The striking similarities in the metabolic associations of female androgen excess and male androgen deficiency

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ABSTRACT: Androgen excess in women and androgen deficiency in men facilitate abdominal adiposity and related metabolic disorders. Moreover, obesity-associated gonadal dysfunction consists of hyperandrogenism in women but hypogonadism in men. We have reviewed the existing evidence on the interplay between sex steroids, adipose tissue and lean mass distribution, and developed a novel hypothesis to explain these apparent paradoxes. We hypothesize that the most beneficial adipose tissue distribution and function is that of normal women, who have low androgen and high estrogen concentrations. Any imbalance favoring an increase in androgen levels in women, and the very high androgen levels characteristic of healthy men, influence adipose tissue distribution and function. Sex steroids determine a favorable (female) or unfavorable (male) body fat distribution and function. However, sex hormones also provide defensive mechanisms against visceral fat accumulation: androgens increase lean and muscle mass in men, decreasing the amount of visceral fat relative to total body mass and its negative consequences, whereas estrogens determine the metabolically safer deposition of body fat into the subcutaneous gluteal—femoral depot in women. This delicate equilibrium may be altered by the presence of gonadal dysfunction, a sedentary life-style or the normal ageing process leading to sarcopenia, and by the development of obesity leading to abdominal adiposity and metabolic disorders in both sexes. In conclusion, sex hormones and gonadal dysfunction play important roles in the pathogenesis of diabesity and its metabolic associations.

Key words: adipose tissue / diabesity / diabetes / hypogonadism / polycystic ovary syndrome

Introduction

Adipose tissue plays a central role in the pathophysiology of obesity-dependent type 2 diabetes mellitus (diabetes) and the metabolic syndrome (Astrup and Finer, 2000). Adipose tissue distribution shows a clear sexual dimorphism in humans that results from the balance of androgens and estrogens and develops during puberty (Wells, 2007). The abdominal and visceral deposition of adipose tissue typical of men, as opposed to the gluteal—femoral pattern of subcutaneous fat deposition that characterizes premenopausal women, is paramount because the association between adipose tissue accumulation and metabolic disorders is stronger for visceral adipose tissue (VAT) than for subcutaneous adipose tissue (SAT) excess (Ibrahim, 2010).

Therefore, increasing androgen levels may be expected to result in abdominal adiposity and possibly to adipose tissue dysfunction. While this has been confirmed in women—i.e. women with the androgen excess disorder polycystic ovary syndrome (PCOS) present with abdominal visceral adiposity, insulin resistance, metabolic disturbances and an increased cardiovascular risk (Escobar-Morreale and San Millan, 2007)—in men the opposite actually occurs: males with acquired hypogonadism develop abdominal adiposity and related disorders. We have reviewed the available evidence on the interplay between sex steroids, adipose tissue and lean mass distribution, and developed a novel hypothesis to explain these apparent paradoxes.

Obesity and body fat distribution as major risk factors for cardiometabolic disorders

Obesity and adipose tissue dysfunction from an evolutionary perspective

Human metabolism may be genetically adapted to the dominant conditions that have predominated over time: near-continuous physical
activity, a diet rich in complex carbohydrates and proteins yet poor in fat, and long periods of famine or food shortage (Eaton and Konner, 1985). Survival was then favored by a combination of thrifty genotypes and phenotypes (Neel, 1962), in which abdominal adiposity and insulin resistance played a central role (Fernandez-Real and Ricart, 1999; Escobar-Morreale et al., 2005a). In this context, fertility first genotypes, such as PCOS and oligo-ovulation, by providing additional survival advantages—increased assertive behavior and relatively large intervals between pregnancies that occurred at older ages thereby decreasing the birth rate and favoring maternal and infant survival—might have co-segregated with thrifty genotypes (Witchel et al., 1997; Escobar-Morreale et al., 2005a; Corbett et al., 2009; Corbett and Morin-Papunen, 2013).

Nowadays, the environmental conditions have changed rapidly in many countries where access to food is not restricted, significant trauma and epidemics seldom occur, and life expectancy has increased markedly. Hence, these defensive mechanisms are no longer beneficial and the price to pay is atherosclerosis and cardiovascular disease.

