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Gender Differences in Insulin Resistance, Body Composition, and Energy Balance

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Abstract

Background—Men and women differ substantially in regard to degrees of insulin resistance, body composition, and energy balance. Adipose tissue distribution, in particular the presence of elevated visceral and hepatic adiposity, plays a central role in the development of insulin resistance and obesity-related complications.

Objective—This review summarizes published data on gender differences in insulin resistance, body composition, and energy balance, to provide insight into novel gender-specific avenues of research as well as gender-tailored treatments of insulin resistance, visceral adiposity, and obesity.

Methods—English-language articles were identified from searches of the PubMed database through November 2008, and by reviewing the references cited in these reports. Searches included combinations of the following terms: *gender, sex, insulin resistance, body composition, energy balance, and hepatic adipose tissue.*

Results—For a given body mass index, men were reported to have more lean mass, women to have higher adiposity. Men were also found to have more visceral and hepatic adipose tissue, whereas women had more peripheral or subcutaneous adipose tissue. These differences, as well as differences in sex hormones and adipokines, may contribute to a more insulin-sensitive environment in women than in men. When normalized to kilograms of lean body mass, men and women had similar resting energy expenditure, but physical energy expenditure was more closely related to percent body fat in men than in women.

Conclusion—Greater amounts of visceral and hepatic adipose tissue, in conjunction with the lack of a possible protective effect of estrogen, may be related to higher insulin resistance in men compared with women.

Keywords

gender; insulin; visceral adipose tissue; fat distribution; body composition; energy balance

INTRODUCTION

Marked gender differences have been reported in regard to degrees of insulin resistance (in which a given concentration of insulin is associated with a subnormal glucose response), body composition, and energy balance.¹ With the current rise in the prevalence of obesity,

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the study of insulin resistance and body composition has become an important area of research in public health. Recent data suggest that adipose tissue is a complex endocrine organ, responding to and, in turn, releasing signals that reflect metabolic and cardiovascular risk factors.² In a consensus statement recently published by the American Diabetes Association and the American Heart Association, obesity was considered to be “a visible marker of other underlying risk factors that can be addressed.”³ These underlying risks include visceral adiposity and insulin resistance, as well as a proinflammatory state marked by an increase in C-reactive protein and cytokines, including tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6). Specifically, adipose tissue distribution, in particular the presence of visceral and hepatic adiposity, plays a central role in the development of insulin resistance and obesity-related complications.^{4–16}

To further understand the gender specificity of insulin resistance, body composition, and energy balance, we reviewed the role of gender dimorphic regulators, including sex hormones, adipokines, and appetite regulatory hormones. These findings may provide insight into the pathogenesis of insulin resistance, visceral adiposity, and obesity, thus leading to novel avenues of research and gender-tailored treatments to address this growing public health concern.

METHODS

English-language articles were identified from PubMed searches through November 2008, and by reviewing the references cited in the reports identified by these searches. Combinations of the following search terms were used: *gender*, *sex*, *insulin resistance*, *body composition*, *energy balance*, and *hepatic adipose tissue*.

GENDER DIFFERENCES IN BODY COMPOSITION

Multiple studies have shown the importance of adipose tissue distribution and type in the development of obesity-related complications. The presence of central adiposity, particularly visceral fat, in both men and women is a risk factor for development of insulin resistance and diabetes.^{4–16} In the Diabetes Prevention Program’s population of 3234 patients, baseline waist circumference was the strongest predictor of diabetes in both sexes.¹⁵

Visceral fat and subcutaneous fat differ in histology and metabolic activity, which may explain their divergent roles in terms of metabolic and cardiovascular risk.¹⁷ Specifically, visceral adipocytes are more sensitive to catecholamine-induced lipolysis and less sensitive to insulin’s antilipolytic effect than are subcutaneous adipocytes.¹⁸ This enhanced sensitivity to catecholamines may lead to increased delivery of free fatty acids (FFAs) to the portal system, resulting in increased glucose production, very-low-density lipoprotein secretion, and decreased hepatic insulin clearance. Higher lipolytic activity in the visceral fat, as well as its direct connection with the liver, is associated with elevated FFAs in the portal and systemic circulation.¹⁹ Thus, increases in visceral adipose tissue (VAT) contribute to dyslipidemia, enhanced gluconeogenesis, and insulin resistance.^{18,20}

