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Review

Obesity and testicular function

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ABSTRACT

Obesity in men, particularly when central, is associated with lower total testosterone [TT], free testosterone [FT] and sex hormone-binding globulin [SHBG], and a greater decline in TT and FT with increasing age compared with lean men. Obesity-related conditions such as obstructive sleep apnea, insulin resistance and type 2 diabetes mellitus are independently associated with decreased plasma testosterone. Possible mechanisms include decreased LH pulse amplitude, inhibitory effects of oestrogen at the hypothalamus and pituitary and the effects of leptin and other peptides centrally and on Leydig cells. Obese men have reduced sperm concentration and total sperm count compared to lean men but sperm motility and morphology appear unaffected. The cause and effect relationships between low plasma androgen levels, obesity and the metabolic syndrome, and associated cardiometabolic risk remain unclear. While weight loss normalizes TT and FT in obese men, androgen replacement in the short term does not significantly improve cardiometabolic risk profile despite reducing fat mass.

Contents

1. Introduction

Obesity has increased dramatically worldwide over the past 20–30 years. The risk of developing common chronic diseases such as diabetes mellitus, hypertension, heart disease and stroke increased with the severity of overweight in both men and women,

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particularly with predominant accumulation of visceral fat. Obese men and women with body mass index [BMI] over 35 kg/m^2 have approximately 20 times higher likelihood of developing diabetes mellitus (Field et al., 2001). Obesity has also been shown to be associated with alterations in sex steroid hormone concentrations. Low plasma testosterone concentrations are associated with visceral obesity and the metabolic syndrome and increased cardiovascular risk (Haffner et al., 1993); the cause and effect relationship remain unresolved. In this review, we discuss the effects of obesity on the hypothalamic–pituitary–testicular axis, plasma androgen levels and spermatogenesis, as well as the effects of weight loss on androgen levels and the effects of androgen replacement therapy in this population.

2. Hypothalamic–pituitary–gonadal (HPG) axis

In a normal adult male, the preoptic area and the medial basal region of the hypothalamus secrete gonadotropin-releasing hormone [GnRH] in a pulsatile manner. GnRH interacts with cell-surface receptors coupled to G proteins on the plasma membrane of pituitary gonadotrophs stimulating the release of luteinizing hormone [LH] and follicle-stimulating hormone [FSH]. LH binds to the LH receptor on the plasma membrane of Leydig cells resulting in the synthesis of the enzymes of testosterone biosynthesis. LH secretion is under negative feedback control by gonadal steroids, both testosterone and oestradiol, at the level of the hypothalamus with the androgens effecting a slowing of the hypothalamic pulse generator and consequently a decrease in the frequency of the LH pulsatile release (Griffin and Wilson, 2003).

FSH does not play a major role in the control of Leydig cell function in adults and instead acts in the control of spermatogenesis following its binding to the FSH receptor in the basal aspect of the plasma membrane of Sertoli cells. FSH secretion is modulated by activin and inhibin. Activin is a homodimer produced by the Sertoli cells, peritubular and interstitial cells as well as the pituitary and hypothalamus. Activin binds to activin receptor type II [ACT RII] in the gonadotroph cells in the pituitary and stimulates the secretion of FSH. Increase in FSH secretion is also thought to be via activin stimulation of GnRH in the hypothalamus (Kumanov et al., 2005). Inhibin B is a heterodimeric glycoprotein that is predominantly produced in the Sertoli cells and it shows a diurnal rhythm parallel to that of testosterone. Inhibin's production is stimulated by FSH and it in turn, inhibits the secretion of FSH via a negative feedback mechanism. Inhibin has also been shown to bind to ACT RII, reducing activin binding to the receptor and therefore activin's stimulation of FSH secretion (Meachem et al., 2001; de Kretser et al., 2004). FSH levels increase with the loss of germinal elements in the testis (Van Thiel et al., 1972; Griffin and Wilson, 2003) and FSH has been used as a marker of spermatogenesis. Inhibin B used in combination with FSH is a more sensitive marker of spermatogenesis when correlated with testicular volume and sperm counts but they are not able to predict the presence of sperm in individual testicular tissue sample (Meachem et al., 2001).

