The Dark Side of Testosterone Deficiency: II. Type 2 Diabetes & Insulin Resistance

Short Running Title: Testosterone deficiency, Insulin Resistance & Type 2 Diabetes

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Abstract:

A considerable body of evidence exists suggesting a link between reduced testosterone plasma levels, type 2 diabetes (T2D) and insulin resistance (IR). Hypogonadal men are at higher risk for type-2 diabetes. Here we evaluate the relationships between testosterone, metabolic syndrome (MetS), T2D, and IR and discuss the relationships between androgen deficiency and these factors, especially as it ultimately relates to the development of cardiovascular disease (CVD) and erectile dysfunction (ED). Thus, a comprehensive literature search was carried out using PubMed and relevant articles pertinent to androgen deficiency, T2D, IR, MetS, and ED were reviewed and discussed. Low testosterone precedes elevated fasting insulin, glucose, and hemoglobin A1c (HbA1C) values and may even predict the onset of diabetes. Treatment of prostate cancer patients with surgical or medical castration exacerbates IR and glycemic control, strengthening the link between testosterone deficiency and onset of type-2 diabetes and IR. Androgen therapy of hypogonadal men improves insulin sensitivity, fasting glucose and Hemoglobin A1c levels. We suggest that androgen deficiency is associated with IR, T2D and MetS, and increased visceral fat deposition, which serves as an endocrine organ, producing inflammatory cytokines thus promoting endothelial dysfunction and vascular disease.

Introduction

Androgen deficiency has recently come to the forefront of the medical literature, after being ignored for decades. The prevalence of hypogonadism is greater than previously thought. Important associations are being developed and confirmed in the literature between androgen deficiency and metabolic disorders. The “dark side of testosterone deficiency” extends beyond the symptoms of low testosterone. More specifically, there is an important health impact related to MetS, IR, T2D and ultimately vascular disease (VD) and erectile dysfunction (ED). Low concentrations of testosterone are linked with IR and implicated in hyperglycemia, hypertension, dyslipidemia and in an increased risk of vascular disease [Fukui et al 2007; 2008; Selvin et al 2007; Kappor et al 2006; 2007; Corona et al 2006; Pitteloud et al 2005; Rhoden et al 2005; Simon et al 1997; Dhindsa et al 2004; Oh et al 2002; Stellato et al 2000]. Because of the known epidemic of obesity, and the increasing prevalence of T2D, and their vascular consequences and in view of the increasing evidence linking these pathologies to androgen deficiency, we believe that review and discussion of this topic is very timely. In a previous review (Traish et al., 2008)
we discussed the relationship between testosterone deficiency and MetS and their links to erectile dysfunction. The aim of this mini-review is to explore the relationships between androgen deficiency and IR, T2D and their relationship to endothelial dysfunction vascular disease and erectile dysfunction.

I. Androgen Deficiency and the Link to Glycemic Control, Insulin Resistance and Type-2 Diabetes

It has been well recognized that diabetes and IR are two important components of the metabolic syndrome [Figure 1]. The prevalence of T2D has increased dramatically and it is estimated that the number of individuals diagnosed with diabetes in the US has grown from approximately six million in 1980 to an astounding 15 million by 2004 (Steinbrook et al, 2006). This is mirrored by increased prevalence in overweight and obesity, and a recent analysis found that this trend has been emerging during the past five decades (Parikh, 2007). More disturbing is the fact that the metabolic syndrome (MetS), of which IR is a key component, is showing 4.5% prevalence in adolescents (Ford et al 2008).