For a given body mass index (BMI), there are well-known body composition differences between the sexes, including higher lean mass in men and higher adiposity in women.¹⁶ Men tend to have central fat distribution, whereas women tend to have peripheral fat distribution, which is defined as fat deposited in the limbs and hips, particularly in the lower body.^{16,21–25} Other prevailing terms to describe central versus peripheral fat distribution include android versus gynoid, masculine versus feminine, and “apple” shaped versus “pear” shaped. Compared with women, men generally have more VAT and less subcutaneous adipose tissue (SAT), as measured by magnetic resonance imaging (MRI) or computerized tomography (CT) scans (Figure).^{16,21–24} These are currently the only methods that directly

and accurately measure VAT.^{26,27} However, because of the high cost and technical demands of MRI and CT, anthropometric measures, such as waist circumference and waist-to-hip ratio, are used to measure central obesity.^{9,21} In fact, although the diagnostic criteria of the metabolic syndrome vary by guidelines,^{28–30} the cutoff points for increased risk in men are larger than those for women (eg, waist circumference of 102 vs 88 cm, respectively³¹).

The higher visceral adiposity observed in men is associated with elevated postprandial insulin, FFAs, and triglyceride (TG) level.²⁵ Conversely, the peripheral fat distribution typically found in women, as measured either by hip or thigh circumference or by dual-energy absorptiometry methods, is associated with improved insulin sensitivity, compared with central fat distribution.^{32,33} Although women also have higher intramyocellular TG content, which is associated with lower whole-body insulin sensitivity,³⁴ body composition differences generally favor a more insulin-sensitive environment in women than in men.

In recent years, some researchers have further divided abdominal SAT into superficial and deep portions, and have studied their relationship with insulin resistance.^{35–37} Because most deep SAT is located in the posterior half of the abdomen, whereas superficial SAT is evenly distributed around the abdominal circumference, anterior and posterior adipose tissue compartments have been used to approximate superficial and deep SAT.³⁵ Although some studies have found that deep SAT, which may be more abundant in men than in women,³⁶ was independently associated with insulin resistance,^{35–37} others did not support this finding in either women³⁸ or men.^{39,40} One study also suggested that superficial SAT was independently related to fasting glucose.⁴¹ A recent study, using MRI to examine body composition and euglycemic hyperinsulemic clamp to quantify insulin resistance in 57 Pima Indians, found that the relationship between SAT subdepots and insulin resistance was different in men than in women.⁴² In men, insulin resistance was associated with more deep and less superficial SAT, whereas in women, insulin resistance was associated with more superficial SAT. Because of these inconsistent findings, it is unclear whether subdepots of SAT are independently related to insulin resistance. The role of the gender dimorphism of subdepots of SAT in insulin resistance is also unclear. Furthermore, although deep SAT may be more sensitive to the lipolytic action of catecholamines than is superficial SAT *in vitro*,⁴³ this has not been found in microdialysis studies *in vivo*.⁴⁴

Finally, nonalcoholic fatty liver disease (NAFLD), which is the accumulation of fat in the liver in the absence of excessive alcohol consumption or other specific causes of hepatic steatosis, is independently associated with male gender,⁴⁵ obesity, and diabetes⁴⁶ ($P < 0.001$).⁴⁷ Recent evidence suggests that fatty liver may be involved in the pathogenesis of obesity, diabetes, and the metabolic syndrome.^{45,46} A number of causes have been implicated in the development of NAFLD, among them increased energy intake and sedentary lifestyle, but visceral adiposity has a significant correlation to NAFLD,^{48,49} which may in part explain the association with male sex. Hypotheses explaining the association between increased visceral adiposity and hepatic fat accumulation and hepatic insulin resistance include increased FFA supply to the liver from inflamed, hypertrophied adipose tissue⁵⁰ as well as the combination of decreased adiponectin production with increased proinflammatory cytokine TNF- α and IL-6 production from adipose tissue.^{51–54} The association of NAFLD with visceral adiposity, dyslipidemia,⁵⁵ and insulin resistance may additionally explain the increased insulin resistance observed in men compared with women.

