

Androgens, Obesity, and Sleep-Disordered Breathing in Men

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The widening obesity epidemic and male reproductive function

A worldwide obesity epidemic in genetically predisposed populations, sustained by effortless access to affordable high-caloric food and a sedentary modern lifestyle, threatens health care resources [1–8]. Even seemingly minor energy imbalances can produce massive obesity if sustained over a sufficiently long period [2], particularly if applied over an entire population. One in three Americans is classified as obese, and this number has been steadily rising [9]. Similar trends are apparent across the Pacific ocean, but only one in five Australians are obese [10,11]. These trends are likely to worsen if documented declines in physical activity and larger food intake persist [12,13]. Concern arises because obesity predicts increased mortality [14,15], particularly through its linkage with important comorbidities such as diabetes mellitus, cardiovascular disease, the metabolic syndrome, and obstructive sleep apnea (OSA) [8,16–37].

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A fundamental relationship between energy balance and reproductive function exists from an evolutionary perspective in many mammalian species to ensure that population growth is controlled during times of famine. Epidemiologic evidence also links male reproductive function (and one of its key prerequisites, normal androgen action) with obesity. Reduced fertility has been documented recently in a large cohort of 1329 overweight and obese men [38]. Obese men may have lower sperm concentration [39] and reduced sperm quality [40]. However, such studies relying on semen collection are known to be unrepresentative of the population being studied. Obesity is associated with sexual and erectile dysfunction [41], and weight loss in obese men improves erectile function [42]. These relationships could be further modulated by altered androgen action because the polyglutamate repeat length in exon 1 of the androgen receptor (which is a known functionally relevant polymorphism that influences androgen receptor sensitivity by modulating transactivation efficiency [43–48]) was found to be weakly associated with central obesity in a study of 99 men [49]. Studies in twins suggest that other polygenic factors govern erectile function, but these remain poorly defined [50].

Interventional studies designed to examine the role of androgens in the energy balance of obese men have been largely contradictory and underpowered. One uncontrolled pilot study reported reduced waist/hip circumference and improved insulin sensitivity in eight men treated for 3 months with transdermal testosterone (250 mg in 10 g gel daily) but found no effect in another nine men treated for the same duration with transdermal dihydrotestosterone (250 mg in 10 g gel daily) [51]. The same investigators also reported a double-blind study in which 28 middle-aged men who had abdominal obesity were randomized to receive transdermal placebo, testosterone (125 mg in 5 g gel daily), or dihydrotestosterone (125 mg in 5 g gel daily) gel for 9 months [52]. Compared with treatment with dihydrotestosterone and placebo, testosterone treatment inhibited lipid uptake into adipose tissue, decreased serum triglycerides and lipoprotein lipase activity, reduced visceral fat (as shown by CT scan), and increased insulin sensitivity [52,53]. Another study failed to detect any beneficial effect, but an interim change in study design unblinded treatment assignment and reduced power. Although no consistent testosterone effects were reported, the unplanned change in study design limits interpretation [54].

These preliminary data suggest that testosterone treatment may improve body composition, but studies have been underpowered to detect clinically significant weight changes or changes in adipose tissue depots. Reduced fat mass is supported by ancillary data from 32 older men, seven of whom were obese (body mass index greater than 30), which showed that therapeutic androgen therapy decreased total and abdominal fat [55]. A similar trend was seen in young men who had classical androgen deficiency [56].

Strategies to specifically enhance weight loss in obese men within the framework of the core lifestyle interventions of diet restriction and exercise

promotion are needed [57] because obese men have proportionally worse health consequences because abdominal (android) obesity and OSA are more prominent in men and because current antiobesity strategies have generally only been successfully applied to women [30,57,58]. Such methods are likely to succeed because men who participate in weight-loss programs are more likely than women to undergo behavioral modifications [57], and men can lose weight more easily because they require a smaller reduction in energy balance to effect loss of fat [59].

The metabolic syndrome

The metabolic syndrome is a constellation of abdominal obesity, insulin resistance, hypertension, and dyslipidemia, which is variably defined but probably refines and explains many of the health consequences of obesity and highlights the central pathogenic role of visceral (abdominal) obesity and insulin resistance. Whether the syndromic collection of these seemingly diverse factors has consequences beyond those known for each factor alone is debated, leading to the suggestion that a specific diagnosis of the metabolic syndrome is neither useful nor necessary [60]. Furthermore, the World Health Organization, the Third Report of the National Cholesterol Education Program's Adult Treatment Panel, the European Group for study of Insulin Resistance, the American Association of Clinical Endocrinologists, and the International Diabetes Foundation have each advocated slightly different definitions of the metabolic syndrome around similar core features [17,60]. The differences are not trivial because discordant classification occurs in up to 20% of Americans [60]. Nevertheless, approximately one in four American adults has the metabolic syndrome [17], and its definition probably remains a useful contribution to the problem.