3. Plasma androgen levels

3.1. Circulating testosterone levels

Testosterone is present in plasma as free or unbound testosterone, albumin-bound and sex hormone-binding globulin [SHBG]-bound. In lean men, about 2% of testosterone is unbound, 44% is bound to SHBG and 50% is bound to albumin and other proteins (Pardridge, 1986). The proportion of testosterone that is free together with the albumin-bound fraction have been considered to be the biologically active component that is readily available to the tissues and are collectively known as bioavailable testosterone. The term non-SHBG-bound testosterone is more accurate as SHBG-bound testosterone may be bioavailable in some target tissues (Morley et al., 2002), and therefore the most appropriate fraction of testosterone to measure remains unresolved.

A cross-sectional study of healthy elderly men showed that bioavailable testosterone is positively related with muscle strength and total body bone mineral density, and correlate better with clinical symptoms than total testosterone (van den Beld et al., 2000). Free testosterone and albumin-bound testosterone have been shown to decline relatively more with a decrease in serum albumin level than in response to an age-related increase of serum SHBG, especially in men in their 60s and 70s (Hayashi and Yamada, 2008). Conditions that result in a decrease of serum albumin levels may therefore induce symptoms of sex hormone deficiency regardless of total plasma testosterone levels.

The fraction of testosterone bound to SHBG in serum is proportional to the SHBG level. SHBG production in the liver is regulated by a number of hormones. Oestrogen and related steroids, thyroid hormone and insulin increase SHBG levels. SHBG decreases in response to testosterone administration, hypothyroidism, and in the presence of insulin resistance. SHBG levels affect bioavailable testosterone levels especially when serum albumin is low (Hayashi and Yamada, 2008).

3.2. Measurement of plasma testosterone levels

There is a diurnal and seasonal variation in the circulating testosterone levels (Morley et al., 2002); levels should be measured fasting in the morning. Most platform assays for total testosterone are unsatisfactory (Sikaris et al., 2005) and there is no universally recognized testosterone-calibrating standard (Rosner et al., 2007). Well-calibrated assays using a tandem mass spectrometer are optimal (Vieira et al., 2008).

Equilibrium dialysis is the gold standard for the estimation of free testosterone (Vermeulen et al., 1999) but is technically difficult and time-consuming. The calculation of free testosterone is dependent on the accuracy of the assay used to measure total testosterone and on SHBG as measured by an immunoassay for which there is no gold standard (de Ronde et al., 2006), and the dissociation equilibrium constant [Kd] used in the equation changes with increasing age and in the presence of disease. Morning salivary testosterone levels have been shown to be useful in differentiating hypogonadal from eugonadal men and there is good correlation between salivary testosterone and free testosterone (Arregger et al., 2007).

Bioavailable testosterone is measured after precipitation and removal of SHBG using ammonium sulphate and can also be calculated but the same proviso concerning the assay used to measure testosterone and caveats concerning the Kd used apply (de Ronde et al., 2006; Giton et al., 2006, 2007).

4. Obesity and the HPG axis

Obesity is associated with a reduction in serum total testosterone and SHBG levels (Gray et al., 1991; Kaufman and Vermeulen, 2005). In the Massachusetts Male Ageing Study, men who were obese at baseline and at follow-up, whether measured by BMI or central obesity (waist–hip ratio or waist circumference) had a greater decline of free and total testosterone and SHBG compared to men who were never classified as obese (Derby et al., 2006). The mechanism/s by which obesity affects the HPG axis remains to be clarified.