SEX HORMONES, ADIPOSE DISTRIBUTION, AND INSULIN RESISTANCE

Estrogen

Gender differences in body composition may be due, at least in part, to the effect of sex hormones. It seems that female sex has a favorable effect on insulin sensitivity, despite

women having higher adiposity relative to men.¹⁶ The decrease in insulin sensitivity with menopause, and subsequent improvement with estrogen replacement, suggests that estrogen may play a role in the insulin sensitivity observed in women.^{56,57} Moreover, complete lack of estrogen synthesis or activity in men is associated with insulin resistance.^{58,59} Moran et al⁵⁶ found that during adolescence in males, insulin resistance was significantly increased ($P < 0.003$) despite significant decreases in adiposity ($P < 0.001$), whereas in females, body fat significantly increased ($P < 0.001$) but insulin resistance did not significantly change. Increasing insulin resistance in boys occurred independently of increasing lean mass and decreasing fat mass, possibly due to the relative decrease in estrogen in males compared with females.

Estrogen may have beneficial effects on insulin sensitivity via a number of possible mechanisms: direct effects on insulin and glucose homeostasis, involvement in adipose tissue metabolism and body composition, or effects on proinflammatory markers.^{15,57,60–64} Studies in humans and animals have observed that estrogen plays a role in the maintenance of glucose homeostasis and substrate metabolism.^{60–62,65,66} In humans, higher 17 β -estradiol concentrations may be associated with significantly more lipid and less carbohydrate metabolism during exercise in women than in men.^{65,66} Estrogen has been found to protect against hyperglycemia in animal models of diabetes, by decreasing hepatic glucose production and enhancing glucose transport in the muscle.^{60–62} Estrogen also has antioxidant properties, and has been found to confer increased resistance to oxidative stress in mice and to increase the expression of longevity-associated genes, including those encoding the antioxidant enzymes superoxide dismutase and glutathione peroxidase.⁶⁷ Consequently, animal data have noted that mitochondria from females produced fewer reactive oxygen species than those from males.⁶⁸ Furthermore, in conditions of oxidative stress, estrogen has been found to protect pancreatic β -cell function and survival.⁶⁰ These findings support the hypothesis that estrogen may be protective against the development of insulin resistance and diabetes.

Estrogen may also have beneficial effects on adipose tissue distribution. Compared with premenopause, menopause is associated with increased adiposity and greater risk of metabolic disease. Specifically, many postmenopausal women develop increased visceral adiposity. Kotani et al¹⁴ performed whole-body CT scans in 162 overweight (BMI > 25 kg/m²) men and women to assess the role of aging on adipose tissue distribution. This study found that compared with premenopausal women, postmenopausal women had an ~2.6 times larger increase in VAT volume. Furthermore, in a study comparing 18 women who were receiving hormone replacement therapy (HRT) with 18 women who were never-users, the women receiving HRT had lower waist circumferences than did the never-users, again suggesting that estrogen may reduce central adiposity in humans.⁶³ The preferential deposition of adipose tissue in the periphery (subcutaneous and gluteal) in women versus deposition in the viscera in men may be related to the higher level of estrogen in women compared with men.⁶⁹

Animal studies also suggest that estrogen may play a role in adipose tissue biology and in the prevention of obesity.⁶⁰ Ovariectomized animals have increased adiposity compared with animals with intact ovaries.⁵⁷ Estrogen treatment in ovariectomized animals has been associated with significantly reduced adipose mass and adipocyte size ($P < 0.05$), possibly via decreased expression of lipogenic genes in adipose tissue, liver, and skeletal muscle. In muscle, estrogen appears to promote the use of lipid as fuel by partitioning FFAs toward oxidation and away from TG storage by upregulating the expression of peroxisome proliferation activator receptor- δ . Thus, estrogen may have protective effects against obesity, in particular visceral obesity, in humans and in animals.^{57,63}

Estrogen has been reported to have anti-inflammatory properties.⁶⁴ One study found that circulating levels of TNF- α were 7-fold higher in ovariectomized rats compared with estrogen-replaced ovariectomized rats or those with endogenous estrogen production.⁷⁰ These elevations in TNF- α were associated with impaired vascular function due to decreased nitric oxide levels. Human studies have also noted that menopause is associated with increased cytokine levels, including TNF- α , IL-1, and IL-6; these levels are substantially lower in women receiving HRT.⁷¹ Given the association between increased proinflammatory markers and obesity-related complications such as insulin resistance,⁷² the association between estrogen and decreased cytokines may play a role in gender differences in insulin resistance.