Obesity-related adipose tissue dysfunction as the major determinant of diabesity and cardiometabolic disorders

Adipose tissue is a highly active endocrine and metabolic organ that functions as an integrated unit consisting of adipocytes, connective tissue matrix, nerve tissue, stromavascular cells and immune cells (Kershaw and Flier, 2004). Adipose tissue receives signals from the traditional hormone systems and the central nervous system, expresses and secretes factors with autocrine, paracrine and endocrine functions, and participates in the peripheral metabolism of sex steroids and glucocorticoids (Kershaw and Flier, 2004).

Dysfunctional secretion of adipokines, inflammatory mediators and other molecules by excessive VAT mediates the increased cardiovascular risk associated with diabesity (Kershaw and Flier, 2004). Mechanisms contributing to insulin resistance, metabolic dysfunction, hypertension, dyslipidemia and atherosclerosis in diabesity include increased sympathetic tone, activation of the hypothalamic–pituitary–adrenal axis and increased local generation of cortisol in adipose tissue, activation of the renin-angiotensin system, endothelial dysfunction, increased coagulability and decreased fibrinolysis and low-grade chronic inflammation (Fernandez-Real and Ricart, 2003). In agreement, almost all classic and non-classic cardiovascular risk factors, including surrogate markers derived from molecules involved in these pathophysiological mechanisms, aggregate in subjects with obesity, especially in those presenting with abdominal adiposity (Bjorntorp, 1992; Despres and Lemieux, 2006).

Differences in VAT and SAT with regards to metabolic dysfunction and cardiovascular risk

Albeit obesity is a major risk factor for diabetes and cardiovascular disease, there are obese persons that never develop these complications. This may be explained, at least in part, by the fact that insulin resistance and cardiometabolic risk appear to be specifically associated with intra-abdominal adiposity for any given amount of body fat, even in lean individuals (Despres and Lemieux, 2006).

There are several non-mutually excluding possibilities to explain the association of visceral adiposity with insulin resistance, diabetes and cardiovascular disease. The ectopic fat model proposes that energy excess may be stored in a healthy manner in insulin-sensitive SAT in some individuals, whereas in others this energy surplus goes into a lipid overflow that is deposited in ectopic places (i.e. liver, muscle, heart or the intraperitoneal area) in the form of a dysfunctional adipose tissue (Despres and Lemieux, 2006). Factors associated with this unhealthy management of energy excess include environmental factors, such as smoking, and certain genetic backgrounds (Despres and Lemieux, 2006). The adipose tissue expandability hypothesis complements previous explanations proposing that adipose tissue expands to accommodate increased lipid surplus, but this capacity is not unlimited and likely varies between individuals depending on genetic and environmental influences (Virtue and Vidal-Puig, 2010). When adipose tissue expansion limits are reached ectopic lipid accumulation develops, causing adipose tissue dysfunction, insulin resistance, apoptosis, inflammation and cytokine-mediated activation of the hypothalamic–pituitary–adrenal axis (Virtue and Vidal-Puig, 2010).

These hypotheses imply that SAT and VAT have different characteristics. Mounting evidence, from anatomy to the pathophysiological and molecular levels, suggests this is the case. VAT is mostly located within the intraperitoneal cavity draining directly to the liver through the portal circulation facilitating an influence of its secretory products on intermediate metabolism (Ibrahim, 2010). VAT is more cellular, vascular, innervated and contains more inflammatory and immune cells than SAT (Ibrahim, 2010). The preadipocyte differentiating capacity of VAT is reduced and the percentage of large dysfunctional adipocytes is increased compared with SAT (Ibrahim, 2010). VAT adipocytes are more active metabolically, more sensitive to lipolysis and more insulin-resistant than SAT adipocytes (Marin et al., 1992). Therefore, VAT has a greater capacity to generate free fatty acids and for glucose uptake than SAT and is more sensitive to adrenergic stimulation, while SAT is more active in the absorption of circulating free fatty acids and triglycerides (Marin et al., 1992; Ibrahim, 2010).