I. a. Is there a relationship between reduced T levels and T2D?

Several studies have suggested that men with low T are at a greater risk of developing T2D, and may even predict the future onset of diabetes (Oh et al, 2002; Shores et al 2006; Selvin et al 2007 Stellato et al, 2000; Rhoden et al, 2005 a, b; Haffner et al 1997). A systematic review of 43 studies comprising 6427 men by Ding et al (2006) suggested that higher T plasma levels were associated with lower risk of T2D and vice versa. Similarly, Haffner et al [1996] demonstrated that low SHBG and testosterone predict higher glucose and insulin levels and increased obesity. Low plasma testosterone (T) levels are commonly observed in men with T2D and IR (Grossman et al 2008). Stellato et al [2000] reported findings from the Massachusetts Male Aging Study in which low levels of T and SHBG were thought to play some role in the development of IR and subsequently T2D. Fukui et al [2007] demonstrated that serum T levels are lower in a large number of Japanese patients with type-2 diabetes when compared to healthy men and suggested that testosterone supplementation in hypogonadal men could decrease IR and atherosclerosis. These observations suggest that androgen deficiency plays a central role in the various pathologies encompassing the metabolic syndrome components, including T2D, IR, obesity and ED [Figure 2]
I. b. Is there a relationship between reduced T levels and IR?

Other observational studies have confirmed a significant inverse relationship between total T and IR in men (Simon et al, 1997, Andersson et al, 1994; Pitteloud et al, 2005; Osuna et al, 2006), with a stronger correlation with free T than total T (Rhoden et al, 2005 a, b; Basaria et al, 2006). Grossmann et al., (2008) found that 43% of men with T2D have reduced total T, while 57% had reduced calculated free T. In type 1 diabetes, 7% had reduced total T, but 20% had low calculated free T, with similar incidence after age-adjustments. Simon et al (1997) reported that total T concentrations were significantly associated with fasting plasma insulin, two-hour plasma insulin levels, and glucose levels. Lower total T led to elevated insulin values and the authors hypothesized that body fat distribution might influence this relationship. Osuna et al (2006) correlated waist circumference (WC), body mass index (BMI), insulin, and homeostatic model assessment HOMA\textsubscript{IR} to T levels and, in each case, found a significant negative correlation. Taken together, these findings raise the possibility that T may have a protective function against diabetes in men.

I. c. Bidirectional relationship between hypogonadism, T2D and IR

Hypogonadism and type 2-diabetes are often diagnosed together in the same patient (Dhindsa et al, 2004; Kapoor et al, 2007). Hypogonadism was more prevalent in diabetic patients with increasing BMI, or those who are severely obese (BMI>40). In a large cohort of more than 1,100 men Corona et al (2007) showed that hypogonadism had a better correlation with visceral fat than diabetes. Dhindsa et al (2004) also showed that above the age of 50, with each successive decade (until 79), the prevalence of hypogonadism increased, with 55% of individuals in the 70-79 age group having hypogonadism as compared to 24% in the 50-59 age group. Pasquali et al (1991; 1997) found that individuals with T2D are often obese – and obesity may be a major risk factor for significantly lower free and total T and elevated fasting insulin levels compared to non-obese male subjects. The authors (Pasquali et al 1991; 1997) further elucidated these relationships by inducing glucose abnormalities with diazoxide in healthy human subjects and in men with obesity but no diabetes (Pasquali, et al 1995). He found that insulin was capable of stimulating T production \textit{in vivo} and simultaneously reducing SHBG concentrations in both normal weight and obese men. Isidori et al (2000) confirmed that
individuals with a BMI>30 had significantly higher fasting plasma insulin, fasting IR index, C-peptide, and lower serum T than subjects with a BMI<30. Blouin et al (2005) suggested that body fat distribution may influence the relationship between low total T and elevated insulin levels. Pitteloud et al (2005b), however, found body composition to have no effect on the relationship between serum T concentrations and insulin sensitivity, as compared to BMI, percent body fat, and waist to hip ratio (WHR).

In a large study, Laaksonen et al (2003) evaluated the characteristics of 1,896 non-diabetic middle-aged men according to the presence of the MetS (Kuopio Ischaemic Heart Disease Risk Factor Study KIHD). The authors found that individuals with MetS had elevated fasting insulin levels as well as decreased total T when compared with controls, a finding that is relevant in the pathogenesis of T2D. Furthermore, Muller et al (2005) concluded that elevated T and SHBG led to increased insulin sensitivity and reduced risk of MetS. Hypogonadism was a stronger risk factor for the development of elevated insulin and glucose levels compared to overweight/obesity (Pagotto et al 2003). This is substantiated by lower total T and free T levels in hypogonal men than overweight/obese men, and consequently, exhibited higher fasting insulin, HOMA, and fasting glucose values.