The effect of exogenous and endogenous estrogen on insulin sensitivity, however, is controversial. Whereas some studies reported that HRT in postmenopausal women increased insulin resistance,^{73,74} others found that it was associated with insulin sensitivity.^{75,76} These findings may have been influenced by the fact that, generally, HRT studies have used nonhuman (equine) preparations of estrogen. Additionally, several studies have observed that women taking oral contraceptives (OCs) had significantly decreased insulin sensitivity ($P < 0.05$)^{77–79} and significantly increased plasma FFAs ($P < 0.05$),⁷⁷ cholesterol, and TG levels⁸⁰ compared with women not taking OCs. However, this may be related to estrogen dose; OCs historically contained higher estrogen levels than those currently in use. Also, women not taking exogenous estrogen have been reported to have significantly increased plasma FFAs compared with men ($P < 0.01$),²⁵ though this does not seem to adversely affect their insulin sensitivity⁷⁷ and has not been confirmed in other studies.²⁵ Finally, pregnancy, a high estrogen state, is characterized by insulin resistance, but other hormonal changes during pregnancy also affect insulin sensitivity.⁵⁶ The lower truncal adiposity in women versus men, whether due to estrogen effects or other causes, possibly confers higher insulin sensitivity, despite the higher FFAs and intramyocellular TGs observed in women.⁷⁷

Testosterone

Androgens may have a depot- and gender-specific effect on adipose tissue and insulin resistance. In women, testosterone and androstenedione levels correlated positively with waist diameter on CT¹⁶ and were independently associated with significantly increased abdominal fat.^{81,82} Similarly, obese postmenopausal women treated with testosterone for 9 months developed significantly increased visceral fat compared with women receiving placebo ($P < 0.05$).⁸³ Moreover, polycystic ovarian syndrome, a common cause of hyperandrogenism and anovulation in women, is generally an insulin-resistant state,⁸⁴ and excess androgen in women is associated with increased insulin resistance.^{85,86} Animal studies have also found that testosterone significantly increased insulin gene expression and release ($P < 0.05$),⁸⁷ significantly decreased muscle insulin sensitivity ($P < 0.001$),⁸⁸ and resulted in the development of impaired peripheral insulin sensitivity and adipocyte insulin resistance in female rats, even after transient hyperandrogenemia.⁸⁹ However, hypogonadal states in men were also associated with insulin resistance,⁹⁰ and testosterone replacement in hypogonadal men improved insulin sensitivity.⁹¹

In men, testosterone and androstenedione have been found to be significantly associated with decreased total and central adiposity.^{16,92,93} Specifically, in a study of 178 men, waist-to-hip ratio was significantly inversely associated with free testosterone.⁸⁹ Treatment with testosterone in men decreases visceral adiposity,⁹⁴ and increases adipose tissue lipolysis by inhibiting lipoprotein lipase activity.^{92,94} This decrease in VAT is associated with improved glucose disposal rate with euglycemic-hyperinsulinemic clamps in men treated with testosterone.⁹⁵ A possible explanation for this apparent paradox is that in men, both extremes in testosterone level are associated with insulin resistance and adverse body composition, because excess androgens also reduce insulin sensitivity in men.^{96,97}

Testosterone has been found to reduce the concentration of adiponectin, an antidiabetic and anti-atherogenic adipokine. In an observational study of 442 men and 137 women, plasma adiponectin concentrations were significantly lower in men than in women ($P < 0.01$), but were not significantly different between pre- and postmenopausal women.⁹⁸ This study also reported high concentrations of plasma adiponectin in castrated mice; testosterone treatment reduced plasma adiponectin concentrations. Decreases in testosterone levels with castration were associated with improved insulin sensitivity. In addition, in vitro studies have reported that testosterone reduced adiponectin secretion in adipocytes cells. These findings suggest that androgens may decrease plasma adiponectin and that decreased levels of adiponectin may be associated with increased insulin resistance.