Recent epidemiologic data have implicated the role of androgens in the pathogenesis of the metabolic syndrome in men. In non-obese Caucasian men residing in the greater Boston area, sex hormone-binding globulin (SHBG), testosterone, and symptomatic androgen deficiency independently predict development of the metabolic syndrome [61]. These data largely confirm previous data in other populations [62] and extend existing knowledge that SHBG and testosterone predict diabetes mellitus and central adiposity [63–65]. The longitudinal and population-based nature of these cohorts from around the world is an important design strength. Conversely, metabolic syndrome can predict future development of hypogonadism [66]. These data suggest that reproductive function and metabolic syndrome are interlinked, perhaps independently of the aforementioned relationships between reproductive function and obesity.

Abdominal obesity (indicated clinically by waist circumference) is a central component of the metabolic syndrome and may be more important than total fat mass (indicated by body mass index) as a cardiovascular risk marker [67]. Visceral abdominal fat is independently associated with

increased blood pressure, waist circumference, triglycerides, fasting plasma glucose, and low high-density lipoprotein cholesterol levels, each of which is an independent risk factor for cardiovascular disease [68]. Visceral abdominal fat is also an independent predictor of all-cause mortality, as shown in a community-based randomly selected nested case-control study [69]. For these reasons, abdominal obesity is the primary target for the treatment of the metabolic syndrome [17]. Androgen therapy reduces visceral abdominal fat in a wider range of men, including those who are older [55], abdominally obese, and middle-aged [51,70] or hypogonadal [56]. This effect is probably potentiated by the greater androgen receptor expression in visceral abdominal rather than subcutaneous fat [71].

Insulin resistance is the other central component of the metabolic syndrome and is associated with shortened lifespan and reduced quality of life [8]. Insulin resistance is associated with obesity, particularly abdominal obesity, and with low serum testosterone concentrations [64,65]. Although testosterone replacement should theoretically decrease insulin resistance by increasing muscle and decreasing (abdominal) fat, interventional studies suggest otherwise (Table 1) [72–77]. Mainly equivocal effects of androgen supplementation on insulin sensitivity have been reported in a wide range of men with or without reproductive disorders (see Table 1). This could be explained by other counteracting effects of testosterone. For example, adiponectin, a fat-secreted hormone, is normally observed with favorable changes in body composition and has beneficial systemic effects, such as improved insulin sensitivity [78]. However, testosterone therapy seems to decrease serum adiponectin concentrations [79,80].

Obstructive sleep apnea

OSA affects approximately 25% of middle-aged men [81]. It is characterized by repeated episodes of nocturnal upper airway occlusion leading to hypoxemia and is commonly associated with sleep fragmentation and loss of normal sleep architecture [82]. Sleepiness, attention deficit, and neurocognitive impairment cumulatively increase accident risk [83,84]. Independent of obesity, men who have OSA have proportionally greater all-cause mortality and stroke [85], cardiovascular mortality [86], hypertension and arrhythmia [87], diabetes mellitus [88], visceral abdominal fat, and insulin resistance [89–93]. These manifestations occur largely due to apnea-associated sleep fragmentation and intermittent hypoxemia, both of which are prevented with the standard therapy, nasal continuous positive airway pressure (CPAP). This treatment delivers pressurized air to the nose via a nose mask, thereby splinting open the upper airway during sleep and re-establishing normal breathing and sleep patterns.

The male preponderance of OSA provides preliminary evidence that gonadal function is related. This rationale is strengthened by its association with obesity, decreased blood testosterone concentrations, metabolic

Table 1
Effect of androgenic supplementation on insulin sensitivity in men

Study	Subjects	Androgen	No	RCT	Effect
Non-intramuscular					
Liu, 2003 [72]	Normal	Subcutaneous r-hCG	30	+	0
Marin, 1993 [70]	Centrally obese	Transdermal T or DHT	27	+	+ or 0
Marin, 1992 [51]	Centrally obese	Oral T	25	+	+
Intramuscular					
Singh, 2002 [73]	Normal	T	61	+	0
Lovejoy, 1995 [54]	Centrally obese	Oral oxandrolone then intramuscular nandrolone, or intramuscular T	30	–	0 or 0
Hobbs, 1996 [74]	Normal	T or nandrolone	11	–	0 or ±
Saad, 2001 [75]	Pubertal delay	DHT	10	–	0
Arslanian, 1997 [76]	Pubertal delay	T	7	–	0
Tripathy, 1998 [77]	Gonadotropin deficient	T	10	–	0

Abbreviations: DHT, dihydrotestosterone; RCT, randomized, placebo-controlled trial; r-hCG, recombinant human chorionic gonadotropin; T, testosterone; 0, no significant change; ±, equivocal change.