5. Effect of distribution of adipose tissue on plasma androgen levels

There is an inverse relationship between plasma total testosterone, free testosterone and SHBG with visceral fat (Haffner, 2000)

that is considerably stronger than inverse relationship between plasma total testosterone, free testosterone and SHBG with BMI (Svartberg et al., 2004). Plasma levels of free testosterone and SHBG (Abate et al., 2002) correlate inversely with both truncal and peripheral adiposity in men with and without diabetes. Nielsen et al. investigated the role of visceral adipose tissue and subcutaneous tissue on circulating sex hormones in a population-based study of 783 Danish 20–29-year-old men using dual-energy X-ray absorptiometry and magnetic resonance imaging (Nielsen et al., 2007), and showed that visceral adipose tissue correlated independently with bioavailable and free testosterone. The inverse relationship between total testosterone and subcutaneous adipose tissue appeared to be due to variations in SHBG levels. Almost one in every four obese men had total testosterone levels below the reference limit of non-obese men and every other obese man with low total testosterone had bioavailable testosterone levels below the lower limit of non-obese men (Nielsen et al., 2007).

Visceral adiposity is associated with elevated concentrations of insulin, C-peptide and glucose intolerance, which are negatively correlated to total and calculated free testosterone levels (Seidell et al., 1990; Pasquali et al., 1991). Elevated insulin concentration is thought to be the cause of reduced SHBG levels in visceral obesity as basal secretion of SHBG by cultured human hepatoma cell line (Hep G2) was greatly reduced by the physiological concentration of insulin (Plymate et al., 1988; Kalme et al., 2003). Visceral obesity is associated with decreased basal cortisol secretion and increased cortisol response to exogenous adrenocorticotropin stimulation which may contribute to higher insulin levels and decreased SHBG levels (Hautanen, 2000). The effects of insulin resistance on plasma androgen levels appear to be reversible as treatment of hypogonadal men with type 2 diabetes mellitus with Rosiglitazone, an insulin-sensitizer increased total testosterone, SHBG, free testosterone and bioavailable testosterone levels (Kapoor et al., 2008).

5.1. Central effects and LH pulsatility

It has recently been shown that total and free testosterone levels in obese men were lower compared to non-obese men independent of the decrease in SHBG with unchanged or decreased LH levels, suggesting a failure at the hypothalamic–pituitary level (Wu et al., 2008). LH pulsatility remains undisturbed in severely obese men but LH amplitude is significantly attenuated compared to non-obese controls (Vermeulen et al., 1993). In this group of obese and non-obese control subjects, there was a highly significant linear correlation between the sum of LH amplitudes in each subject and plasma free testosterone. The decreased LH levels and LH pulse amplitude depends on the degree of obesity and are observed mainly in the massively obese men with BMI > 40 kg/m^2 (Giagulli et al., 1994).

5.2. Androgen metabolism and effect of oestrogens

Obese men have been shown to have elevated circulating oestrogen levels (Schneider et al., 1979; Zumoff et al., 1981) predominantly derived from the aromatization of circulating testosterone, mostly in adipose tissue where the enzyme aromatase is present in higher levels compared to other tissues. The overall rate of aromatization of testosterone to oestradiol increases with age and fat mass (Vermeulen et al., 2002). This results in alteration in the testosterone to oestradiol ratio that leads to further abdominal fat deposition and a greater degree of testosterone deficiency, which has been shown to lead to hypogonadotrophic hypogonadism and infertility in the setting of morbid obesity (Roth et al., 2008). Oestrogen has dual sites of negative feedback on the HPG axis, acting at the hypothalamus (Veldhuis and Dufau, 1987; Hayes et al., 2000) to decrease GnRH pulse frequency and at the pituitary (Finkelstein et al., 1991; Bagatell et al., 1994; Hayes et al., 2000) to decrease LH secretion.