Depot-Specific Adipose Tissue Sex Steroids

Gender dimorphic adipose tissue distribution, with higher lower-body subcutaneous adiposity in women and higher visceral adiposity in men, may result not only from the effects of circulating sex hormones, but also from depot-specific adipose tissue sex-hormone metabolism.² Although gonads and adrenal glands contribute the majority of sex hormones to the circulation, adipose tissue, via enzyme activation and conversion, can contribute up to 50% of circulating testosterone in premenopausal women and 100% of circulating estrogen in postmenopausal women.^{99,100} For example, adipose tissue aromatase converts androgens to estrogens: androstenedione to estrone and testosterone to estrogen. Additionally, adipose tissue 17 β -hydroxysteroid dehydrogenase (17 β HSD) converts weaker hormones to stronger hormones: androstenedione to testosterone and estrone to estradiol. SAT expresses relatively more aromatase than 17 β HSD, whereas VAT expresses more 17 β HSD than aromatase. Therefore, higher visceral adiposity may be associated with relatively more 17 β HSD expression, resulting in more local androgen production. In addition, animals with no aromatase activity have been found to have increased visceral adiposity and insulin resistance.^{101,102} These data suggest that both circulating and local adipose tissue production of sex hormones may have important effects on adipose tissue distribution, and vice versa—adipose tissue distribution may contribute to gender differences in insulin resistance via metabolism and release of sex hormones.

Other Hormone Regulators

Sex Hormone–Binding Globulin—Sex hormone–binding globulin (SHBG), the major carrier of androgens and estrogens in the blood, is reduced in states of increased abdominal, particularly visceral, adiposity^{16,82,103–105} and has a positive association with insulin sensitivity in both sexes.^{106,107} Compared with baseline, SHBG levels decrease during androgen treatment and increase during estrogen treatment.¹⁰⁸ SHBG levels tend to be higher in women than in men,¹⁶ likely due to the effects of higher estrogen concentration. Thus, elevated SHBG levels in women compared with men may be related to the lower visceral adiposity and higher insulin sensitivity observed in women.

Dehydroepiandrosterone—In adipose tissue cultures, dehydroepiandrosterone (DHEA) inhibits adipocyte development and differentiation.¹⁰⁹ Plasma levels of DHEA¹¹⁰ and dehydroepiandrosterone sulfate (DHEAS)¹¹¹ have a negative association with total body fat, subcutaneous fat, and particularly visceral fat, as measured by CT. Additionally, one randomized, double-blind study found that, compared with baseline, treatment with DHEA for 1 month was associated with a 30% decrease in body fat in healthy men.¹¹² The mechanisms of these effects are not clear, but in animals, DHEA may increase resting metabolic rate.¹¹³ Gender differences in DHEAS have been reported, with increased serum levels in men compared with women.^{16,111} Furthermore, in vitro studies noted that DHEAS increases lipolysis preferentially in SAT taken from women after 2 hours, whereas in men, lipolysis occurs preferentially in VAT but only after 24 hours.¹¹¹ The significance of these

findings remains to be determined, because one would expect that the negative association between DHEAS and total and visceral fat would result in decreased VAT in men compared with women, but in fact, we know that men have higher VAT compared with women. Further investigation into the role of DHEAS in adipose tissue gender dimorphism is needed.

Adipokines and Gender Differences in Body Composition and Insulin Resistance

Leptin—Leptin concentrations have been reported to be up to 4 times higher in women than in men,^{16,114,115} a finding associated with the higher body fat content and intramyocellular content observed in women.⁷⁷ The cause of higher leptin concentrations in women is not clearly understood, but may be due to sex hormone effects. Androgens have been found to have a negative association with leptin concentrations in men,^{116,117} and androgen treatment decreases leptin levels in hypogonadal men.⁹¹ Moreover, estrogen increases leptin concentration,¹¹⁸ which also appears to be correlated to adipose distribution and adipocyte size in women but not in men.^{16,115} In women, higher leptin concentrations are associated with larger adipocytes and subcutaneous but not visceral fat area on CT,¹⁶ which is in agreement with other studies reporting that leptin expression is significantly higher in SAT versus VAT ($P < 0.001$).^{119,120} Significantly higher leptin concentrations in women compared with men could also reflect the higher adiposity, particularly subcutaneous adiposity, found in women, given leptin's role as a metabolic signal of energy sufficiency¹²¹ as well as the leptin resistance observed in states of increased adiposity.¹²²