II. Androgen Deprivation Therapy (ADT) and the Link to Insulin Resistance, Glycemic Control, and Type 2 Diabetes

A considerable body of clinical evidence exists suggesting that acute induced hypogonadism has the same effects as a gradual decline in testicular function. Androgen deprivation therapy (ADT) increases IR, alters glycemic control and may contribute to development of T2D.

II. a. Relationship between ADT and onset of T2D

Lage (2007) found that the estimated risk of incident diabetes associated with receiving ADT was 1.36, and that these patients were more likely to develop diabetes within one year, even when correcting for the factors of older age, poorer health and increased likelihood of other medical co-factors, especially hypertension. Haider et al (2007) managed diabetic prostate cancer patients with ADT and kept their diabetes under control by administration of insulin. Upon ADT, insulin requirement increased progressively. The authors suggested that androgen deprivation
has a negative impact on IR and glycemic control in prostate cancer patients (Haider et al 2007).
In large study of 396 men over five years, Derweesh (2007) included 77 men with pre-existing diabetes. The diabetic men had an increase in HbA1C of > 10% was seen in 20%, while fasting glucose levels elevated to this magnitude in 29%. In the remaining men, there was a 4.65-fold chance of developing T2D when the BMI was > 30%. Taken together, these data strongly suggest long-term ADT produces unfavorable hormonal and metabolic profiles, including IR, hyperglycemia, independent of age and BMI and increase the risk of T2D.

II. b. Interplay between androgen deficiency and insulin sensitivity

Recently, Yialamas et al (2007) demonstrated that acute sex steroid withdrawal for two weeks reduced insulin sensitivity in young healthy men with idiopathic hypogonadotrophic hypogonadism (IHH), suggesting that T modulates insulin sensitivity directly and further suggesting that this pathway is not mediated by changes in body composition. On the other hand, Chen et al (2006), argues that androgen deficiency is a consequence of, and is not a cause of, poor metabolic status. Thus, it is possible that such interplay is bidirectional. Smith et al (2001) investigated the effects of ADT on insulin levels in patients with prostate cancer. GnRH agonist treatment in men for 12 weeks elevated HbA1c and decreased insulin sensitivity index and HOMA$_{IR}$ measurements (Smith et al, 2001). The authors reported that patients treated with GnRH agonist for three months had significantly elevated fasting insulin levels, at one and three month time points when compared to baseline.

II. c. Relationship between androgen deficiency and insulin levels

Change in insulin levels also positively correlated with changes in fat mass. T suppression led to hyperinsulinaemia (Dockery et al (2003) and ADT produced elevated fasting glucose levels (Nishiyama et al, 2005). Yannucci et al (2006) demonstrated that the effect of ADT on change from baseline in HbA1c levels is independent of statin therapy, assessed after 85 days of treatment. Patients treated with ADT had elevated glucose and increased IR, as measured by HOMA index levels; these findings were independent of age and BMI. Basaria et al (2006) reported that even after adjusting for age and BMI, patients receiving ADT had significantly higher fasting insulin levels than patients with prostatic cancer who did not receive ADT and healthy controls. These findings suggest that the ADT, rather than age or BMI, is
directly responsible for elevated fasting insulin levels. Additionally, Basaria et al (2006) found a significant negative correlation between fasting glucose, fasting insulin, and HOMA levels in relation to total and free T in these three groups of men. The proportion of men with fasting glucose $\geq 126\text{mg/dL}$, as defined by the American Diabetes Association for diagnosis of type 2 D, in patients with prostate cancer on ADT, or in patients with prostate cancer without ADT, or healthy controls, was 44%, 12%, and 11% respectively. Shahani et al (2008) suggested that ADT produces early metabolic changes (3-6 months) associated with development of hyperinsulinemia and that long-term ($\geq 12$ months) ADT results in higher prevalence of diabetes and metabolic syndrome when compared to controls.

