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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 $HOMA_{IR}$ 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 *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 hypogondal 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 hypogonadotropic 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 ≥126mg/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 (>/= 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. Hypogonadsim 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 ecompassing 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-inflamatory 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 withy increased levels of proinflamatory factors and decreased anti-infllamatroy 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-inflamatory 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 tadalafil 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 predominates in type 2 diabetes. Kovanecz et al (2006) used the insulin sensitizer, 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; Benıtez & Perez Dıaz, 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 my 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

proinflamatory 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.

REFERENCES

Akkus E, Kadioglu A, Esen A, Doran S, Ergen A, Anafarta K, Hattat H; Turkish Erectile Dysfunction Prevalence Study Group. Prevalence and correlates of erectile dysfunction in Turkey: a population-based study. *Eur Urol*. 2002; 41:298-304.

Allan CA, Strauss BJ, Burger HG, Forbes EA, McLachlan RI.Testosterone therapy prevents gain in visceral adipose tissue and loss of skeletal muscle in nonobese aging men. *J Clin Endocrinol Metab*. 2008a 93:139-146.

Allan CA, Forbes EA, Strauss BJ, McLachlan RI. Testosterone therapy increases sexual desire in ageing men with low-normal testosterone levels and symptoms of androgen deficiency. *Int J Impot Res.* 2008b;20:396-401.

Andersson B, Marin P, Lissner L, Vermeulen A, Bjorntorp P. Testosterone concentrations in women and men with NIDDM. *Diabetes Care*. 1994; 17:405-411.

Basaria S, Muller DC, Carducci MA, Egan J, Dobs AS. Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy. *Cancer.* 2006;106: 581-588.

Ballester J, Muñoz MC, Domínguez J, Rigau T, Guinovart JJ, Rodríguez-Gil JE. Insulin-dependent diabetes affects testicular function by FSH- and LH-linked mechanisms. *J Androl.* 2004;25:706-719.

Benitez A, Perez Diaz J. Effect of streptozotocin-diabetes and insulin treatment on regulation of Leydig cell function in the rat. *Horm Metab Res*. 1985 ;17:5-7

Blouin K, Despres JP, Couillard C, Tremblay A, Prud'homme D, Bouchard C, Tchernof A. Contribution of age and declining androgen levels to features of the metabolic syndrome in men. *Metabolism*. 2005;54:1034-1040.

Bodie J, Lewis J, Schow D, Monga M. Laboratory evaluations of erectile dysfunction : an evidence based approach. *J Urol*. 2003;169:2262-2264.

Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *Aging Male*. 2003;6: 1-7.

Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Engelmann U. Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. *Int J Impot Res*. 2000 ;12: 305-11.

Caprio M, Isidori AM, Carta AR, Moretti C, Dufau ML, Fabbri A 1999 Expression of functional leptin receptors in rodent Leydig cells. *Endocrinology*. 140: 4939–4947

Cartledge JJ, Eardley I, Morrison JF. Impairment of corpus cavernosal smooth muscle relaxation by glycosylated human haemoglobin. *BJU.* 2000; 85:735-741.

Cersosimo E, DeFronzo RA.Insulin resistance and endothelial dysfunction: the road map to cardiovascular diseases. *Diabetes Metab Res Rev*. 2006;22 :423-436.

Chen RYT, Wittest GA, Andreson GR. Relative androgen deficiency in relation to obesity and metabolic status in older men. *Diab Obes Metab.* 2006; 8: 429-435.

Corona G, Mannucci E, Mansani R, Petrone L, Bartolini M, Giommi R, Forti G, Maggi M. Organic, relational and psychological factors in erectile dysfunction in men with diabetes mellitus. *Eur Urol*. 2004; 46: 222-228.

Corona G, Mannucci E, Petrone L, Ricca V, Balercia G, Mansani R, Chiarini V, Giommi R, Forti G, Maggi M. Association of hypogonadism and type II diabetes in men attending an outpatient erectile dysfunction clinic. *Int J Impot Res*. 2006;18:190-197.

Corona G, Mannucci E, Petrone L, Balercia G, Paggi F, Fisher AD, Lotti F, Chiarini V, Fedele D, Forti G, Maggi M. NCEP-ATPIII-defined metabolic syndrome, type 2 diabetes mellitus, and prevalnce of hypogonadism in male patients with sexual dysfunction. *J Sex Med* 2007;4: 1038-1045.