5.3. Effects of leptin

Obesity is associated with increased plasma levels of leptin, the obese gene product secreted from adipocytes. Isidori et al. examined the relationship between leptin concentrations and basal and human chorionic gonadotropin [hCG]-stimulated sex hormone levels in adult men aged less than 60 years old, subdivided into non-obese [BMI < 30], moderately obese [BMI 30–40] and massively obese [BMI > 40] (Isidori et al., 1999). They found that circulating leptin correlated with total and free testosterone even after controlling for SHBG, LH and oestradiol and that leptin was the best hormonal predictor of lower androgen levels in obese men. Leptin receptors are present in testicular tissue and leptin may play a role in reduced androgen levels in obese men.

5.4. Effect of obesity on Leydig cells and testicular function

Male C57Bl/6J-ob/ob [leptin deficient] mice have lower plasma testosterone levels, decreased LH response to GnRH and hyperplasia of pituitary gonadotrophs. In ex-vivo cultures of Leydig cells from these mice, hCG-stimulated testosterone formation and conversion of progesterone to androgens were decreased and there was an increase in lipid accumulation and a decrease in naphthylesterase activity in the Leydig cells. The changes in testicular endocrine function in obese mice were interpreted as consequences of pituitary dysfunction (Kuhn-Velten et al., 1986). In contrast, the Leydig cells of the obese Zucker rat [point mutation in the leptin receptor] testes were hypertrophied, contained numerous fat droplets and few signs of active hormone synthesis, but there was a normal pituitary response to hypothalamic stimulation (Young et al., 1982). The reason for these discrepant findings is unclear.

Dynamic studies using a single dose of hCG showed that obese men had lower peak testosterone concentrations than non-obese men (Isidori et al., 1999). INSL3, a LH-independent measure of Leydig cell function, is unaffected by obesity in men (Anand-Ivell et al., 2006).

Apart from leptin, a number of hormones involved in the regulation of food intake and metabolism are also involved in the regulation of the HPG axis. Adiponectin, resistin, ghrelin and endocannabinoids and their cognate receptors are expressed in the testis in rodents and humans, and appear to be of functional significance (Tosca et al., 2008; Goulis and Tarlatzis, 2008; Caminos et al., 2008; Nogueiras et al., 2004; Kheradmand et al., 2008; Garcia et al., 2007; Ishikawa et al., 2007; Cacciola et al., 2008), although their roles in the interaction between nutritional state, obesity and the metabolic syndrome, and testicular function in humans remains to be elucidated.

6. Obesity, obstructive sleep apnea and hypogonadism

Obstructive sleep apnea [OSA] is associated with severe intermittent hypoxia and sleep fragmentation. Although obesity is not essential for the development of OSA, about two-thirds of patients with OSA are obese (Wittels, 1985). Patients with OSA have been found to have lower free and total testosterone and SHBG independent of ageing and adiposity. Taken together the available data suggests that OSA produces a reversible dysfunction of the hypothalamic–pituitary–gonadal axis, the magnitude of which is related to the severity of the OSA and independent of the concurrent obesity (Meston et al., 2003).

A study comparing serial levels of serum LH and testosterone of 10 men who had OSA with five controls found that patients

with OSA had a significant suppression of their nocturnal testosterone rise even though they maintained a normally oriented diurnal rhythm of testosterone (Luboshitzky et al., 2002). The lower secretion of LH and testosterone at night in these patients was independent of age and degree of obesity. Some (Grunstein et al., 1989), but not all studies (Bratel et al., 1999) have shown that active treatment with nasal continuous positive airway pressure [nCPAP] increases total plasma testosterone. Another study has shown no effect of treatment with nCPAP on testosterone pulse characteristics and testosterone levels during nCPAP treatment were still lower than control men of similar ages (Luboshitzky et al., 2002). After treatment with nCPAP, patients with OSA had similar LH pulse frequency but of shorter duration and higher increment than before treatment (Luboshitzky et al., 2003).

