, K.H., Gooren, L.J., Asscheman, H., Bakker, A. & Heine, R.J. (1994) Induction of insulin resistance by androgens and estrogens. Journal of Clinical Endocrinology and Metabolism, 79, 265–271.
61. Smith, E.P., Boyd, J., Frank, G.R., Takahashi, H., Cohen, R.M., Specker, B., Williams, T.C., Lubahn, D.B. & Korach, K.S. (1994) Estrogen resistance caused by a mutation in the estrogen receptor gene in a man. New England Journal of Medicine, 331, 1056–1061.
62. Herrmann, B.L., Saller, B., Janssen, O.E., Gocke, P., Bockisch, A., Sperling, H., Mann, K. & Broecker, M. (2002) Impact of estrogen replacement therapy in a male with congenital aromatase deficiency caused by a novel mutation in the CY19 gene. Journal of Clinical Endocrinology and Metabolism, 87, 5476–5484.
63. Bjorntorp, P. (1996) The regulation of adipose tissue distribution in humans. International Journal of Obesity and Related Metabolic Disorders, 20, 291–302.
64. Marin, P., Oden, B. & Bjorntorp, P. (1995) Assimilation and mobilization of triglycerides in subcutaneous abdominal and femoral adipose tissue in vivo in men: effects of androgens. Journal of Clinical Endocrinology and Metabolism, 80, 239–243.
65. Tsai, E.C., Boyko, E.J., Leonetti, D.L. & Fujimoto, W.Y. (2000) Low serum testosterone level as a predictor of increased visceral fat in Japanese-American men. International Journal of Obesity and Related Metabolic Disorders, 24, 485–491.
66. Cohen, P.G. (1999) The hypogonadal–obesity cycle. Medical Hypotheses, 52, 49–51.
67. Saffele, J.K.V., Goemaere, S. & Bacquer, D.D. (1999) Serum leptin levels in healthy aging males: are decreased serum testosterone and increased adiposity in elderly men the consequence of leptin deficiency? Clinical Endocrinology, 55, 81–88.
68. Luukkaa, V., Pesonen, U., Huhtaniemi, I., Lehtonen, A., Tilvis, R., Tuomilehto, J., Koulu, M. & Huupponen, R. (1998) Inverse correlation between serum testosterone and leptin in men. Journal of Clinical Endocrinology and Metabolism, 83, 3243–3246.
69. Tan, R.S. & Pu, S.J. (2002) Impact of obesity on hypogonadism in the andropause. International Journal of Andrology, 25, 195–201.
70. Marin, P., Krotkiewski, M. & Bjorntorp, P. (1992) Androgen treatment of middle-aged,

obese men: effects on metabolism, muscle and adipose tissues. European Journal of Medicine, 1, 329–336.
71. Holmang, A. & Bjorntorp, P. (1992) The effects of testosterone on insulin sensitivity in male rats. Acta Physiologica Scandinavica, 146, 505–510.
72. Tyagi, A., Rajalakshmi, M., Jeyaraj, D.A., Sharma, R.S. & Bajaj, J.S. (1999) Effects of long-term administration of testosterone enanthate on glucose metabolism in rhesus monkeys. Contraception, 59, 333–337.
73. Centol, I., Lopez-Blanco, F., Deniz, A., Benitez, L., Marrero- Arencibia, I., Fanjul, L. & Ruiz de Galarreta, C.M. (1988) Serum androgen levels after streptozotocin administration in the male rat. Revista Espanola de Fisiologia, 44, 31–34.
74. Blanco, F.L., Fanjul, L.F. & Ruiz de Galarreta, C.M. (1981) The effect of insulin and luteinizing hormone treatment on serum concentrations of testosterone and dihydrotestosterone and testicular 3β hydroxysteroid-dehydrogenase activity in intact and hypophysectomized rats. Endocrinology, 109, 1248–1253.
75. Charreau, E.H., Calvo, J.C., Tesone, M., Beille de Souza Valle, L. & Barano, J.L. (1978) Insulin regulation of Leydig cell luteinizing hormone receptors. Journal of Biological Chemistry, 253, 2504–2506.
76. Thaddea, S. & Hampe, H. (1940) The effect of the sex hormones on metabolism in diabetes of late onset. Klinicheskaia Meditsina, 137, 760.
77. Landon, J., Wynn, V. & Cooke, J.N.C. (1962) Effects of anabolic steroid methandienone on carbohydrate metabolism in man. Metabolism, 2, 501.
78. Godsland, I.F., Shennan, N.M. & Wynn, V. (1986) Insulin action and dynamics modelled in patients taking the anabolic steroid methandienone. Clinical Science, 71, 665–673.
79. Woodward, T., Burgen, G.A., Kitabchi, A.E. & Wilimas, J.A. (1981) Glucose intolerance and insulin resistance in aplastic anemia treated with oxymethalone. Journal of Clinical Endocrinology and Metabolism, 53, 905–908.