Derweesh IH, DiBlasio CJ, Kincade MC, Malcolm JB, Lamar KD, Patterson AL, Kitabchit AE, Wake RN. Risk of new-onset diabetes mellitus and worsening glycemic variables for established diabetes in men undergoing androgen-deprivation therapy for prostate cancer. *BJU Int.* 2007; 100: 1060-1065.

Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab.* 2004;89:5462-5468.

Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA.* 2006;295:1288-1299.

Dockery F, Bulpitt CJ, Agarwal S, Donaldson M, Rajkumar C. Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia. *Clin Sci.* 2003;104:195-201.

Esposito K, Ciotola M, Giuliano F, Schisano B, Improta L, Improta MR, Beneduce F, Rispoli M, DeSio M, Giuliano D. Endothelial microparticles correlate with erectile dysfunction in diabetic men. *Int J Imp Res.* 2007; 19: 161-166.

Fonseca V, Seftel A, Denne J, Fredlund P. Impact of diabetes mellitus on the severity of erectile dysfunction and response to treatment: analysis of data from tadalafil clinical trials. *Diabetologia*. 2004; 47:1914-1923.

Ford ES, Li C, Zhao G, Pearson WS, Mokdad AH. Prevalence of the metabolic syndrome among U.S. adolescents using the definition from the international diabetes federation. *Diabetes Care.* 2008; 31: 587-589.

Fukui M, Soh J, Tanaka M, Kitagawa Y, Hasegawa G, Yoshikawa T, Miki T, Nakamura N. Low serum testosterone concentration in middle-aged men with type 2 diabetes. *Endocr J*. 2007; 54:871-877.

Ginsberg HN. Insulin resistance and cardiovascular disease. *J Clin Invest*. 2000;106 :453-458.

Giuliano FA, Leriche A, Jaudinot EO, de Gendre AS. Prevalence of erectile dysfunction among 7689 patients with diabetes or hypertension, or both. *Urology*. 2004; 64:1196-1201.

Grossman M, Thomas ME, Sanagiotopoules S, Sharpe K, MacIsaac RJ, Clark S, Zajac JD, Jerums G. Low testosterone levels are common and associated with insulin resistance in men with diabetes. *J Clin Endocrinol Metab.* 2008 (in press).

Guay A, Seftel A. Multiple chronic illnesses are associated with hypogonadism in men with erectile dysfunction. *Int J Imp Res.* 2008; submitted for publication.

Gustafson B, Hammarstedt A, Andersson CX, Smith U. Inflamed adipose tissue: a culprit underlying the metabolic syndrome and atherosclerosis. Arterioscler Thromb Vasc Biol. 2007; 27:2276-2283.

Haffner SM, Shaten J, Stern MP, Smith GD, Kuller L. Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. MRFIT Research Group. Multiple Risk Factor Intervention Trial. *Am J Epidemiol*. 1996;143:889-897.

Haffner SM, Miettinen H, Karhapa¨a¨ P, Mykka¨nen L, Laakso M Leptin concentrations, sex hormones, and cortisol in nondiabetic men. *J Clin Endocrinol Metab* 1997; 82:1807–1809.

Haidar A, Yassin A, Saad F, Shabsigh R. Effects of androgen deprivation on glycaemic control and on cardiovascular biochemical risk factors in men with advanced prostate cancer with diabetes. *Aging Male* 2007; 10: 189-196.

Hong CY, Park JH, Ahn RS, Im SY, Choi HS, Soh J, Mellon SH, Lee K.Molecular mechanism of suppression of testicular steroidogenesis by proinflammatory cytokine tumor necrosis factor alpha. *Mol Cell Biol*. 2004;24:2593-2604.

Hutson JC, Stocco DM, Campbell GT, Wagoner J. Sertoli cell function in diabetic, insulin-treated diabetic, and semi-starved rats. *Diabetes*. 1983;32:112-116.

Isidori AM, Caprio M, Strollo F, Moretti C, Frajese G, Isidori A, Fabbri A. Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. *J Clin Endocrinol Metab.* 1999;84: 3673-3680.