Targeted studies support the existence of differences between VAT and SAT in the ability to synthesize and release adipokines and adipose tissue-secreted molecules, including cholesterol ester transfer and phospholipid transfer proteins, proinflammatory cytokines, angiostatin and plasminogen activator inhibitor-1 (Dusserre et al., 2000). Recently, non-targeted approaches support the existence of substantial differences in the gene expression patterns and proteomic profiles of VAT and SAT (Wolfs et al., 2010; Insenser et al., 2012), and that these differences are present in adipose tissue stem cells in parallel to functional differences (Baglioni et al., 2012).

Sexual dimorphism in body fat distribution and adipose tissue function

Animal models supporting that prenatal exposure to androgens programs adipose tissue toward metabolic dysfunction in adult life

Androgens and estrogens influence the distribution and function of adipose tissue through binding to their specific receptors, yet it should be emphasized that the effects of sex steroid hormones on the regulation
of adipocyte metabolism occur only in concert with glucocorticoids, which are always present ( Pasquali et al., 2008 ). The local production and action of glucocorticoids in adipose tissue is also regulated by sex steroids ( Blouin et al., 2009 ). Sex hormone receptors show different densities and activities in SAT and VAT ( Rodriguez-Cuenca et al., 2005 ), and these adipose depots also differ in the expression of enzymes involved in steroid hormone metabolism, modulating the amount of sex hormones that bind their specific receptors ( Blouin et al., 2009 ).

In several mammal models, prenatal exposure of female fetuses to androgens ( in doses that result in fetal testosterone levels similar to that of untreated male fetuses ) influences adipose tissue distribution and metabolic function in adult life leading to abdominal adiposity, insulin resistance and metabolic disorders ( Padmanabhan et al., 2010 ). Therefore, in normal male fetuses the active androgen secretion from the testis might not be only responsible for the masculinization of internal and external genitalia, but might also induce prenatal programming of adipose tissue distribution and function, facilitating the android distribution of body fat in adult life ( Abbott et al., 2009 ). Interestingly, abdominal adiposity and metabolic dysfunction are frequent in girls exposed prenatally to androgen excess such as those with congenital adrenal hyperplasia ( Charmandari and Chrousos, 2006 ) or in girls born from mothers with PCOS ( Sir-Petermann et al., 2007 ) who might have inherited a hyperandrogenic trait.

Sexual dimorphism in body fat distribution throughout the life cycle, from puberty to menopause

Even though sex differences in body composition are present very early in life, with boys showing larger lean mass than girls at birth, the sexual dimorphism in body composition emerges most dramatically during puberty driven by the action of sex hormones ( Wells, 2007 ). During reproductive years, women have substantially greater mean percentage fat and relatively less lean mass than adult men, with women showing greater subcutaneous fat and men presenting with significantly greater visceral fat ( Wells, 2007 ). The difference in accumulation of visceral fat among men and women decreases with age: men begin to lose muscle mass from the fifth decade, whereas post-menopausal women, who show a similar decline in lean mass, often gain more fat mass than men and increase their amount of visceral fat ( Wells, 2007 ). The participation of androgen deficiency in the loss of muscle and lean mass and that of estrogen deficiency in the accumulation of visceral fat are strongly supported by very recent evidence in healthy men ( Finkelstein et al., 2013 ). Hence, the loss of protection from estrogens in post-menopausal women may contribute to explaining why the prevalence of diabetes and metabolic complications, which is higher in men compared with women during most of adulthood, equalizes in the sexes after menopause ( Soriguier et al., 2012 ).

Sexual dimorphism in adipose tissue function and the role of sex hormones

Recent data suggest that sex steroids not only influence the accumulation of body fat into the different depots, but also influence adipose tissue function. In accordance, sexual dimorphism is present in the circulating concentrations of adipokines involved in intermediary metabolism both in the fasting state and during an oral glucose load ( Luque-Ramirez et al., 2013 ).

Non-targeted genomic and proteomic studies of visceral omental fat in severely obese women showed substantial differences in the gene expression and protein abundance profiles of women presenting with androgen excess compared with those of women who showed no evidence of reproductive dysfunction ( Corton et al., 2007, 2008 ). Such differences involved genes and proteins previously linked to PCOS and to several biological pathways linked to insulin and Wnt signaling, oxidative stress, inflammation, immune function, adipocyte differentiation and intermediary metabolism ( Corton et al., 2007, 2008 ). The existence of putative androgen response elements in the promoter regions of several of these genes supported the hypothesis that these differences were related to androgen excess ( Corton et al., 2007 ).