**III. Androgen Therapy and the Link to Glycemic Control, Insulin Resistance and Type-2 Diabetes**

T treatment in hypogonadal men reduces fasting insulin and IR by HOMA. Increased insulin sensitivity (measured as a change in glucose disposal rate) is negatively and significantly correlated with baseline T levels (Pagotto et al, 2003; Marin et al 1992, 1993, 1995, 1996). Boyanov et al (2003) also showed that men with T2D receiving three months of T supplementation have decreased fasting glucose, postprandial glucose, mean daily glucose, and HbA1c values, when compared to baseline. Kapoor et al (2006) reported that testosterone treatment in insulin-dependent patients reduced their insulin dosages by a mean of seven units. Naharci et al (2007) demonstrated that long term T-therapy improved insulin sensitivity and reduced body fat mass. Naharci et al (2007) also showed that the higher the delta in T, the greater the insulin sensitivity. This is consistent with Pitteloud et al (2005 a, b) observations in which they demonstrated such “dose relationship”. This is particularly important since it points to the need to achieve high normal T levels rather than low normal T levels. Apart from testosterone’s effect on insulin sensitivity, it may have a direct effect on the pancreas and the beta cell Morimoto et al (2005). Early apoptotic damage induced by streptozotocin in castrated animals was reversed by testosterone replacement, suggesting a protective effect on the pancreas. More work is needed to determine if testosterone replacement in hypogonadal men will ameliorate the parameters of type 2 diabetes, IR and MetS, as suggested above, and in doing so reduce cardiovascular risks.
IV. Insulin Resistance, Glycemic Control, Type 2 Diabetes, and Erectile Dysfunction (ED)

IV. a. The relationship between T2D and ED

Several studies have investigated the relationship between diabetes and erectile dysfunction. In a survey of 2,869 men, Ponholzer et al (2005) found that having diabetes increases the odds of having ED. The authors found that patients with diabetes were at the greatest risk for developing ED (with an odds ratio of 3) versus patients having other conditions such as hyperlipidemia (OR 2.29), hypertension (OR 2.05), psychological stress (OR 1.68) or low physical activity (OR 1.35). Odds ratios (OR) for ED were also calculated in population-based studies in Germany (Braun et al, 2000), Italy (Parazzini et al, 2000), and Turkey (Akkus et al, 2002), with data from all three countries showing that patients with diabetes having a higher OR than those with hypertension (and cardiac disease in Turkey). Sun et al (2006) found that 20.0% of men with ED had diabetes mellitus and that 7.5% of the non-ED group of men had diabetes. The authors adjusted for census regions and seven co-morbidities and report that ED is associated with diabetes especially in young men, with the highest odds occurring in the 26-35 age range. They suggested using ED as a clinical marker for the onset of diabetes in men. Giuliano et al (2004) found that the prevalence of ED in patients with diabetes was 70.6% in a survey of 7,689 men, while Shabsigh et al (2005) found, conversely, that 25% of patients with severe ED had diabetes in the cross-national survey on men’s health issues. Bodie et al (2003) assessed laboratory abnormalities for 3,547 men with ED and found that a large number of men presenting with a primary complaint of ED had elevated HbA1c levels. Additionally, Yamasaki et al (2004) measured the prevalence of ED (defined by IIEF<18) in Japanese men with T2D and found that compared to healthy controls (20% ED prevalence), age-matched diabetics had three times this prevalence of ED (60%). Taken together, the aforementioned studies suggest that a strong link exists between diabetes and ED, with either condition being a risk factor for the other.

