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Metabolic Syndrome, Androgens, and Hypertension

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Abstract

Obesity is one of the constellation of factors that make up the definition of the metabolic syndrome. Metabolic syndrome is also associated with insulin resistance, dyslipidemia, hypertriglyceridemia, and type 2 diabetes mellitus. The presence of obesity and metabolic syndrome in men and women is also associated with increased risk of cardiovascular disease and hypertension. In men, obesity and metabolic syndrome are associated with reductions in testosterone levels. In women, obesity and metabolic syndrome is associated with increases in androgen levels. In men reductions in androgen levels is associated with inflammation. Androgen supplements reduce inflammation in men. In women, increases in androgens are associated with increases in inflammatory cytokines, and reducing androgens reduces inflammation. In this review the possibility that androgens may have different effects on metabolic syndrome and its sequelae in males and females will be discussed.

Keywords

polycystic ovary syndrome; menopause; aging; inflammation; androgens; metabolic syndrome; postmenopausal hypertension

Introduction

Obesity with the concomitant metabolic dysfunction that includes insulin resistance, type II diabetes, hyperlipidemia and hypertension is becoming an epidemic in developed countries around the world. The epidemic is spreading to most states in the US with the highest prevalence in the Southeast [1, 2]. Obesity and metabolic syndrome in men is associated with reductions in serum testosterone [3, 4]. In contrast, obesity in women, including women with polycystic ovary syndrome [5] and those who are postmenopausal, is associated with increases in serum testosterone [6]. These data suggest that androgens may affect males and females differently with regard to metabolic syndrome, increases in body weight, cardiovascular disease (CVD) and hypertension. In this short review, what is known about the effect of androgens and obesity in males and females will be discussed.

Androgens and obesity in males

Most chronic disease states in men are associated with reductions in serum testosterone. For example, men who have CVD, chronic renal disease, hypertension, or atherosclerosis have reduced levels of serum testosterone [7–9]. In fact the disorders of erectile dysfunction,

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hypogonadism, and metabolic syndrome are called a triad of symptoms that often occur together in middle-aged and older men [10, 11]. Obesity, metabolic syndrome and hypertension are associated with reductions in androgens in men, regardless of ethnic group [4, 12]. In general, androgen deficiency occurs in approximately 30% of men, aged 40–79 years, and was found by Traish and colleagues to be more highly associated with atherosclerosis than gender itself [7, 13]. Akishita and colleagues reported that low testosterone levels were associated with increased body mass index (BMI), hypertension, hypertriglyceridemia, and dyslipidemia in Japanese subjects with average age 49 ± 9 years [14]. Androgen deficiency was also shown in the CHIANTI study to be a strong predictor of mortality in men [15], although these individuals were older. Khaw and colleagues reported that androgen levels predicted mortality from both cardiovascular diseases and all cause in men, aged 40–79 years [16].

Obesity in animals is also associated with reductions in serum testosterone. For example, male obese Zucker rats (fa/fa; OZR) have lower levels of androgens and are infertile, compared to their lean counterparts (LZR) [17]. They also exhibit the characteristics of metabolic syndrome with morbid obesity, dyslipidemia, insulin resistance and hypertension with aging [17]. These animals have a genetic deficiency in the leptin receptor, and leptin activity is necessary for adequate reproductive funciton[18]. Thus it is possible that the reduction in leptin may be responsible for the reduced levels of androgens in these animals rather than the reduction in androgens causing the obesity. However, Perez-Torres and colleagues found that serum testosterone levels were reduced by almost 90% in insulin resistant, obese male rats fed sucrose following weaning to 24 weeks of age [19]. Estradiol levels were not changed in the sucrose-fed rats, suggesting that the mechanism for the reduction in testosterone and consequences of metabolic syndrome was not merely due to increased conversion of androgens to estradiol in body fat.

Obesity in men and rats is also associated with increases in inflammatory cytokines [7, 20]. Androgens have been found to be anti-inflammatory, and hypogonadal men treated with androgen supplements experience reductions in inflammatory cytokine levels [21]. Thus it is possible that the reduction in androgens in obese men may also contribute to the increase in inflammation.