7. Ageing, obesity and plasma testosterone

Normal ageing is characterized by changes in body composition, including a preferential increase in abdominal fat and a loss of skeletal muscle mass (Seidell and Visscher, 2000). Ageing is associated with decreased levels of testosterone and dihydrotestosterone, however age-related differences in androgen levels are partly mediated by variation in fat distribution (Couillard et al., 2000). The prevalence of the metabolic syndrome increases with age and is independently associated with lower androgen levels (Rodriguez et al., 2007) and higher oestrogen levels (Maggio et al., 2008). The absence of obesity and chronic disease and the presence of a healthy lifestyle are more important determinants of androgen levels than ageing per se (Mohr et al., 2005; Yeap et al., 2008). In multivariate models, age, waist circumference and health status were associated with low androgen levels and symptomatic androgen deficiency, and of all variables, waist circumference was the most important contributor (Hall et al., 2008).

8. Obesity and spermatogenesis

Obesity is associated with alterations in spermatogenesis. In subfertile men, obesity was three times more prevalent compared to male partners of couples with idiopathic or female factor infertility (Hammoud et al., 2006).

A cross-sectional study of 1558 Danish men found that men with both a low BMI [<20 kg/m^2] and a high BMI [>25 kg/m^2] had a reduction in sperm concentration and total sperm count compared to men with BMI between 20 and 25 kg/m^2 after correction for disorders of reproductive organs, in utero exposure to smoking and period of abstinence prior to semen sampling, although sperm morphology and motility remain normal (Jensen et al., 2004). The reduction in sperm concentration and total sperm count may be related to both the decrease in serum testosterone, SHBG and inhibin B and increased oestradiol levels with increasing BMI (Jensen et al., 2004).

Type-1 cannabinoid [CB] receptor and fatty acid amide hydrolase are particularly expressed in elongating spermatids and spermatozoa suggesting that endocannabinoids affect spermiogenesis and sperm physiology (Cacciola et al., 2008), and in the epididymis promote sperm motility through CB1 receptors (Ricci et al., 2007). Marijuana use leads to decreases in sperm concentration, defective sperm function or alteration of sperm morphology (Battista et al., 2008). The endocannabinoid system is postulated to be overactive in obesity, but the consequences of this for spermatogenesis and fertility remain unknown.

Some obesity syndromes with known genetic defects are specifically associated with abnormalities of spermatogenesis due to loss of function of a single gene responsible for both, for example the Alms1 gene in Alström Syndrome (Arsov et al., 2006) or a number of genes in a chromosomal region (15q11–q13) leading to obesity and impaired spermatogenesis, for example Prader–Willi Syndrome and Angelman Syndromes (Buiting et al., 2003). A testis-specific gene [C15orf2] is found in the Prader–Willi syndrome region on chromosome 15 (Farber et al., 2000), along with HERC2, abnormal function of which leads to sperm acrosome defects and neuromuscular abnormalities (Ji et al., 1999).

9. Obesity and hypogonadism: cause or effect?

The cause and effect relationship between obesity, insulin resistance, the metabolic syndrome, type 2 diabetes mellitus and androgen deficiency remains unclear. Data from the Massachusetts Male Aging Study showed that lower levels of total testosterone and SHBG were predictive of the development of the metabolic syndrome, particularly in men with BMI < 25 kg/m^2 (Kupelian et al., 2006). In contrast other data suggests that the metabolic syndrome is an independent risk factor for hypogonadism in middle-aged men (Goulis and Tarlatzis, 2008), and relative androgen deficiency appears to be a marker for, rather than the cause of, metabolic syndrome or diabetes mellitus in older men (Chen et al., 2006). On balance the available data suggests that hypoandrogenism is an early marker for disturbances in insulin and glucose metabolism that may progress to the metabolic syndrome or frank diabetes and may contribute to their pathogenesis (Laaksonen et al., 2004).

9.1. Effect of androgen ablation on body composition and metabolism

Androgen ablation therapy to treat advanced prostate cancer over a period of 1–5 years induces a significant increase in total body fat mass and reduction in lean body mass (Chen et al., 2002), and up to 50% of such men in one study fulfilled criteria for the metabolic syndrome by one year (Braga-Basaria et al., 2006). Greenfield et al. evaluated the prevalence of androgen deficiency in a cross-sectional, observational study of 176 cancer survivors aged 25–45 years who had received chemotherapy and/or radiotherapy (Greenfield et al., 2007). They found that 13.6% of the young cancer survivors had frankly low total testosterone levels <10 nmol/L and that this was associated with increased fat mass and increased insulin levels.