IV. b. The relationship between T2D, ED and endothelial dysfunction

Peripheral vascular disease caused by endothelial dysfunction is common in both diabetes and erectile dysfunction. Cell-derived micro-particles are involved in endothelial dysfunction, and Esposito et al (2007) showed that these particles correlated with erectile dysfunction in diabetic men. HbA1c levels have been shown to increase with the severity of ED (Rhoden et al,
2005 a, b) and was found to be an independent predictor of the erectile function score in 78 men with T2D (Romeo et al, 2000). Besides usually having elevated HbA1c levels, compared to non-diabetics, diabetics typically have a higher incidence of organic ED (Corona et al, 2004). These authors found that in 1,027 consecutive patients presenting with ED, those with diabetes mellitus, compared to those with impaired or normal fasting glucose, had significantly elevated BMI, hypertension, HDL-c, cardiovascular disease, and triglyceride levels, suggesting that there are multiple metabolic parameters for ED in men with diabetes. Lindmark et al (2006) found that glucotoxicity was associated with increased IR but also increased levels of adipokines like TNF-α and CRP, which may contribute to the IR. Weyer et al (2001) showed an association between reduced levels of adiponectin in type-2 diabetes and obesity with IR. The many factors that are associated with cardiovascular disease are also active in ED. These can include advanced glycation end products, prothrombotic states, hypertension and dyslipidemias (Rader et al 2007).

Corona et al (2006) found a relationship between the prevalence of hypogonadism in 1,027 diabetic and non-diabetic patients presenting with ED, with diabetics having a significantly greater prevalence of hypogonadism, especially in the sixth decade of life compared to non-diabetics. Taking into account all ages, diabetics had a significantly increased prevalence of hypogonadism than did non-diabetics and hypogonadism has been discussed earlier as a risk factor for ED. Corona et al (2006) also investigated the presence of hypogonadism in 1200 men with ED and 16% had diabetes mellitus. Hypogonadism was found in 24.5% of men with diabetes, versus 12.6% in the rest of the sample. A predominance of secondary hypogonadism over primary testicular failure was also noted. Guay et al (2008; personal communication) reported that in 990 men with ED, 23.1% had T2D. In this group, 35.6% also were hypogonadal, approaching the 36.0% found in the entire population, emphasizing that numerous chronic illnesses related to hypogonadism in men with ED. Secondary hypogonadism was also predominant over primary testicular failure, 30.0% vs 6.0%.

The pathophysiological mechanisms encompassing the complexity of testosterone deficiency, IR, T2D, and vessel damage may stem from the unrecognized endocrine function of the adipose tissue resulting from visceral obesity [Gustafson et al 2007; Jang et al 2003]. This adipose tissue of the visceral fat responds to multiple signals to produce pro-inflammatory substances and adipokines, resulting in altered lipid and glucose metabolism, oxidative stress, endoplasmic reticulum stress, increased fatty acid content and adipose tissue necrosis (Gustafson
2007). The effects of these factors are not limited to the adipose tissue but may affect also skeletal muscle and liver. The adipokines and inflammatory factors produced by the visceral fat include IL-6, IL1b, PAI-1, TNF-α, ACE, VEGF, angiotensinogen, SAA, among others. Some of these adipokines and pro-inflammatory factors may stimulate recruitment of macrophages, which stimulate increased adipogenesis, with concomitant reduction in anti-inflammatory factors, such as adiponectin. Furthermore, IL6 and TNF-a are associated with obesity and IR and impair insulin signaling in mature adipocytes. Further, androgens have been shown to inhibit the expression and release of cytokines and chemokines (Norata et al; 2006; Malkin et al 2004; Kapoor et al 2006). Androgen deprivation therapy is thought to be associated with increased levels of proinflammatory factors and decreased anti-inflammatory cytokines [Maggio et al 2005; 2006]. Interestingly, testosterone therapy prevents gain in visceral adipose tissue in non-obese aging men, and reduces the production of pro-inflammatory cytokines [Allan et al 2008 a,b, ; Nielson et al 2007; Schroeder et al 2004]. It is therefore reasonable to suggest that androgens attenuate adipogenesis as well as inflammatory factor production. Since androgen deficiency is linked to the development of IR and T2D and the latter contribute profoundly to endothelium dysfunction [Cersosinmo & DeFronzo 2006; Ginsberg 2000], the concept of androgen deficiency reinforces the important role of androgens in vascular health [Figure 2].