We have compared the proteomes and expression profiles of chemerin and lipocalin-2 in VAT and SAT from obese subjects, including women presenting with androgen excess, non-hyperandrogenic women and men ( Martinez-Garcia et al., 2013; Montes-Nieto et al., 2013 ). The results from patients with PCOS were similar to those in men and not to those of control women, supporting masculinization of the adipose tissue gene expression and protein abundance profiles of obese women with PCOS ( Martinez-Garcia et al., 2013; Montes-Nieto et al., 2013 ), and that sex steroids, and not only adipose tissue distribution, might influence adipose tissue dysfunction.

Obesity and reproductive dysfunction in men and women

The relationship between sex steroids and adipose tissue dysfunction is bidirectional, because weight excess and obesity have a major impact on reproductive and gonadal function, both in women and in men ( Pasquali et al., 2008 ).

Obesity-related androgen excess and PCOS in women

Obesity has a major impact on fertility in women ( Pasquali et al., 2003; Gosman et al., 2006 ). Aside from the pregestational association with anovulation and PCOS, obesity contributes to gestational complications, such as diabetes, hypertension and dyslipidemia ( Ramsay et al., 2006 ), and is associated with preterm birth and low-birthweight infants ( McDonald et al., 2010 ). Accordingly, even modest increases in maternal BMI are associated with increased risk of fetal death, stillbirth, and neonatal, perinatal and infant death ( Aune et al., 2014 ).

However, the association between obesity, androgen excess and PCOS is firmly established ( Pasquali et al., 2003 ). Androgen excess and PCOS are present in as many as 28% of premenopausal women with weight excess ( Alvarez-Blasco et al., 2006 ), especially those presenting with severe obesity in whom the prevalence is above 50% ( Escobar-Morreale et al., 2005 ). However, not every obese woman develops PCOS, and not every patient with PCOS is obese.

We hypothesized that PCOS results from a vicious circle in which androgen excess determines abdominal adiposity and visceral fat accumulation facilitates further androgen excess. Visceral fat accumulation leads to further androgen excess indirectly by favoring insulin resistance, compensatory hyperinsulinemia and further androgen secretion by the adrenal and the ovaries, or directly by the action of adipokines and inflammatory mediators that influence the functions of these glands ( Fig. 1; Escobar-Morreale and San Millan, 2007 ). The increase in visceral fat
that occurs in parallel with a decrease in SAT in female-to-male transsexual humans treated with testosterone (Elbers et al., 2003), together with the finding that treatment with antiandrogens reduces visceral adiposity in women with PCOS (Gambineri et al., 2006), suggests a causal role for androgen excess in the development of abdominal adiposity in women with hyperandrogenism (Escobar-Morreale and San Millan, 2007). Conversely, weight loss in women is followed by a decrease in androgen levels in parallel to a decrease in VAT (Leenen et al., 1994) and the PCOS phenotype may resolve after the marked and sustained weight loss attained after bariatric surgery in severely obese women, supporting a causal role of obesity on the development of PCOS in lean patients (Escobar-Morreale and San Millan, 2007). The absence of such a defect in androgen secretion facilitates androgen excess only when triggering factors, such as those derived from abdominal adiposity, are present (Fig. 2; Escobar-Morreale and San Millan, 2007).

However, in order to develop PCOS, women must have an intrinsic defect in steriodogenesis consisting of an exaggerated androgen secretion by ovarian theca cells that results from the overexpression and overactivity of several enzymes involved in the steriodogenic pathway (Wickenheisser et al., 2000, 2004, 2005). In some cases, a mild steriodogenic defect facilitates androgen excess only when triggering factors, such as those derived from abdominal adiposity, are present (Fig. 2; Escobar-Morreale and San Millan, 2007). The absence of such a primary steriodogenic defect explains the large fraction of women who do not show any evidence of androgen excess even in the presence of severe obesity and insulin resistance (Escobar-Morreale et al., 2005b; Escobar-Morreale and San Millan, 2007). Conversely, women with more severe steriodogenic defects may develop the PCOS phenotype even in the absence of any triggering factor, such as abdominal adiposity, explaining the development of PCOS in lean patients (Fig. 2; Escobar-Morreale and San Millan, 2007). Obviously, the most severe PCOS phenotypes appear in patients sharing a severe steriodogenic defect and severe obesity.