Isidori AM, Strollo F, More M, Caprio M, Aversa A, Moretti C, Frajese G, Riondino G, Fabbri A. Leptin and aging: correlation with endocrine changes in male and female healthy adult populations of different body weights. *J Clin Endocrinol Metab*. 2000;85: 1954-1962.

Jang Y, Kim OY, Ryu HJ, Kim JY, Song SH, Ordovas JM, Lee JH. Visceral fat accumulation determines postprandial lipemic response, lipid peroxidation, DNA damage, and endothelial dysfunction in nonobese Korean men. *J Lipid Res*. 2003; 44 :2356-64.

Kalinchenko SY, Kozlov GI, Gontcharov NP, Katsiya GV. Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. *Aging Male*. 2003; 6: 94-99.

Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. *Eur J Endocrinol*. 2006;154:899-906.

Kapoor D, Aldred H, Clark S, Channer K, Jones T. Clinical and Biochemical Assessment of Hypogonadism in Men With Type 2 Diabetes. *Diabetes Care*. 2007; 30: 911-917.

Kovanecz I, Ferrini MG, Vernet D, Nolazco G, Rajfer J, Gonzalez-Cavadid NF. Pioglitazone prevents corporal veno-occlusive dysfunction in a rat model of type 2 diabetes mellitus. *BJU Int.* 2006; 98: 116-124.

Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Salonen R, Rauramaa R, Salonen JT. Sex hormones, inflammation and the metabolic syndrome: a population-based study. *Eur J Endocrinol.* 2003;149:601-608.

Lage MJ, Barber BL, Markus RA. Association between androgen-deprivation therapy and incidence of diabetes among males with prostate cancer. *Urology.* 2007; 70: 1104-1108.

Lindmark S, burein J, Ericksson JW. Insulin resistance, endocrine function and adipokines in type 2 diabetes patients at different glycemic levels: potential impact for glucotoxicity *in vivo*. *Clin Endocrinol.* 2006; 65: 301-309.

Luukkaa V, Pesonen U, Huhtaniemi I, Lehtonen A, Tilvis R, Tuomilehto J, Houlu M, Huupponen R 1998 Inverse correlation between serum testosterone and leptin in men. *J Clin Endocrinol Metab* 83:3243–3246

Maggio M, Blackford A, Taub D, Carducci M, Ble A, Metter EJ, Braga-Basaria M, Dobs A, Basaria S. Circulating inflammatory cytokine expression in men with prostate cancer undergoing androgen deprivation therapy. *J Androl*. 2006;27:725-728.

Maggio M, Basaria S, Ceda GP, Ble A, Ling SM, Bandinelli S, Valenti G, Ferrucci L.The relationship between testosterone and molecular markers of inflammation in older men. *J Endocrinol Invest*. 2005;28 (11 Suppl Proceedings):116-9.

Malkin CJ, Pugh PJ, Jones RD, Kapoor D, Channer KS, Jones TH. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. *J Clin Endocrinol Metab.* 2004 ;89 :3313-3318.

Marin P, Holmang S, Gustafsson C, Jonsson L, Kvist H, Elander A, Eldh J, Sjostrom L, Holm G, Bjorntorp P. Androgen treatment of abdominally obese men. *Obes Res.* 1993;1:245-251.

Marin P, Holmang S, Jonsson L, Sjostrom L, Kvist H, Holm G, Lindstedt G, Bjorntorp P. The effects of testosterone treatment on body composition and metabolism in middle-aged obses men. *Int J Obes Relat Metab Disord*. 1992;16:991-997.

Marin P. Testosterone and regional fat distribution. *Obes Res*. 1995;3 Suppl 4:S609-S612.

Marin P, Lonn L, Andersson B, Oden B, Olbe L, Bengtsson BA, Bjorntorp P. Assimilation of triglycerides in subcutaneous and intraabdominal adipose tissues in vivo in men: effects of testosterone. *J Clin Endocrinol Metab.* 1996;81:1018-1022.

Muller M, Grobbee DE, den Tonkelaar I, Lamberts SW, van der Schouw YT. Endogenous sex hormones and metabolic syndrome in aging men. *J Clin Endocrinol Metab*. 2005;90:2618-2623.

Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int J Clin Pract*. 2006 ;60:762-769.

