Review Article

Androgen deficiency and metabolic syndrome in men

Ashley G. Winter[1], Fujun Zhao[2], Richard K. Lee[1]

[1]James Buchanan Brady Foundation, Department of Urology, Weill Medical College of Cornell University, New York, NY 10065, USA; [2]Department of Urology, Shanghai First People's Hospital, Shanghai Jiao Tong University, Shanghai 20080, China

Correspondence to: Dr. Richard K. Lee, MD, MBA, Instructor. James Buchanan Brady Foundation, Department of Urology, Weill Medical College of Cornell University, 425 E. 61st Street, 12th floor, New York, NY 10065, USA. Email: ril9010@med.cornell.edu.

Abstract: Metabolic syndrome (MetS) is a growing health concern worldwide. Initially a point of interest in cardiovascular events, the cluster of HTN, obesity, dyslipidemia, and insulin resistance known as MetS has become associated with a variety of other disease processes, including androgen deficiency and late-onset hypogonadism (LOH). Men with MetS are at a higher risk of developing androgen deficiency, and routine screening of testosterone (T) is advised in this population. The pathophysiology of androgen deficiency in MetS is multifactorial, and consists of inflammatory, enzymatic, and endocrine derangements. Many options for the concomitant treatment of both disorders exist. Direct treatment of MetS, whether by diet, exercise, or surgery, may improve T levels. Conversely, testosterone replacement therapy (TRT) has been shown to improve MetS parameters in multiple randomized controlled trials (RTCs).

Keywords: Androgen deficiency; metabolic syndrome (MetS); obesity; late-onset hypogonadism (LOH); testosterone deficiency

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Introduction

Metabolic syndrome (MetS) is a multi-system disorder marked by combinations of glucose intolerance, obesity, hypertension, and dyslipidemia. Broad medical awareness of this condition has come hand in hand with the rapidly expanding population of adults afflicted with obesity and diabetes. Initially linked to risk factors for cardiovascular disease, the components of MetS have been implicated in a range of other disease processes. Study of men with MetS has indicated a strong relationship to adult androgen deficiency and late-onset hypogonadism (LOH). This review intends to summarize our current understanding on the epidemiology, pathophysiology, and dual treatment of these disorders.

Definitions

Metabolic syndrome (MetS)

A singular definition of MetS does not exist. Medical organizations have developed diagnostic criteria with specific, and different, end-goals such as prediction of cardiovascular events or subsequent development of diabetes (1). There are four major definitions of MetS (*Table 1*), developed by the World Health Organization (WHO) (2), the European Group for the Study of Insulin Resistance (3), the Adult Treatment Panel of the National Cholesterol Education Program (NCEP-ATPIII) (4), and the International Diabetes Federation Consensus Group (5). Across all of these definitions are common elements, including insulin resistance, central obesity, hypertension, and dyslipidemia. For this review, we focused on studies involving men that formally meet MetS criteria, as well as men afflicted with varying degrees of individual components (i.e., obesity).

Androgen deficiency

Defining androgen deficiency is a somewhat daunting task, as the physiologic, pathologic, and biochemical implications of this definition are complex and still evolving. For the

Table 1 Definitions of metabolic syndrome

Source	Parameters defining metabolic syndrome
International Diabetes Federation [2005]	Central obesity and at least 2 of the following: Hypertension ≥130/85 mmHg or drug treatment TG ≥150 mg/dL or drug treatment HDL-C <40 mg/dL Fasting glucose ≥100 mg/dL
US National Cholesterol Education Program Adult Treatment Panel III [2005]	At least 3 of the following: Waist circumference: ≥40 in (102 cm) Hypertension ≥130/85 mmHg or drug treatment TG ≥150 mg/dL or drug treatment HDL-C <40 mg/dL Fasting glucose ≥100 mg/dL or drug treatment
European Group for the Study of Insulin Resistance [1999]	Insulin resistance (fasting insulin level within top 25% of non-diabetics), and at least 2 of the following: Waist circumference: ≥94 cm Hypertension ≥140/90 mmHg or drug treatment TG ≥2.0 mmol/L and/or HDL-C <1.0 mmol/L Fasting glucose ≥6.1 mm/L
World Health Organization [1999]	Presence of: diabetes mellitus, impaired glucose tolerance, impaired fasting glucose OR insulin resistance, and at least 2 of the following: Waist:hip ratio >0.9 (male); or BMI >30 kg/m^2 Hypertension ≥140/90 mmHg TG ≥1.7mmol/L and HDL-C ≤0.9 mmol/L Urinary albumin excretion ratio ≥20 μg/min or albumin:creatinine ratio ≥30 mg/g