Adiponectin—Adiponectin is a hormone secreted exclusively by adipose tissue, and is reduced in states of insulin resistance¹²³ and obesity.¹²⁴ Adiponectin lowers glucose production in the liver¹²⁵ and improves insulin sensitivity in the muscle and liver by increasing FFA oxidation.¹²⁶ Adiponectin levels have been reported to be significantly higher in women than in men ($P < 0.001$)¹²⁷; one cross-sectional study of >1000 participants found that median adiponectin levels were significantly higher in women than in men ($P < 0.001$), even after adjusting for differences in BMI.¹²⁸ This study also found that lower adiponectin levels were more closely associated with hyperglycemia and diabetes in women than in men ($P = 0.011$ vs $P = 0.05$ I, respectively), though both sexes exhibited an association between low plasma adiponectin levels and other features of the metabolic syndrome including abdominal adiposity, which was significantly associated in both women and men ($P = 0.001$ and $P = 0.015$, respectively). Sexual dimorphism has not been shown to be associated with differing estrogen concentrations, because this study also found no significant difference between adiponectin levels in pre- and postmenopausal women or in postmenopausal women receiving HRT. Potential reasons for lower adiponectin levels in men than in women may be due to the previously described inhibitory effect of androgens on adiponectin levels,⁹⁸ higher visceral adiposity, or lower insulin sensitivity in men.

GENDER DIFFERENCES IN ENERGY BALANCE

Energy Expenditure, Food Intake, and Body Composition

Resting energy expenditure, measured by indirect calorimetry, is significantly lower in women than in men,^{77,129,130} but similar in some studies when normalized to kilograms of body weight or kilograms of lean body mass, the major contributor to resting energy expenditure.^{77,131} In one cross-sectional study including 150 white adults, lean mass contributed to 63%, fat mass to 6%, and age to 2% of the variability of basal metabolic rate between subjects.¹³¹ After these factors are accounted for, gender does not appear to play an independent role in modulating resting energy expenditure. Another study noted that organ masses are the body compartments that predominantly contribute to resting energy expenditure: organs including the brain, liver, kidney, and heart have a much higher resting

metabolic rate than does skeletal muscle.¹³⁰ Compared with men, women have a larger fraction of their fat-free mass as high metabolic-rate organs and tissues. This may explain why women have a larger ratio of resting energy expenditure to fat-free mass than do men and, similarly, why lean subjects have a larger ratio of resting energy expenditure to fat-free mass than do their obese counterparts.

Other investigators, however, have reported lower total and physical activity energy expenditure, as well as resting energy expenditure, in women than in men.¹²⁹ Because men have more skeletal muscle than do women,¹³² the lower physical activity expenditure in women may be at least partly explained by body composition differences. Physical activity energy expenditure is related to percent body fat in men but not in women.¹²⁹ In other words, more-active men tend to have less body fat than do less-active men, but this is not necessarily the case for women. Another study confirmed that exercise is not associated with significant fat loss in women.¹³³

An explanation for the poor relationship between physical activity and body fat in women could be that women may compensate for higher energy expenditure by increasing energy intake to a greater extent than do men.^{134–136} However, one interventional study (8 lean females and 8 males of similar percentage of body fat), which found a significant decrease in body mass in women but not in men after a short-term exercise program ($P < 0.001$), postulated the opposite—that women did not compensate for the increased exercise by increasing energy intake.¹³⁷ Body composition also seems to have a closer relationship to type of food intake in women than it does in men. Women with higher fat intake and lower carbohydrate intake were found to have a significantly higher percentage of body fat ($P < 0.05$), but this was not true for men.¹²⁹ Whether these gender differences in the relationship between energy expenditure and body composition are explained by food intake or differences in metabolism has not yet been clarified.