Morimoto S, Mendoza-Rodríguez CA, Hiriart M, Larrieta ME, Vital P, Cerbón MA. Protective effect of testosterone on early apoptotic damage induced by streptozotocin in rat pancreas. J Endocrinol. 2005 ;187: 217-224.

Naharci MI, Pinar M, Bolu E, Olgun A. Effect of testosterone on insulin sensitivity in men with idiopathic hypogonadotropic hypogonadism. *Endocr Pract*. 2007 ;13: 629-635.

Nielsen TL, Hagen C, Wraae K, Brixen K, Petersen PH, Haug E, Larsen R, Andersen M. Visceral and subcutaneous adipose tissue assessed by magnetic resonance imaging in relation to circulating androgens, sex hormone-binding globulin, and luteinizing hormone in young men. *J Clin Endocrinol Metab*. 2007;92 :2696-2705.

Nishiyama T, Ishizaki F, Anraku T, Shimura H, Takahashi K. The influence of androgen deprivation therapy on metabolism in patients with prostate cancer. *J Clin Endocrinol Metab.* 2005;90:657-660.

Norata GD, Tibolla G, Seccomandi PM, Poletti A, Catapano AL. Dihydrotestosterone decreases tumor necrosis factor-alpha and lipopolysaccharide-induced inflammatory response in human endothelial cells. J Clin Endocrinol Metab. 2006 ;91:546-554.

Oh JY, Barrett-Connor E, Wedick NM, Wingard DL; Rancho Bernardo Study. Endogenous sex hormones and the development of type 2 diabetes in older men and women; the Rancho Bernardo study. *Diabetes Care*. 2002; 25: 55-60.

Osuna JA, Gomez-Perez R, Arata-Bellabarba G, Villaroel V. Relationship between BMI, total testosterone, sex hormone-binding-globulin, leptin, insulin and insulin resistance in obese men. *Arch Androl.* 2006;52:355-361.

Pagotto U, Gambineri A, Pelusi C, Genghini S, Cacciari M, Otto B, Castaneda T, Tschop M, Pasquali R. Testosterone replacement therapy restores normal ghrelin in hypogonadal men. *J Clin Endocrinol Metab.* 2003;88:4139-4143.

Parazzini F, Menchini Fabris F, Bortolotti A, Calabro A, Chatenoud L, Colli E, Landoni M, Lavezzari M, Turchi P, Sessa A, Mirone V. Frequency and determinants of erectile dysfunction in Italy. *Eur Urol.* 2000;37:43-49.

Parikh NI, Pencine MJ, Wang TJ, Lanier KJ, Fox CS, d'Agostino RB, Ramachandran SV. Increasing trends in incidence of overweight and obesity over 5 decades. *Amer J Med.* 2007; 120: 242-250.

Park K, Ku JH, Kim SW, Paick JS. Risk factors in predicting a poor response to sildenafil citrate in elderly men with erectile dysfunction. *BJU Int.* 2005;95:366-370.

Pasquali R, Casimirri F, Cantobelli S, Melchionda N, Morselli Labate AM, Fabbri R, Capelli M, Bortoluzzi L. Effect of obesity and body fat distribution on sex hormones and insulin in men. *Metabolism.* 1991;40:101-104.

Pasquali R, Casimiri F, De iasio R, Mesini P, Boschi S, chierici r, Flamia R, Biscotti M, vicennata V. Insulin regulates testosterone and sex hormone-binding globulin concentrations in adult normal weight and obese men. *J Clin Endocrinol Metab.* 1995; 80: 654-658.

Pasquali R, Macor C, Vicennati V, Novo F, De lasio R, Mesini P, Boschi S, Casimirri F, Vettor R. Effects of acute hyperinsulinemia on testosterone serum concentrations in adult obese and normal-weight men. *Metabolism.* 1997;46:526-529.0

Pitteloud N, Hardin M, Dwyer AA, Valassi E, Yialamas M, Elahi D, Hayes FJ. Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. *J Clin Endocrinol Metab*. 2005a; 90:2636-2641.

Pitteloud N, Mootha VK, Dwyer AA, Hardin M, Lee H, Eriksson KF, Tripathy D, Yialamas M, Groop L, Elahi D, Hayes FJ. Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. *Diabetes Care*. 2005b; 28:1636-1642.