**IV. c. The relationship of androgens in phosphodiesterase action in diabetic patients with ED**

An animal study conducted by Zhang et al (2006) used two different models of chemical diabetes and found that T reinstates sildenafil responsiveness in both, suggesting that T supplementation in human diabetics with ED receiving pharmacological treatment might be advantageous in the diabetic men in whom phosphodiesterases-type5 (PDE5) inhibitors given for ED do not work. Indeed, studies have tested this concept and Kalinchenko et al (2003) assessed diabetic ED patients and found that different baseline T levels in these patients determined a differential response to sildenafil. Responders typically had a total T value of 18.6±1.2nmol/L, while non-responders had a total value of 6.9±1.3 nmol/L. The authors found that while sildenafil therapy alone was insufficient to reverse ED in diabetic patients with low T levels, administration of oral T in combination with sildenafil reverses ED in these patients. In addition to low T levels predicting a poor response to sildenafil in diabetic individuals, Park et al (2005) found that uncontrolled diabetes, itself, to be a risk factor in predicting poor response to
sildenafil in 162 consecutive elderly ED patients (mean age 64.1 yrs). Fonseca et al (2004) also showed that the efficacy of tadalfil treatment in 519 diabetic patients was a function of glycemic control. The authors found that though this treatment had a significant benefit in all HbA1c ranges, there was a downward trend of drug efficacy with increasing HbA1c values. As such, predicting the efficacy of pharmacological treatment in patients with ED and diabetes is tenuous, and may be governed by the severity of the metabolic and hormonal profile of these individuals. Apart from lowering blood sugar, another approach is to affect the IR, which predominaates in type 2 diabetes. Kovaneč et al (2006) used the insulin sensitizier, pioglitizone, in diabetic rats with corpora cavernosa fibrosis. This drug treatment ameliorated the fibrosis, oxidative stress and veno-occlusive dysfunction, suggesting a separate protective effect on the smooth muscle.

V Cellular Mechanisms linking Androgen Deficiency to IR, Glycemic Control and Type 2 Diabetes

V. a. Insulin action on Leydig cell function

T biosynthesis is regulated primarily by pulsatile secretion of LH and compelling evidence exists that Leydig cell steroidogenesis is further modulated locally by circulating hormones, growth factors, and cytokines (Saez 1994). Serum T levels reflect the integrity of the hypothalamic pituitary gonadal (HPG) axis and low T levels noted in cases of insulin-resistance may indicate a defect at one or more functional levels of the HPG axis. In the insulin-resistance state Leydig cell function may be impaired, particularly steroidogenesis, by changes in the production of hormones and cytokines locally in the target tissue and in adipose tissue. While several studies suggested that increasing IR may be attributed to a decrease in T secretion in men, it is not fully clear how the hypothalamo-pituitary-gonadal (HPG) axis mediates the interplay between T and insulin levels. Pitteloud et al (2005, 2008) explored the effect of suppression of endogenous reproductive hormones, followed by sequential stimulation of the pituitary and the testes with GnRH and hCG, respectively. hCG stimulated T levels at 48hrs were positively correlated with insulin sensitivity as well as baseline serum T levels. The authors suggested that alteration in Leydig cell function may account in part for the mechanisms by which a decrease in T leads to IR.
A framework is needed to explain the potential biochemical and physiological mechanisms involved in reduction of T biosynthesis due to changes in insulin/glucose levels in diabetes and how this may alter the function of the pituitary/testicular axis remains under intensive investigation. Several observations have suggested that a relationship exist between insulin/glucose and LH/FSH levels. Diabetic men often have reduced serum levels of FSH, LH, prolactin, and growth hormone, consistent with secondary hypogonadism (Hutson et al, 1983; Benitez & Perez Diaz, 1985).