Obesity-related late-onset hypogonadotropic hypogonadism in men

Although aggravation of androgen excess may be a consequence of obesity in women, the opposite actually occurs in men. Male obesity-associated secondary hypogonadism (MOSH; Saboor Aftab et al., 2013), as suggested by decreased serum testosterone concentrations, is present in as many as 40% of men presenting with a BMI 30 kg/m² (Dhindsa et al., 2013). In accordance, in men presenting with components of the metabolic syndrome, serum estradiol concentrations correlate with the amount of VAT (Gautier et al., 2013). The importance of this mechanism is exemplified by the normalization of serum testosterone concentrations in some patients with MOSH after administration of aromatase inhibitors (de Boer et al., 2005). However, other mechanisms must be involved since this putative increase in estrogen levels is not universal in patients with MOSH, a
finding that may be the consequence of their reduced serum testosterone concentrations, which is the main aromatase substrate. In fact, estradiol concentrations may be decreased in some of these patients, further contributing to visceral adiposity (Tian et al., 2012; Finkelstein et al., 2013). Other mechanisms potentially involved include insulin resistance at the hypothalamic and pituitary levels (Bruning et al., 2000) and an inhibitory effect of inflammatory mediators secreted by adipose tissue on gonadotropin secretion, including increased leptin concentrations, possibly indicating leptin resistance, characteristic of obesity (Landry et al., 2013; Saboor Aftab et al., 2013).

Similar to PCOS, the pathophysiology of MOSH may involve a vicious circle whereby obesity and abdominal adiposity lead to reduced androgen concentrations, and the resulting testosterone deficiency (and perhaps estradiol deficiency in some cases) is associated with further deposition of body fat in visceral depots in parallel to a decrease in muscle and lean body mass (Fig. 3). In this regard, local hypercortisolism may attenuate the inhibition of adipocyte differentiation induced by androgens and, on the contrary, the decrease in androgen levels may favor glucocorticoid-mediated adipocyte differentiation (Blouin et al., 2009). The causal role of obesity in the development of MOSH is highlighted by its reversal with weight loss (Corona et al., 2013), especially in severely obese patients submitted to bariatric surgery (Botella-Carretero et al., 2013; Calderon et al., 2014). Conversely, administration of testosterone to male hypogonadal patients improves body composition and several metabolic markers (Isidori et al., 2005; Saad et al., 2013; Yassin and Doros, 2013; Zitzmann et al., 2013; Traish et al., 2014).

**A unifying hypothesis to explain the association of obesity-related reproductive dysfunction with metabolic disorders and increased cardiovascular risk**

Why are the metabolic consequences of female androgen excess and of male androgen deficiency so similar? (Fig. 4) Furthermore, how is it possible that the impact of obesity on gonadal function is the opposite in the two sexes, with obese women frequently developing androgen excess and obese men frequently developing hypogonadism?

To explain these apparent paradoxes, we propose that the most beneficial adipose tissue distribution and function is that of normal women, who have low androgen and high estrogen concentrations. We hypothesize that androgens, by negatively influencing adipose tissue distribution and function, predispose healthy men and hyperandrogenic women toward the development of abdominal visceral adiposity and adipose tissue dysfunction.

Such an influence may start very early in humans, at least peripubertally and possibly even during fetal life, because fetal gonads, especially the testis, secrete sex steroids during fetal and early post-natal life. Prenatal androgenization in rat, sheep and non-human primate models leads to abdominal adiposity, adipose tissue dysfunction, insulin resistance and metabolic dysfunction during adult life in the progeny (Padmanabhan et al., 2010).