BMI, body mass index; TG, triglycerides; HDL-C, high density lipoprotein cholesterol.

Table 2 Signs and symptoms associated with late-onset hypogonadism

Hot flashes
Body hair loss
Fatigue
Depression
Decreased bone mass
Decreased muscle mass
Erectile dysfunction
Loss of libido

purpose of this review, androgen deficiency refers to testosterone (T) deficiency, and indicates failure of the testes to produce T due to either (I) an impairment of the hypothalamic/pituitary axis; or (II) a local deficit of the testes (6). From a clinical perspective, androgen deficiency is intrinsically linked to male hypogonadism, which is the group of signs and symptoms specifically due to either androgen deficiency or impaired action of sex steroids in effector organs (6).

Male hypogonadism consists of a spectrum of disorders that vary depending on when androgen deficiency occurs. In the context of the MetS, this specifically refers to LOH. LOH is due to low androgen levels beginning after puberty and therefore do not affect development of male anatomy or secondary sex characteristics (7). The symptoms of LOH are vague, non-specific, and commonly overlap with symptoms of aging. These symptoms include, but are not limited to, sexual symptoms, such as low libido and erectile dysfunction, loss of muscle mass and bone density, depression, and hot flashes (*Table 2*) (8). Due to the vague nature of these symptoms, questionnaires are generally plagued by low specificity (30-59%) (9). Nevertheless, in a population-based study of 3,369 men, the three sexual symptoms of poor morning erections, low sexual desire, and erectile dysfunction were found to have a syndromic association with low T levels (10). Assessment of symptoms is therefore considered an integral factor when deciding on whom to perform laboratory T testing; asymptomatic, healthy men generally do not qualify (11,12).

Prior to discussing specific values used to define androgen deficiency, it is important to highlight the complexities associated with T testing. T bioavailability is broken up into several parts. Specifically, T circulates

Table 3 Basic laboratory evaluation of male hypogonadism

Hormone	Recommendations
TT	Measure on at least two separate occasions Draw sample during morning hours, ideally between 700 and 1,100 Indications for supplementation: TT >12 nmol/L (350 ng/dL)—TRT not indicated TT <8 nmol/L (230 ng/dL)—TRT generally indicated TT between 8 and 12 nmol/L—borderline
FT	Assess when TT is borderline (8-12 nmol/L) Methodology: Calculate FT from measured SHBG, or Measure FT directly using equilibrium dialysis Indications for supplementation: FT <225 pmol/L (65 pg/mL)—TRT generally indicated
LH	To differentiate between primary and secondary hypogonadism

TT, total testosterone; FT, free testosterone; TRT, testosterone replacement therapy; SHBG, sex hormone binding globulin; LH, luteinizing hormone.

in four forms: (I) tightly bound to sex-hormone binding globulin (SHBG) (~44%); (II) loosely bound to albumin (~50%); (III) loosely bound to corticosteroid binding globulin (CBG) (~4%), and unbound, or free testosterone (FT) (~2-3%) (13). The bioavailable, or active, T, consists of the free portion in addition to the CBG and albumin-bound T (13). There is no reference range for normal T that has been derived from a cohort of reproductive-age men with normal sexual function and fertility (13). T can vary over three orders of magnitude within the population. Further, T varies up to 50% in younger men with diurnal and seasonal variation (13). Common assays for T have less sensitivity in the low to low normal range (6).