Pitteloud N, Dwyer AA, DeCruz S, Lee H, Boepple PA, Crowley WF Jr, Hayes FJ. Inhibition of luteinizing hormone secretion by testosterone in men requires aromatization for its pituitary but

not its hypothalamic effects: evidence from the tandem study of normal and gonadotropin-releasing hormone-deficient men. J Clin Endocrinol Metab. 2008 ;93:784-791.

Ponholzer A, Temml C, Mock K, Marszalek M, Obermayr R, Madersbacher S. Prevalence and risk factors for erectile dysfunction in 2869 men using a validated questionnaire. *Eur Urol*. 2005;47:80-86.

Rader DJ. Effect of insulin resistance, dyslipidemia, and the intra-abdominal adiposity on the development of cardiovascular disease and diabetes mellitus. *Amer J Med.* 2007; 120: 512-518.

Rhoden EL, Ribeiro EP, Riedner CE, Teloken C, Souto CA. Glycosylated haemoglobin levels and the severity of erectile function in diabetic men. *BJU Int.* 2005;95:615-617.

Rhoden EL, Ribeiro DP, Teloken C, Souto CA. Diabetes mellitus is associated with subnormal serum levels of free testosterone in men *BJU Int.* 2005;96:867-870.

Romeo JH, Seftel AD, Madhun ZT, Aron DC. Sexual function in men with diabetes type 2: association with glycemic control. *J Urol.* 2000;163:788-791.

Saez JM. Leydig cells: endocrine, paracrine, and autocrine regulation. *Endocr Rev*. 1994 ;15: 574-626.

Schroeder ET, Zheng L, Ong MD, Martinez C, Flores C, Stewart Y, Azen C, Sattler FR. Effects of androgen therapy on adipose tissue and metabolism in older men. *J Clin Endocrinol Metab.* 2004 ;89:4863-4872.

Selvin E, Feinleib M, Zhang L, Rohrmann S, Rifai N, Nelson W, Dobs A, Basaria S, Golden S, Platz E. Androgens and diabetes in men. *Diabetes Care.* 2007;30:234-238.

Shabsigh R, Perelman MA, Lockhart DC, Lue TF, Broderick GA. Health issues of men: prevalence and correlates of erectile dysfunction. *J Urol.* 2005;174:662-667.

Shahani S, Braga-Basaria M, Basaria S. Androgen Deprivation Therapy in Prostate Cancer & Metabolic Risk for Atherosclerosis. *J Clin Endocrinol Metab*. (2008) in press.

Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. *Arch Intern Med.* 2006;166:1660-1665.

Simon D, Charles MA, Nahoul K, Orssaud G, Kremski J, Hully V, Joubert E, Papoz L, Eschwege E. Assocation between plasma total testosterone and cardiovascular risk factors in healthy adult men: The Telecom Study. *J Clin Endocrinol Metab.* 1997;82: 682-685.

Smith JC, Bennett S, Evans LM, Kynaston HG, Parmar M, Mason MD, Cockcroft JR, Scanlon MF, Davies JS. The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. *J Clin Endocrinol Metab.* 2001;86:4261-4267.

Steinbrook R. Facing the diabetes epidemic-mandatory reporting of glycosylated hemoglobin values in New York City. *N Engl J Med.* 2006;354:545-548.

Stellato RK, Feldman HA, Hamdy O, Horton ES, McKinlay JB. Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts male aging study. *Diabetes Care.* 2000;23:490-494.

Sun P, Cameron A, Seftel A, Shabsigh R, Niederberger C, Guay A. Erectile dysfunction-an observable marker of diabetes mellitus? A large national epidemiological study. *J Urol.* 2006;176:1081-1085.

Traish AM, Guay AT, Feeley R, Saad F. The Dark Side of Testosterone Deficiency:I. Metabolic Syndrome & Erectile Dysfunction. J Androl. 2008 Jul 17. [Epub ahead of print]

Wabitsch M, Blum WF, Muche R, Braun M, Hube F, Rascher W, Heinze E, Teller W, Hauner H Contribution of androgens to the gender difference in leptin production in obese children and adolescents. *J Clin Invest*. 1997; 100: 808–813.

Weyer C, Funahashi T, Tanaka S, Hotla K, Matsuzawa Y, Pratley RE, Tataranni A. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab.* 2001; 86: 1930-1935.