According to our present hypothesis, men are predisposed toward abdominal adiposity and adipose tissue dysfunction by default as a result of their early and chronic exposure to androgens. However, such an exposure, together with regular physical exercise, also results in a much larger lean and muscle mass compared with women. Hence, the amount of abdominal visceral fat in young and adult men, relative to their total body fat, is not increased markedly compared with that of premenopausal women. In addition, because these women have higher total fat mass than men, the absolute amounts of visceral fat are similar in both sexes, with the female excess in total body fat being deposited mostly into the subcutaneous gluteal–femoral region in premenopausal women (Wells, 2007).

The inverse association of muscle mass with insulin resistance and prediabetes supports this interpretation (Srikanthan and Karlamarga, 2011). Furthermore, the much larger muscle mass of men, especially when exercised regularly, may provide protection against metabolic dysfunction by maintaining the amount of visceral fat relative to total body mass at healthy levels and because the exercised skeletal muscle reduces the energy surplus (Felig and Wahren, 1975) that may lead to visceral adiposity. Also, skeletal muscle secretes several molecules, such as irisin, with a favorable impact on intermediary metabolism (Boström et al., 2012; Pedersen and Febbraio, 2012). In other words, sex steroids and their balance not only determine a favorable or unfavorable distribution of body fat, but provide the defensive mechanisms against the accumulation of visceral fat.

This delicate equilibrium may, however, be altered by the presence of gonadal dysfunction, by a sedentary life-style and by the normal ageing process or by the development of obesity, leading to abdominal adiposity and metabolic disorders in both sexes.

Regarding gonadal dysfunction, androgen excess in women (i.e. PCOS) favors global and particularly abdominal adiposity (Borrue et al., 2013), and masculinizes adipose tissue function (Martínez-Garcia et al., 2013; Montes-Nieto et al., 2013), yet because their serum androgen concentrations are still much lower than those of normal men, these women lack the metabolic protection offered by an increase in lean and muscle mass (Fig. 5). In men, androgen deficiency reduces lean and...
Figure 4 Adipose tissue distribution and dysfunction as a function of serum testosterone concentrations. The Y-axis represents the percentage of women and men in the general population. Serum testosterone concentrations show a marked sexual dimorphism, with men presenting with a 10–30-fold increase compared with normal women. We propose that the most beneficial adipose tissue distribution and function is that of normal women, who have low androgen and high estrogen concentrations. Any imbalance favoring the increase in androgen levels in women, and the very high androgen levels characteristic of men, alters adipose tissue distribution and function from early stages leading to the metabolic disorders included in the grey area. However, healthy adult men do not develop metabolic complications because their high androgen levels increase their lean and muscle mass markedly, maintaining the relative amount of visceral fat at amounts that are comparable with those of healthy women, thereby compensating for the negative metabolic consequences of visceral fat accumulation.

Figure 5 Gonadal dysfunction facilitates visceral adiposity and adipose tissue dysfunction in women and men by different mechanisms. The Y-axis represents the percentage of women and men in the general population. Androgen excess in women increases the amount of visceral fat leading to an unfavorable metabolic profile, whereas in men androgen deficiency leads to a marked reduction in lean and muscle mass thereby increasing the relative amount of visceral fat explaining the development of metabolic disorders. The vicious circles described in Figs 1 and 3 further contribute to maintaining the association between gonadal dysfunction and visceral adiposity both in women and in men.

Conclusions and future perspectives

Existence of these vicious circles highlights the need for strategies targeting not only obesity but also diagnosing and treating gonadal dysfunction when managing obese patients with abdominal adiposity and metabolic comorbidities.

Of note, current guidelines for the management of obesity do not usually consider obesity-associated gonadal dysfunction among the complications of obesity and do not explicitly recommend its routine screening (Expert Panel on the Identification, Evaluation and Treatment of Overweight in Adults, 1998; Tsigos et al., 2008; Sharma and Kushner, 2009). Hence, PCOS in women and MOSH in men are frequently left undiagnosed in obese patients and may contribute to their cardiometabolic risk and decreased quality of life.

Hopefully, increasing awareness of the key role that sex hormones and gonadal dysfunction play in the pathogenesis of diabesity will lead to their consideration as important factors in the study, diagnosis and management of diabesity and related cardiometabolic comorbidities.

Authors’ roles

All authors contributed to data acquisition, revision and interpretation, drafted and revised critically the article for important intellectual content, wrote and approved the final version of the manuscript. The authors have no competing interest to disclose.
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