As with MetS, several organizations have issued guidelines detailing the specific parameters that define androgen deficiency. These include the International Society for the Study of Aging Male (ISSAM), the International Society of Andrology (ISA), the European Associate of Urology (EAU), the European Society of Andrology (ESA), and the American Society of Andrology (ASA) (8,14,15). There are several generally agreed upon principles across guidelines (*Table 3*). Although there is no clear number separating low total testosterone (TT) from normal TT, 12 nmol/L or 360 ng/dL, is usually considered normal, while 8 nmol/L, or 240 ng/dL, is low. In men with a borderline value, assess FT, either by equilibrium dialysis, or by measurement of SHBG and calculation of FT level. Other methodologies of FT assessment are considered unreliable (6,13,15).

Recent investigation has focused on broader definitions of androgen deficiency/hypogonadism which consider molecular-cellular mechanisms in addition to the traditional measurement of circulating hormones (16,17). For instance, genetic variants in the androgen receptor (AR) may alter its activity, and the stability intracellular proteins, such as heat-shock protein 70 (HSP70), may subdue androgen-regulated transcription (16). Such investigations have led to a mechanistic understanding of how certain patients can exhibit symptoms of androgen deficiency in the presence of normal laboratory testing (16).

Epidemiology

According to CDC data, approximately 34% of United States adults meet NCEP/ATPIII criteria for MetS (18). The prevalence increases with age, and more than 50% of men above 60 years of age have the condition (18). Individual components of MetS are becoming increasingly common. For example, obesity rose from 27.5% of U.S. adult men in 2000 to 35.5% of U.S. adult men in 2010 (19); prevalence of MetS is considered to mirror this trend.

Epidemiologic data regarding androgen deficiency is not as robust as that for MetS. The true prevalence is unknown, with reports varying between 2.1% and 40% of adult men (6). Different definitions of androgen deficiency employed and populations studied likely account for the range in reported prevalence. The occurrence of androgen deficiency is much higher in men who have MetS than their healthy counterparts (7), and this trend has been shown reliably. Barrett-Connor, *et al.* reported on a group of men aged 40-79 where TT level below 350 ng/dL was found in 21% of diabetic men *vs.* only 13% of non-diabetic men (20). In a study of symptomatic men over 73 years of age, TT levels under 300 ng/dL were found in 64% of men with DM, but only 38% of non-diabetic men (21). The Study of Health In Pomerania (SHIP) showed that men with low TT concentrations showed a highest risk of incident MetS (22). This trend is so prominent that presence of MetS is considered an independent indication for T screening by most guidelines (8,14,15).

Mechanism and pathophysiology

The link between MetS and androgen deficiency is clear, but the exact mechanism by which men with MetS develop

Table 4 Mechanisms of metabolic syndrome-related male hypogonadism

Mechanism	Comment
Leptin	Direct effect on leydig cells—decreased T production
Inflammation	Disruption of steroid testicular steroid synthesis
Increased aromatase activity	Increased T → estradiol conversion → increased negative feedback on hypothalamic and pituitary → hypogonadotrophic hypogonadism
Decreased SHBG	Reduced TT
	Low SHBG independent risk factor for DM
Sleep apnea	Hypothalamic and pituitary suppression → hypogonadotrophic hypogonadism
Endogenous opioids	Decrease LH secretion
Testicular environment	Increased testicular temperature

T, testosterone; SHBG, sex hormone binding globulin; TT, total testosterone; LH, luteinizing hormone.

low T is most likely multifactorial. Several mechanisms have been elucidated (*Table 4*).

Leptin

MetS may influence hypogonadism through leptin, a hormone produced in adipocytes. Leptin acts on the hypothalamus, regulating energy intake (23). Leptin levels have been directly correlated to body mass index (BMI) (24). Interestingly, leptin concentration varies inversely with serum T, even when controlling for BMI and insulin levels (25). Leptin has direct, receptor-mediated actions on leydig cells in rats, providing a likely mechanism for the clinical observations in humans (26). Rat leydig cells incubated with leptin had a significant decrease in β-HCG mediated T production (26).