Yamasaki H, Ogawa K, Sasaki H, Nakao T, Wakasaki H, Matsumoto E, Furuta H, Nishi M, Ueda K, Iwo K, Nanjo K. Prevalence and risk factors of erectile dysfunction in Japanese men with type 2 diabetes. *Diabetes Res Clin Pract*. 2004; 66S:S173-S177.

Yannucci J, Manola J, Garnick MB, Bhat G, Bubley GJ. The effect of androgen deprivation therapy on fasting serum lipid and glucose parameters. *J Urol.* 2006;176:520-525.

Yialamas MA, Dwyer AA, Hanley E, lee H, Pitteloud N, Hayes FJ. Acute sex steroid withdrawal reduces insulin sensitivity in healthy men with idiopathic hypogonadotropic hypogonadism. *J Clin Endocrinol Metab.* 2007; 92: 4254-4259.

Zhang XH, Filippi S, Morelli A, Vignozzi L, Luconi M, Donati S, Forti G, Maggi M. Testosterone restores diabetes-induced erectile dysfunction and sildenafil responsiveness in two distinct animal models of chemical diabetes. *J Sex Med.* 2006;3:253–266.

Zirkin BR, Chen H. Regulation of Leydig cell steroidogenic function during aging. Biol Reprod. 2000 ;63: 977-981.

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.

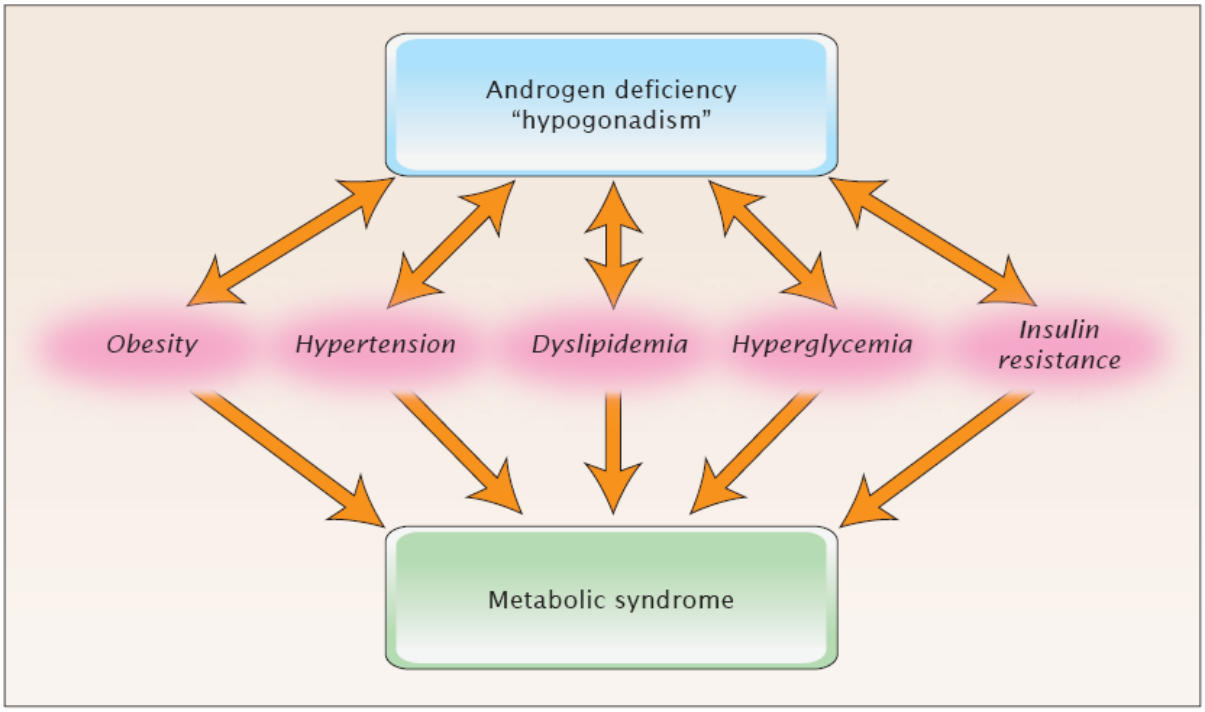

FIGURE 2, Traish et al.