9.2. Effect of weight loss on plasma androgen levels

In response to weight loss, SHBG has been reported to either increased (Strain et al., 1988; Vermeulen et al., 1996) or remained unchanged (Stanik et al., 1981; Pasquali et al., 1988). Similarly total and free testosterone levels either increased (Stanik et al., 1981; Strain et al., 1988; Pasquali et al., 1988), remained unchanged or decreased in response to weight loss (Klibanski et al., 1981; Hoffer et al., 1986; Leenen et al., 1994).

More recent studies looked at the effects of rapid weight loss as well as weight maintenance on plasma androgen levels. Substantial weight loss induced by very low energy diets induced an increase in SHBG and total (Kaukua et al., 2003) as well as free testosterone (Niskanen et al., 2004), with some decrease in SHBG during the weight maintenance phase but with sustained effect on free testosterone up to 12 months of weight maintenance (Niskanen et al., 2004). In this group of obese men with biochemical hypogonadism, weight loss and maintenance normalized total testosterone and bioavailable testosterone levels in 70% and 50%, respectively.

The relationship between the magnitude, rapidity of weight loss, macronutrient intake, and effects within specific patient populations (generalized obesity, predominant visceral obesity, metabolic

syndrome, and presence of obstructive sleep apnea) on plasma testosterone and SHBG remains to be determined.

9.3. Effects of testosterone replacement therapy

Testosterone replacement therapy consistently decreases fat mass and increases lean body mass in men with acquired hypogonadism over 18 months (Katznelson et al., 1996) as well as in middle-aged (Allan et al., 2008) and older men with relatively low testosterone levels over either 12 (Wittert et al., 2003) or 36 months (Page et al., 2005). Testosterone therapy reduces visceral fat accumulation in proportion to the increase in testosterone levels (Allan et al., 2008).

Despite the consistently observed beneficial effects of androgen supplementation on body composition, the evidence for beneficial effects on metabolic profile is limited. In general LDL-cholesterol and triglyceride levels decrease but neither HDL-cholesterol nor insulin sensitivity are significantly altered in viscerally obese men (Page et al., 2005; Liu et al., 2003a). A recent meta-analysis failed to find that testosterone use in men was associated with significant cardiovascular benefits (Haddad et al., 2007).

The current combined international recommendations suggested that testosterone treatment for men with hypogonadism and diabetes or the metabolic syndrome is not recommended as treatment for the metabolic disturbance (Wang et al., 2008). Nevertheless given the effects of testosterone on body composition it remains possible that testosterone supplementation has a role in preventing the progression of obesity-related metabolic disturbance in men with associated low plasma testosterone.

In hypogonadal men with OSA, androgen replacement therapy should be used with caution because although physiological studies have previously indicated that testosterone administration increased ventilation (White et al., 1985) it has been shown that testosterone therapy given to hypogonadal men shortened sleep, worsened sleep apnoea and disrupted breathing during sleep (Liu et al., 2003b; Schneider et al., 1986).

10. Conclusion

Obesity, the metabolic syndrome, and type 2 diabetes mellitus are associated with low plasma testosterone levels which should be regarded as a marker of, and possibly risk factor for progression of disordered metabolism. The mechanisms and cause and effect relationships remain to be determined. In addition although there is an association between obesity and abnormalities of spermatozoa, the prevalence and functional consequences, similarly remain to be determined.

Lifestyle intervention is of benefit for the prevention of cardiovascular disease and type 2 diabetes mellitus and weight loss is also associated with improvement in plasma testosterone levels. In contrast the benefit of weight loss for abnormalities of spermatozoa is unknown. The role, if any for androgen supplementation remains to be determined.

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