Inflammation

MetS is associated with a systemic inflammatory state, with increased levels of IL1, IL6, and TNF-α (27,28). Inflammatory agents predominantly affect testicular steroid production. TNF-α inhibits steroid-mediated transcription in leydig cells through NF-kB (29). IL1 inhibits cytochrome P450 mediated cholesterol side chain cleavage in leydig cells (30).

Aromatase

P450 aromatase is highly expressed in fat tissue, and catalyzes the conversion of T to estrogen. Men with MetS and central obesity develop estrogen-induced negative feedback on the hypothalamus and pituitary. Aromatase inhibitor use raised T level in obese men in several studies (31-34).

Decreased sex-hormone binding globulin

Insulin has been shown to decrease SHBG in hepatocytes *in vitro* (35). In a prospective analysis of men from the Massachusetts Aging Study, lower levels of both FT and SHBG independently predicted subsequent diabetes. The odds ratio (OR) for diabetes was 1.89 for a 1 SD decrease in SHBG [95% CI (range, 1.14-3.14)]. SHBG increases with age, but obese men had a slower age-adjusted increase in SHBG, leading to more rapid decline in TT with age (36).

Sleep apnea

Obstructive sleep apnea (OSA) has been correlated with MetS (37). Multiple studies have associated OSA with low baseline T levels in men (38,39). Researchers recently found apnea indicators, such as hypopnea index and percent time below SpO_2 90% and 80%, to be independently associated with decreased T levels (40). Prospective data regarding the efficacy of OSA treatment on T levels is mixed. Several studies report increase of T with continuous positive pressure ventilation (CPAP) (41,42), whereas other studies note a change in SHBG, prolactin, or sexual function parameters independent of T (43-45). OSA suppresses the hypothalamic pituitary axis, disrupting LH secretion and inducing hypogonadotropic androgen deficiency (46).

Endogenous opiods (extremely obese)

In extremely obese men, the opioid antagonist naloxone was found to increase LH by 43%, indicating that endogenous opioids found in the morbidly obese may contribute to a hypogonadal state (47).

Direct effect on testicular environment

In men with MetS associated obesity, T levels may be further impaired as fat deposition in the lower abdomen increases testicular temperature (48).

Other

It should be noted that a number of studies have suggested that androgen deficiency causes MetS, rather than vice versa. SHIP for instance showed that men with low TT concentrations demonstrated the highest risk of incident MetS (22).

Treatment

Many treatments for MetS-associated androgen deficiency lack efficacy data from randomized controlled trials (RCTs). Comparing existing studies can be difficult, as definitions, patient populations, and treatment goals are heterogeneous. There are two major ways of categorizing treatments: (I) by which disease process is targeted, either MetS or androgen deficiency directly; (II) non-surgical *vs.* surgical interventions.

Behavioral modification

A number of RCTs have assessed the effect of weight loss on androgen levels (48-53). Results are conflicting; some studies demonstrate T rise with low-calorie diet (52,53), while others showing no change (48,49,51). A recent meta-analysis found that weight loss improved TT in obese men (P<0.0001) (54). Meta-regression analysis of the included studies found testosterone rose more in younger men and men without diabetes (P<0.0001) (54). Consistent with previously mentioned mechanisms, weight loss resulted in decreased estradiol and increased gonadotropin levels (54). Niskanen *et al*. showed that the improvement in testosterone levels was directly correlated with the degree of weight loss (55).

Metformin

Metformin is a commonly prescribed diabetes medication. Data regards its utility in treating androgen deficiency is conflicting. Ozata *et al*. administered metformin 850 mg twice daily to 40 obese men for three months in conjunction with a hypocaloric diet. They noted a decrease in FT in obese non-diabetic men and a decrease in TT in obese men with type 2 diabetes (56). Casulari *et al*. studied 35 men with MetS following four months of metformin 850 mg BID and a normo-caloric diet. Both FT and TT increased, regardless of whether or not they were baseline androgen deficient (57). Morgante *et al*. gave 45 men with MetS metformin for six months. At the end of the study period, both FT and semen parameters were significantly improved (58). TT rose an average of 0.9 ng/mL (P<0.02), FT rose an average of 14 pg/mL (P<0.001), and semen concentration, % motility, and normal morphology all increased (P<0.001) (58).