Data from Liu PY, Swerdloff RS, Veldhuis JD. Clinical review 171: the rationale, efficacy and safety of androgen therapy in older men: future research and current practice recommendations. *J Clin Endocrinol Metab* 2004;89:4789–96.

syndrome, and cardiovascular disease. Men who have OSA have suppressed pituitary-gonadal function; this may be due to recurrent hypoxia, sympathetic overstimulation, or other mechanisms. Low systemic testosterone concentrations in such men (and its reversibility with nasal CPAP therapy) have been long recognized [94] and more recently confirmed in other cohorts [95,96] and by multiple overnight blood sampling of leuteinizing hormone and testosterone concentrations [97]. These studies also implicate the degree of hypoxia and disordered breathing independently of increasing age or obesity in the pathogenesis of pituitary-gonadal dysfunction. The direction of this association and its reversibility have recently been examined for the first time in a randomized sham CPAP, placebo-controlled study of 101 men [96]. Total testosterone and leuteinizing hormone significantly fell in men who had moderate OSA randomized to receive 1 month of subtherapeutic nasal CPAP but did not change in the adequately treated men. Although significant

between-group increases in total testosterone and SHBG were seen, the modest changes observed contrast with those found in the earlier, less well controlled report [94] and may be explained by shorter duration of treatment and less severe baseline disease. Nevertheless, the fact that these large studies [94,96] show reversal of OSA-associated hypogonadism with CPAP is consistent with similar trends observed in smaller studies [98,99].

Increased visceral abdominal fat and decreased insulin sensitivity commonly occur together, possibly because visceral abdominal fat strongly determines lipid supply to liver and muscle. Increased intrahepatic and intramyocellular lipid causes insulin resistance [100]. Insulin resistance and diabetes mellitus are associated with OSA in large, population-based, epidemiologic studies [88,89]. Mechanistically, impaired glucose tolerance follows recurrent hypoxia [101]. On one hand, insulin resistance may be related to alterations in autonomic (sympathetic overactivity indicated by increased blood catecholamines) and neuroendocrine function induced by recurrent hypoxemia and sleep fragmentation. On the other hand, excessive release of inflammatory cytokines and adipokines may be responsible [89,102–104]. For these reasons, OSA most likely causes insulin resistance, although few studies have examined whether reversal of sleep-disordered breathing with CPAP can improve insulin sensitivity. Controlled trials (using a no-treatment control group) are not available, and only two studies adequately measured insulin sensitivity by gold standard methods (such as hyperinsulinemic euglycemic clamp or minimal model analysis) [89]. These two uncontrolled studies showed that CPAP improved insulin sensitivity in men with [105] or without diabetes mellitus [106]. In 40 men who had at least moderate OSA (apnea-hypopnea index greater than 20 events/h) without diabetes mellitus, CPAP improved insulin sensitivity (5.75 ± 4.2 baseline versus 6.79 ± 4.91 $\mu\text{mol/kg/min}$; $P = .003$) within 2 days, and this improvement was sustained for 3 months [106]. The rapid improvement in insulin sensitivity was much greater in non-obese men. These data implicate recurrent OSA in the pathogenesis of insulin resistance, which is one of the core components of the metabolic syndrome. Potential mediators involved in this relationship include altered adrenergic function, direct effect of hypoxemia on glucose regulation, and release of proinflammatory cytokines that alter metabolism [89].

Only two longitudinal (uncontrolled) studies have examined the effect of CPAP therapy on visceral abdominal fat in men who have severe OSA [107,108]. In the earlier study of 22 men [107], visceral abdominal fat area decreased by 50 cm^2 after 6 months of CPAP irrespective of any change in total body weight. In a more recent study of 29 men [108], at least 3 months of CPAP decreased visceral abdominal fat by 8% in 19 post-hoc classified regular CPAP users. Randomized, sham-controlled, CPAP-controlled trials are not available but are needed to properly address this question.