The mechanisms by which androgens are decreased in obese men have not been elucidated. There is a better correlation between visceral adiposity and plasma total and free testosterone and steroid hormone binding globulin (SHBG) than with body mass index (BMI) and testosterone levels and SHBG [22]. Neilson showed that the level of visceral adiopose, as measured by dual-energy X-ray absorptiometry (DEXA) and magnetic resonance imaging, correlated with bioavailable testosterone in young men (aged 20–29yrs) [23]. The inverse relationship between subcutaneous adipose tissue and androgen levels appeared to be due to the variance in levels of SHBG. Morbidly obese men have normal luteinizing hormone (LH) pulsatility, but the LH amplitude is severely reduced [24]. However, this depends on the degree of obesity and is consistent only in the morbidly obese (BMI>40 kg/m^2) [25].

Leptin may also play a role in the decrease in testosterone with obesity in men. Leptin is a hormone secreted by adipocytes, and Isidori and colleagues found that circulating levels of leptin in men correlate with total and free testosteroone even after controlling for SHBG, LH, and estradiol [26]. Leptin is necessary for successful reproduction and leptin receptors are present in testis. Exactly how leptin may impact reproduction in males is not clear, nor is the interaction between insulin resistance, glucose homeostasis and androgens levels in men been elucidated. (There is more information in women and this will be discussed below).

However, type 2 diabetic, hypogonadal men treated with rosiglitazone, a thioglitazone that is an insulin sensitizer, exhibited increases in bioavailable testosterone [27].

Studies in male rats show that high caloric diets, either from fat or fructose, cause reductions in serum testosterone levels [28–30]. Olivares and colleagues reported that high fat diet reduced testosterone levels, and caused a reduction in pituitary and serum luteinizing hormone (LH) [28]. In high fat diet–fed rats, 24 hr patterns of thyroid-stimulating hormone were also reduced, and there was no correlation between LH and testosterone levels. Plasma corticosterone was significantly elevated, however, and correlated well with plasma glucose levels [30].

Because men with chronic diseases such as obesity, CVD, renal insufficiency, coronary artery disease, and heart failure have low levels of serum testosterone, it is not clear whether reductions in androgens are a cause or consequence of these diseases. It is possible that men who have low testosterone levels are more susceptible to CVD and renal disease and thus exhibit poorer outcomes. Studies in androgen receptor knockout mice showed that doxorubicin-induced cardiomycyte oxidative stress and apoptosis was significantly higher than in wild type controls [31]. Angiogenesis studied in endothelial cells from male and female mice was augmented in male cells, but not female cells, and female-derived endothelial cells could be made to become androgen sensitive with over-expression of the androgen receptor and addition of androgens [32]. Thus future studies will be necessary to determine whether the reduction in androgens causes chronic disease or is a consequence of chronic disease and exacerbates the negative outcomes.

With regard to obesity, androgen replacement and CVD risk, Mah and Wittert reported that reductions in body weight improved the levels of total and free testosterone in obese men, but that androgen supplements in the short term did not significantly improve cardiovascular risk despite reducing fat mass [33]. Marin and colleagues found that androgen supplements in obese men reduced their diastolic blood pressure [34]. Zitzmann and Nieschlag found similar reductions in resting systolic and diastolic blood pressure in obese men treated with testosterone undecanoate [35]. These data are opposite of studies in normal weight men and women in which men have higher blood pressures throughout their lives until women reach menopause when the incidence of hypertension is greater in women [36]. In rats that are hypertensive, but not obese, androgens increase their blood pressure [37, 38]. Thus several questions remain with regard to androgen supplements and hypertension. The data suggest that metabolic syndrome and obesity in men lead to the reductions in androgens and hypertension. Thus when androgens are supplemented in men, they may reduce body weight and symptoms of metabolic syndrome and thus reduce blood pressure. Future studies will be necessary to separate the effects of hypoandrogenemia from obesity and metabolic syndrome on hypertension.

However, because men, both lean and obese, do have increased incidence of CHD and other CVD compared to age-matched women, and there is concern that androgen supplements will promote prostate cancer [39], clinicians have been reluctant to prescribe long term androgen supplements for these men in case that they might promote further CHD, CVD and hypertension. Clinical trials are necessary to determine if obese men with low levels of androgens can safely ingest androgens and whether chronic androgen supplements will reduce cardiovascular disease risk in men.