Gonadotropin and Gonadotropin-releasing hormone (GnRH)

Gonadotropin and pulsatile GnRH administration has been used in men with LOH who desire fertility. Due to cost and complexity of administration, these agents are no considered first line therapy in absence of fertility concerns. Data regarding the use of these agents in men with MetS are limited (59).

Testosterone replacement therapy (TRT)

To date, there are six RCTs assessing the effect of TRT on men with MetS or diabetes (52,60-64). Combined, these RCTs include 483 patients with an average of 57 weeks follow-up. A recent meta-analysis of this data showed that TRT improved fasting blood glucose by a mean of 0.48 mmol/L (P<0.001), lowered triglyceride levels by a mean of 0.4 nmol/L (P<0.001), and reduced waist circumference by approximately 4.1 cm (P=0.03) in men with MetS (6). From a pathophysiologic standpoint, TRT has been shown to decrease cytokine production in men with MetS; TRT may positively impact these individuals through an anti-inflammatory effect (7).

Antiestrogens

In the male, selective estrogen receptor modulators (SERMs) exert an antagonist effect on estrogen receptors in the hypothalamus and pituitary gland that regulate gonadotropin release. SERM administration leads to increased FSH, LH and testis activity (6). Guay *et al*. demonstrated that treatment with clomiphene citrate increased LH, FSH, TT and FT significantly in men with secondary hypogonadism and ED (65). Given the estrogen-mediated component of hypogonadism in MetS, this may represent a useful therapy in this population.

Surgery: bariatric

The positive impact of bariatric surgery on TT levels appear to be greater than those of non-surgical weight loss and are associated with significant improvement of erectile function and sex-related quality of life (49,66). A recent meta-analysis, for example, demonstrated improved TT following bariatric surgery, with a more significant association between TT rise and bariatric surgery than between TT rise and low-calorie diet (54). Only two RCTs exist analyzing the connection between bariatric surgery and hypogonadism (49,50). Reis *et al*. randomized 20 men to either gastric bypass or control, and noted increased TT, FT, and FSH in men undergoing surgery relative to control at 20 months follow-up (49). Mingrone *et al*. randomized 27 men to either diet or malabsorptive surgery and followed them for one year. Men undergoing malabsorptive surgery had a significant increase in SHBG level, with an average rise of 40 nmol/L (P<0.0001), whereas men randomized to low-calorie diet did not (50).

Surgery: varicocelectomy

Varicocele has traditionally been associated with male infertility, although more recent data suggests that it may be a risk factor for low T levels. The exact pathophysiology of the negative effects of varicocele on testicular function, however, is not well understood, and the empiric experience has been limited to infertile patients. Recent data suggests that microsurgical varicocelectomy improves T levels in infertile men with varicocele (64,67,68).

Ozturk *et al*. investigated the influence of MetS on success of varicocele repair. A total of 56 men without MetS *vs*. 48 men with MetS underwent varicocele repair. Spontaneous pregnancy rate at two years follow up was 45% in the non-MetS group *vs*. 34% in the MetS group (P<0.05) (69). Varicocelectomy may improve T levels in fertile patients with hypogonadism, but empiric evidence is currently lacking.

Summary

MetS is a growing health concern worldwide. Initially a point of interest in cardiovascular events, the cluster of HTN, obesity, dyslipidemia, and insulin resistance known as MetS has become associated with a variety of other disease processes, including androgen deficiency and LOH. Men with MetS are at a higher risk of developing androgen deficiency, and routine screening of T is advised in this population. The pathophysiology of androgen deficiency in MetS is multifactorial, and consists of inflammatory, enzymatic, and endocrine derangements. Many options for the concomitant treatment of both disorders exist. Direct treatment of androgen deficiency with MetS, whether by diet, exercise or surgery, will improve T levels. Conversely, TRT has been shown to treat MetS in multiple RTCs.

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Footnote

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