V. b. Effects of T2D on Leydig cell function

Leydig cell function is under regulation by LH and other hormones (Saez 1994; Zirkin & Chen 2000), therefore, it is possible that increased IR or hyperglycemia may result in reduced T biogenesis due to decreased central stimulation. Interestingly, Pitteloud et al (2005; 2008) did not observe a correlation between insulin sensitivity and parameters of LH secretion or LH response to exogenous GnRH, suggesting low T levels associated with IR are not attributed to a major decrease in hypothalamic or pituitary hormone secretion. The authors have demonstrated a strong positive correlation between hCG-stimulated T secretion and insulin sensitivity in men using physiological doses of hCG in the presence of experimentally induced hypogonadism. Ballester et al (2004) proposed several potential mechanisms that affect T biogenesis in diabetes. The authors suggested that diminished Leydig cell function and T production in insulin-dependent diabetes is attributed to reduced or absent stimulatory effect of insulin on leydig cells. Oltmanns et al (2001) presented data suggesting that hypoglycemia but not insulin suppresses T secretion and this is mediated by pituitary decrease in LH output. Adipose tissue, which is considered an endocrine organ and produces a host of hormones and cytokines, may modulate insulin action and regulate Leydig cell function. Leptin production is tightly coupled to IR and may play a key role in steroid-biogenesis and reduced T levels. Leptin levels have been shown to be inversely correlated with serum T levels (Luukkaa et al 1998; Wabitsch et al 1997; Haffner et al 1997), and increased circulating leptin may be involved in the pathogenesis of Leydig cell dysfunction (Isidori et al 1999). The expression of leptin receptors in Leydig cells, and the inhibition of hCG-stimulated T secretion from rat Leydig cells by leptin suggests a role of this hormone in the biogenesis of T (Caprio et al., 1999). Hong et al [2004] proposed that TNF-α inhibits steroid biosynthesis in Leydig cells and proposed a molecular mechanism by which
proinflammatory factors can contribute to inhibition of androgen biosynthesis. Clearly additional studies are needed to fully delineate the biochemical and physiological mechanisms underlying reduced T synthesis in diabetes.

**Discussion**

Androgen deficiency may be central to the metabolic syndrome components, which encompasses IR and T2D, obesity among others [Figures 1, 2]. The relationship between these various components and androgen deficiency is depicted in the diagram in Figure 2. The postulated potential interactions between decreased T deficiency and the various pathological states, including IR and T2D represents a framework from which the interplay between the various pathology need be investigated. T plays a crucial role in maintaining metabolic homeostasis, thus this hormone may play a vital role in maintaining glycemic control. The exact mechanism by which diabetes and or/IR impairs T biosynthesis and how reduced T levels increase IR and development of T2D remain poorly understood. Low T levels in men with hypogonadism or patients receiving ADT for prostate cancer are considered risk factors for IR and T2D. T therapy may provide protective effects against onset of diabetes or may ameliorate the pathology of diabetic complications. Low T levels represent a risk factor for IR and T2D, thus contributing to the onset of metabolic syndrome and vascular consequences, including ED.

We postulate that androgen deficiency plays a central role in the pathology of the metabolic syndrome, type 2 diabetes and insulin resistance and contributes significantly to processes of adipogenesis and increased accumulation of visceral fat, resulting in obesity. Visceral fat serves as an endocrine organ, which produces pro-inflammatory cytokines affecting multiple tissues organs and further increasing the risk for IR, T2D, MetS and endothelial dysfunction. We conclude that androgen deficiency is of a central importance in the development of the various pathologies contained within the definition of MetS, leading to vascular complications.
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FIGURE LEGENDS

**Figure 1:** A Framework representing the interplay between Androgen Deficiency and Obesity, Insulin resistance and hyperglycemia among others lead to the Metabolic Syndrome Components. This diagram depicts the important links between androgen deficiency and key components of the MetS, especially glucose abnormalities (hyperglycemia), insulin resistance and obesity, together with hypertension, dislipidemia (Mulligan et al., 2006)

**Figure 2:** Postulated relationship between Androgen Deficiency, Diabetes, IR, metabolic Syndrome and Erectile Dysfunction (ED). The framework presented in this diagram postulates bidirectional relationship between obesity and IR, as well as between obesity and MS, and IR and T2D. We further suggest that ED contributes to androgen deficiency though stress and/or depression. A bidirectional relationship between androgen deficiency and T2D is well known and this may further contribute ED. The indirect relationship between ED and T2D is likely to be mediated by multiple overlapping factors common to both pathologies.
FIGURE 1, Traish et al.
FIGURE 2, Traish et al.

- Insulin Resistance
- Obesity
- Androgen Deficiency
- Diabetes
- Metabolic Syndrome
- Erectile Dysfunction