Androgens and obesity in females

Androgens in men are approximately 20 fold higher than in women [40]. Obese women have elevated levels of testosterone although the levels are only increased 2–3 fold and thus are still significantly lower than in men [41]. Women with polycystic ovary syndrome

(PCOS) have hyperandrogenemia and also exhibit insulin resistance, increase in inflammation with increased inflammatory cytokines, dyslipidemia and metabolic syndrome [5, 42]. The incidence of obesity in women with PCOS is 50–70% [43]. Lean women who have PCOS also have insulin resistance, however. Treatment of women who have PCOS and elevated androgen levels with metformin to improve insulin resistance, exhibit a reduction in testosterone levels [44]. This has lead investigators to presume that insulin resistance was responsible for the increase in androgens in women with PCOS rather than that androgens mediated the insulin resistance. However, Manneras and colleagues reported that a model of hyperandrogenemia, produced by implanting juvenile female rats with dihydrotestosterone pellets, caused features of metabolic syndrome, including insulin resistance, increases in cholesterol and visceral fat deposits [45]. In addition, female-to-male transsexuals, who take male levels of androgens, have an increased incidence of PCOS [46]. Thus whether the increase in androgens causes obesity and insulin resistance or whether obesity causes increases in androgens in females with PCOS is not clear as yet.

Another group of women in whom androgens may be elevated are postmenopausal women. Barrett-Connor and colleagues reported that serial measurements of testosterone in postmenopausal women over 9 years showed that testosterone levels decrease sharply after menopause transition along with estradiol levels, but increased slowly with age, such that by 70 years of age, the androgen levels were similar to levels found in premenopausal women [6]. The difference between pre- and post-menopausal women was that the androgen levels were unopposed by estrogen levels in the post-menopausal women. These studies are the only ones known to this investigator in which serial measurements were made in the same women over a prolonged period. The consequence of increasing levels of androgens in postmenopausal women is unknown. However, women exhibit shifts in fat deposition following menopause transition, even with no increase in body weight, to increased abdominal fat rather than lower body fat [47, 48]. Whether the change in androgens with age plays a role in this change in body fat distribution is not clear. However, changes of body fat distribution to more abdominal fat deposition (presumably more visceral fat) is associated with increased cardiovascular disease risk in both men and women [49].

Prior to 10 months of age, female spontaneously hypertensive rats have lower blood pressure than age-matched males [50]. Female SHR stop estrous cycling at 10–12 months of age, and by 16 months of age, their blood pressures are similar to, or significantly higher than in males [50]. The changes in blood pressure are not due to reductions in males with age, but rather to increases in females. There is approximately 3–4 fold increase in serum testosterone in aged female SHR compared to young females, and they weigh approximately 25% more than young females [50]. The old female SHR also have 2 fold more perirenal fat when factored for body weight, abnormal oral glucose tolerance test and elevated cholesterol levels compared to young females (unpublished data, Yanes and Reckelhoff). Whether the increase in androgens contribute to these metabolic changes in old female SHR is not clear.

It is very clear that the role that androgens play in mediating obesity and later coronary heart disease and CVD in women needs much more study. The field is complicated by lack of serial studies in pre- to peri- to post-menopausal women to determine if there is a correlation between body mass, body composition, insulin resistance and androgen levels. In addition, serial studies in young women with PCOS to follow their body weight, androgen level and insulin resistance changes from early adolescence and menarche through their adulthood would also be helpful to determine if indeed it is the increase in body fat that promotes the increases in androgens, or whether the increase in androgens increases body weight and visceral fat deposition as in androgen-supplemented young female rats. In any case the combination of increased androgens, obesity and metabolic syndrome cause increased CVD and CHD risk in both young women with PCOS and older postmenopausal women. In

addition, women who have had PCOS when young also have a higher risk for CVD later in life [42]. Thus more studies are necessary to sort out the relationships between androgens and CVD in women.

Conclusion: Sex differences in androgens and obesity?

Keeping in mind the data that obesity in women is associated with increases in androgens and CVD, and obesity in men is associated with reductions in androgen levels and CVD, it is possible that androgens may have different effects in men and women. The data mentioned above that rosiglitazone in hypoandrogenemic, obese men increases serum testosterone levels [27], while metformin in hyperandrogenemic obese women reduces androgens [44], suggest that men and women respond to androgens differently or that insulin resistance has different effects on androgens in men and women. It is realized that metformin and rosiglitazone have different modalities, but they both attenuate insulin resistance. These data point to a bigger problem: there is no information available on the simplest of questions regarding androgens in males and females, namely whether androgens and androgen receptor expression and, more importantly, androgen regulation are the same in males and females. Nor is there any information regarding whether the activity of androgen receptor as a transcription factor is similar in males and females. Thus the role that androgens may play in obesity and hypertension and CVD in men and women is a long way from being clear.

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