The interrelationships among testosterone, obesity, and obstructive sleep apnea

The preceding discussion strongly implicates an interdependence among gonadal function, obesity, and OSA. We propose that low blood testosterone, obesity, and OSA are linked in men by two interrelated cycles (Fig. 1), in which depressed testosterone plays a central role. Decreased testosterone is a metabolic consequence of obesity. Men who are obese have lower serum testosterone concentrations and lower SHBG compared with age-matched, non-obese men, and this may be due to hypothalamic dysfunction [109,110] or increased testosterone metabolic clearance rate [111]. Weight loss restores systemic gonadotropin and testosterone concentrations to the reference range of healthy, young adult men [112]. Increasing obesity predicts lower future serum testosterone [113,114], possibly due to decreased lipolysis of abdominal fat [53]. In a randomized, controlled study of 28 middle-aged, abdominally obese men, 9 months of testosterone therapy inhibited directly measured lipoprotein lipase activity in biopsied abdominal fat. Cross-sectional representative, population-based studies show that increasing abdominal obesity is related to decreasing serum testosterone [115,116]. Conversely, low blood testosterone concentrations predict the future development of obesity, particularly visceral obesity [63,117], and organic androgen deficiency is associated with increased fat mass [118]. Androgen therapy rapidly increases muscle and decreases fat mass in hypogonadal and eugonadal young and older men [119–122].

The apparent bidirectional relationship between low serum testosterone and visceral obesity leads to a vicious cycle whereby low testosterone concentrations contribute to visceral obesity, and visceral obesity further reduces circulating testosterone (see Fig. 1). This suggests that obesity is a state of relative androgen deficiency.

OSA is also associated with morbid obesity and androgen deficiency [94,96,97]. Adequate treatment of OSA by CPAP therapy or with surgery reverses these hormonal deficits, suggesting that OSA causes androgen

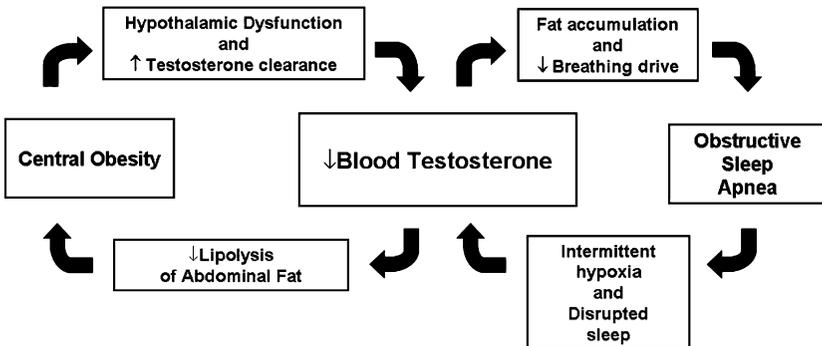


Fig. 1. The inter-relationships among low blood testosterone, obesity, and OSA.

deficiency [94,96,123]. These longitudinal data [94,123] have been verified by an aforementioned randomized, sham-controlled trial of CPAP therapy, which additionally showed a strong negative correlation between OSA severity and blood testosterone [96]. Low systemic testosterone exposure could be the consequence of severe oxygen desaturation [95] or decreased or disrupted sleep [124]. Conversely, decreased testosterone levels alter fat distribution and breathing drive, either of which could further impair sleep breathing [102,125]. Hence, we also propose that there is a vicious cycle of testosterone deficiency and sleep apnea (see Fig. 1).

We and others have shown that high-dose (two to four times the conventional dose), supraphysiologic, short-acting androgen administration acutely increases sleep apnea in a small proportion of hypogonadal and elderly men [122,126]. These systematic reports follow earlier nonrandomized case reports [127–129]. It may be that either either insufficient (by promoting fat gain) or supraphysiologically high testosterone exposure promotes sleep-disordered breathing. More physiologic, lower-dose, and near steady-state testosterone therapy has no negative effects on sleep breathing [119,130], a finding that has been supported by a recent rigorously conducted meta-analysis [131]. Three years of transdermal testosterone patch therapy titrated to maintain a young eugonadal blood testosterone concentration in 96 men over 65 years of age does not adversely affect breathing during sleep [119,132]. Disordered breathing was detected by pulse oximetry (not standard overnight laboratory polysomnography) in this study, indicating that subtle changes in sleep breathing may have been undetected. This observation is pertinent because one third of United States men in this age group will have (largely undiagnosed) OSA [133].

Summary

Impaired gonadal function, obesity, metabolic syndrome, and OSA are interlinked in men by two vicious cycles. Evolving data implicate androgen action in metabolic syndrome and disordered sleep breathing. Future studies confirming the molecular basis for these relationships are needed. Such data have implications for the efficacy and safety of androgen therapy in other populations, such as older men who have relative age-associated androgen deficiency [121].

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