Gender Differences in Metabolic Response to Food Intake

In a study of 88 men and women, Couillard et al²⁵ found that compared with women, men have significantly higher postprandial insulin, FFA, and TG levels after a standardized meal ($P < 0.01$). Another study also noted this gender dichotomy in postprandial TG response.¹³⁸ However, the difference in postprandial TG level did not persist after visceral adiposity was accounted for, and therefore VAT accumulation was a significantly important contributing factor to the exaggerated postprandial TG response in men ($P < 0.001$).²⁵ Liver fat content, which, as stated previously, is significantly higher in men than in women,⁴⁵ is also associated with postprandial lipemia.^{139,140} Furthermore, fasting triglyceridemia is also an important factor in predicting postprandial levels, and men have been reported to have substantially higher fasting TG levels than do women.¹⁴¹ Other factors may also contribute to the metabolic response to food intake, and estrogens have been suggested to have a favorable effect on postprandial TG levels.¹⁴²

Gender Differences in Ghrelin Secretion

Ghrelin is a 28-amino acid peptide hormone that is produced in the stomach, has orexigenic properties, and stimulates growth hormone and adrenocorticotropin release from the pituitary.^{143,144} Ghrelin has been implicated in meal initiation, with high concentrations before meals, and a decrease post-prandially.¹⁴⁵ Ghrelin is also decreased in obesity, possibly with insufficient postprandial suppression,¹⁴⁶ and has an unclear relationship to insulin—several studies found ghrelin to be suppressed by insulin,^{147–150} whereas others did not.^{151,152}

Ghrelin dynamics may be sexually dimorphic, with some studies reporting that women have higher concentrations than do men.^{153,154} Specifically, Greenman et al¹⁵⁴ found that in 24 non-diabetic adults of mixed weights, women had significantly higher ghrelin concentrations, both fasting ($P < 0.04$) and after glucose ($P < 0.001$) and lipid ($P < 0.029$) loads, compared with men. This relationship persisted even after correction for BMI, age, and homeostasis model assessment index ratio. However, other studies have not confirmed this finding, and have reported similar ghrelin concentrations in men and women^{155,156} and among pre- and postmenopausal women.¹⁵⁵ One study also did not find a correlation between ghrelin concentrations and body composition or abdominal fat distribution,¹⁵⁵ supporting the belief that ghrelin concentrations are associated with body weight and not body fat. Whether ghrelin concentrations differ between men and women, and what its potential role is in the gender dimorphism of body composition, insulin sensitivity, and energy balance, remains to be shown.

CONCLUSIONS

Men and women differ in regard to body composition, insulin resistance, and energy balance. For a given BMI, men have higher lean mass and more visceral and hepatic adipose tissue, whereas women have elevated general adiposity, SAT in particular. These differences in adipose tissue distribution may contribute to a more insulin-sensitive environment in women, as visceral and hepatic adiposity is associated with increased insulin resistance. Estrogen may also play a role in these gender differences, because it has a favorable effect on insulin and glucose homeostasis, adipose tissue distribution, and proinflammatory markers. Adiponectin, an insulin-sensitizing hormone, is also significantly higher in women compared with men, and whether this is due to differences in sex hormones or differences in adipose tissue distribution is not clear. Finally, the resting energy expenditure differences between men and women may be explained by differences in lean body mass, particularly the high metabolic-rate organ masses, whereas physical energy expenditure may be more closely related to percent body fat in men.

In summary, the elevated visceral and hepatic adipose tissue reported in men, in conjunction with the lack of a possible protective effect of estrogen and lower adiponectin levels, may contribute to their higher insulin resistance compared with women. Gender-specific avenues of research into insulin resistance should consider these sex differences in adipose distribution and adipokine secretion. In addition, gender-tailored treatment of insulin resistance may benefit from focusing on visceral and hepatic adiposity and hypoadiponectinemia, which are more prominent in men than in women.

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Figure.

Cross-sectional abdominal magnetic resonance grey-level images of an obese woman and an obese man. The woman has more subcutaneous adipose tissue than the man does, and the man has more visceral adipose tissue than the woman does.