80. Cohen, J.C. & Hickman, R. (1987) Insulin resistance and diminished glucose tolerance in powerlifters ingesting anabolic steroids. Journal of Clinical Endocrinology and Metabolism, 64, 960–963.
81. Hobbs, C.J., Jones, R.E. & Plymate, S.R. (1996) Nandrolone, a 19- nortestosterone, enhances insulin independent glucose uptake in normal men. Journal of Clinical Endocrinology and Metabolism, 81, 1582–1585.
82. Singh, A.B., Hsia, S., Alaupovic, P., Sinha-Hikim, I., Woodhouse, L., Buchanan, T.A., Shen, R., Bross, R., Berman, N. & Bhasin, S. (2002) The effects of varying doses of testosterone on insulin sensitivity, plasma lipids, apolipoproteins and C-reactive protein in healthy young men. Journal of Clinical Endocrinology and Metabolism, 87, 136–143.
83. Friedl, K.E., Jones, R.E., Hannan, C.J. Jr & Plymate, S.R. (1989) The administration of pharmacological doses of testosterone or 19- nortestosterone to normal men is not associated with increased insulin secretion or impaired glucose tolerance. Journal of Clinical Endocrinology and Metabolism, 68, 971–975.
84. Simon, D., Charles, M.A., Lahlou, N., Nahoul, K., Oppert, J.M., Gouault-Heilmann, M., Lemort, N., Thibult, N., Joubert, E., Balkau, B. & Eschwege, E. (2001) Androgen therapy improves insulin sensitivity and decreases leptin level in healthy adult men with low plasma total testosterone: a 3-month randomized placebocontrolled trial. Diabetes Care, 24, 2149–2151.
85. Tripathy, D., Shah, P., Lakshmy, R. & Reddy, K.S. (1998) Effect of testosterone replacement on whole body glucose utilisation and other cardiovascular risk factors in males with idiopathic hypogonadotrophic hypogonadism. Hormone and Metabolic Research, 30, 642–645.
86. Sattler, F.R., Schroeder, E.T., Dube, M.P., Jaque, S.V., Martinez, C., Blanche, P.J., Azen, S. & Krauss, R.M. (2002) Metabolic effects of nandrolone decanoate and resistance training in men with HIV. American Journal of Physiology, Endocrinology and Metabolism, 283, 1214–1222.
87. Marin, P., Holmang, S., Jonsson, L., Sjostrom, L., Kvist, H., Holm, G., Lindstedt, G. & Bjorntorp, P. (1992) The effects of testosterone treatment on body composition and

metabolism in middle-aged obese men. International Journal of Obesity and Related Metabolic Disorders, 16, 991–997.
88. Boyanov, M.A., Boneva, Z. & Christov, V.G. (2003) Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. Aging Male, 6, 1–7.
89. Corrales, J.J., Burgo, R.M., Garca-Berrocal, B., Almeida, M., Alberca, I., Gonzalez-Buitrago, J.M., Orfa, A. & Miralles, J.M. (2004) Partial androgen deficiency in aging type 2 diabetic men and its relationship to glycemic control. Metabolism, 53, 666–672.
90. Vermeulen, A. (1995) Dehydroepiandrosterone and ageing. Annals of the New York Academy of Sciences, 74, 121–127.
91. Nestler, J.E., McClanahan, M.A., Clore, J.N. & Blackard, W.G. (1992) Insulin inhibits adrenal 17,20-lyase activity in man. Journal of Clinical Endocrinology and Metabolism, 74, 362–367.
92. Jakubowicz, D.J., Beer, N.A., Beer, R.M. & Nestler, J.E. (1995) Disparate effects of weight reduction by diet on serum dehydroepiandrosterone sulfate levels in obese men and women. Journal of Clinical Endocrinology and Metabolism, 80, 3373–3376.
93. Ravaglia, G., Forti, P., Maioli, F., Sacchetti, L., Nativio, V., Scali, C.R., Mariani, E., Zanardi, V., Stefanini, A. & Macini, P.L. (2002) Dehydroepiandrosterone- sulfate serum levels and common age-related diseases: Results from a cross-sectional Italian study of a general elderly population. Experimental Gerontology, 37, 701–712.
94. Usiskin, K.S., Butterworth, S., Clore, J.N., Arad, Y., Ginsberg, H.N., Blackard, W.G. & Nestler, J.E. (1990) Lack of effect of dehydroepiandrosterone in obese men. International Journal of Obesity, 14, 457–463.
95. Nestler, J.E., Barlascini, C.O., Clore, J.N. & Blackard, W.G. (1988) Dehydroepiandrosterone reduces serum low density lipoprotein levels and body fat but does not alter insulin sensitivity in normal men. Journal of Clinical Endocrinology and Metabolism, 66, 57–61.
96. Kawano, H., Yasue, H., Kitagawa, A., Hirai, N., Yoshida, T., Soejima, H., Miyamoto, S., Nakano, M. & Ogawa, H. (2003) Dehydroepiandrosterone supplementation improves endothelial function and insulin sensitivity in men. Journal of Clinical Endocrinology and Metabolism, 88, 3190–3195.
97. Jedrzejuk, D., Medras, M., Milewicz, A. & Demissie, M. (2003) Dehydroepiandrosterone replacement in healthy men with age related decline of DHEA-S: effects on fat distribution, insulin sensitivity and lipid metabolism. Aging Male, 6, 151–156.
98. Rizza, R.A. (2000) Androgen effect on insulin action and glucose metabolism. Mayo Clinic, 75, S61–S64.
99. Laakso, M. (2002) Insulin resistance and cardiovascular disease. British Journal of Diabetes and Vascular Disease, 2,S9–S11.
100. Ruige, J.B., Assendelft, W.J.J., Dekker, J.M., Kostense, P.J., Heine, R.J. & Bouter, L.M. (1998) Insulin and risk of cardiovascular disease. Circulation, 97, 996–1001.
101. Rayner, M., Mockford, C. & Boaz, A. (1998) British Heart Foundation Statistics Database, British Heart Foundation Education Department, London.
102. Liu, P.Y., Death, A.K. & Handelsman, D.J. (2003) Androgens and cardiovascular disease. Endocrine Reviews, 24, 313–340.
103. Wu, F.C.W. & Eckardstein, A.V. (2003) Androgens and coronary artery disease. Endocrine Reviews, 24, 183–217.
104. English, K.M., Mandour, O., Steeds, R.P., Diver, M.J., Jones, T.H. & Channer, K.S. (2000) Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. European Heart Journal, 21, 890–894.
105. Pugh, P.J., Morris, P.D., Hall, J., Malkin, C.J., Asif, S., Jones, R.D., Channer, K.S. & Jones, T.H. (2003) High prevalence of low testosterone levels in men with coronary heart disease and an association with hypertension and obesity. Endocrine Abstracts, 5, P225.
106. Malkin, C.J., Pugh, P.J., Kapoor, D., Jones, R.D., Channer, K.S. & Jones, T.H. (2004) The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. Journal of Clinical Endocrinology and Metabolism,

89, 3313– 3318.
107. Van Pottelbergh, I., Braeckman, L., De Bacquer, D., De Backer, G. & Kaufman, J.M. (2003) Differential contribution of testosterone and estradiol in the determination of cholesterol and lipoprotein profile in healthy middle-aged men. Atherosclerosis, 166, 95–102.
108. Anderson, R.A., Ludlam, C.A. & Wu, F.C. (1995) Haemostatic effects of supraphysiological levels of testosterone in normal men. Thrombosis and Haemostasis, 74, 693–697.
109. Alexandersen, P., Haarbo, J., Byrjalsen, I., Lawaetz, H. & Christiansen, C. (1999) Natural androgens inhibit male atherosclerosis. Circulation Research, 84, 813–819.
110. Rebuffe-Scrive, M., Marin, P. & Bjorntorp. (1991) Effect of testosterone on abdominal adipose tissue in men. International Journal of Obesity, 15, 791–795.
111. Webb, C.M., McNeill, J.G., Hayward, C.S., de Zeigler, D. & Collins, P. (1999) Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. Circulation, 100, 1690–1696.
112. English, K.M., Steeds, R.P., Jones, T.H., Diver, M.J. & Channer, K.S. (2000) Low dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina. Circulation, 102, 1906–1911.
113. Jones, R.D., Pugh, P.J., Jones, T.H. & Channer, K.S. (2003) The vasodilatory action of testosterone: a potassium-channel opening or a calcium antagonistic action? British Journal of Pharmacology, 138, 733–744.
114. Scragg, J.L., Jones, R.D., Channer, K.S., Jones, T.H. & Peers, C. (2004) Testosterone is a potent inhibitor of 1-type calcium channels. Biochemical and Biophysical Research Communications, 318, 503– 506.
115. Pugh, P.J., Jones, T.H. & Channer, K.S. (2003) Acute haemodynamic effects of testosterone in men with chronic heart failure. European Heart Journal, 24, 909–915.
116. Pugh, P.J., Jones, R.D., West, J.N., Jones, T.H. & Channer, K.S. (2004) Testosterone treatment for men with chronic heart failure. Heart, 90, 446–447.
117. Fushimi, H., Horie, H., Inoue, T., Kameyama, M., Kanao, K., Ishihara, S., Tsujimura, T., Nunotani, H., Minami, T. & Okazaki, Y. (1989) Low testosterone levels in diabetic men and animals: a possible role in testicular impotence. Diabetes Research and Clinical Practice, 15, 297–301.
118. Tchernof, A., Despres, J.P., Dupont, A., Belanger, A., Nadeau, A., Prud'homme, D., Moorjani, S., Lupien, P.J. & Labrie, F. (1995) Relation of steroid hormones to glucose tolerance and plasma insulin levels in men. Diabetes Care, 18, 292–299.

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