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Sex Differences in Obesity-Related Glucose Intolerance and Insulin Resistance

Haifei Shi and Shiva Priya Dharshan Senthil Kumar

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1. Introduction

The prevalence of obesity has increased dramatically over the past decade (1) along with several health risks it encompasses, including non-insulin dependent type 2 diabetes, cardiovascular disease, fatty liver, dyslipidemia, and some types of cancer (2). The economic costs of caring for patients with obesity and diabetic complications are enormously high (3). There are important sex differences in the prevalence of these metabolic diseases. Premenopausal women have much less metabolic disorders than men; however, the prevalence of obesity and diabetes increases dramatically in postmenopausal women (4). Sex steroid hormone estrogen may be protective against the metabolic syndrome and may contribute to the maintenance of insulin sensitivity, and its deficiency leads to development of type 2 diabetes and insulin resistance. This has resulted in the use of estrogen hormone replacement therapy for the treatment of insulin resistance in postmenopausal women (5) and in men with congenital aromatase deficiency (6). Thus, estrogen has enormous potential as a therapeutic agent for use in the prevention or treatment of type 2 diabetes with glucose intolerance and insulin resistance.

1.1. Sex differences in genetic polymorphisms on the development of diabetes

The development and etiology of obesity and related diseases such as type 2 diabetes stems from a conflict between genes which allowed our ancestors to survive extended periods of famine and physiological responses to caloric excess and sedentary lifestyle of the modern world. Some studies have evaluated potential genetic components and reported sex differences in the effects of certain polymorphisms of several enzymes and genes on the development and etiology of diabetes. Several examples are listed below.

First example is protein tyrosine phosphatase, an enzyme involving signal transduction of T cell and insulin receptors. The activity of this enzyme, affected by certain genotypes, is

related to age of onset of type 1 diabetes in a sex-specific manner (7). Specifically, genotypes associated with medium to high enzyme activity are correlated with younger age of onset in females but not in males, whereas low activity genotypes do not display sex differences. Second example is peroxisome proliferator-activated receptor γ_2 (PPAR γ_2), whose polymorphism is correlated with increased insulin sensitivity and reduced risk for type 2 diabetes. Interestingly, in males, a more efficient shift from lipid oxidation in the basal state to carbohydrate oxidation during insulin stimulation has been observed in lean, glucose tolerant males with the polymorphism compared to wild-type males; whereas this difference has not been observed in females (8). Therefore, the PPAR γ_2 polymorphism protects individuals from insulin insensitivity by promoting better suppression of lipid oxidation leading to more glucose disposal in males but not females. Another example is the 3' untranslated region of the *PPP1R3A* gene, a gene involved in glycogen synthase activity and associated with development of type 2 diabetes (9). Males homozygous for the polymorphism of *PPP1R3A* gene are significantly younger at diagnosis than female carriers (10). Additionally, a polymorphism in the promoter region of uncoupling protein (UCP)-2, a mitochondrial inner membrane protein, may be involved in obesity and development of type 2 diabetes (11). In a study of 100 obese subjects, the genotype that causes increased transcription of UCP-2 mRNA is more prevalent in diabetic women than in nondiabetic women. However no difference in distribution of this genotype is detected in men (12). To summarize, sex differences in genetic polymorphisms exist in the development and etiology of diabetes.

1.2. Sex differences in physiologic mechanism on the development of diabetes

Obesity has been recognized as a major and an independent diabetes risk factor. The increase in type 2 diabetes is closely associated with the epidemic of obesity. Body composition is very closely associated with glucose tolerance and insulin sensitivity (13). Development of adverse metabolic complications has been attributed to increased body fat, not just body weight, and the fat distributed particularly in the abdominal visceral compartment, a source of bioactive mediators that directly contribute to insulin resistance (14). To be more specific, intra-abdominal visceral adipose tissue carries a stronger risk for the development of metabolic disorders, such as glucose intolerance and insulin resistance related type 2 diabetes, than subcutaneous adipose tissue. Therefore, risk for diabetes incidence is particularly high in individuals with large amounts of abdominal visceral fat.

Sex differences in the regional fat distribution exist. Males and females differ in terms of how and where they store body fat. In humans, premenopausal women usually have more subcutaneous fat, whereas men have more intra-abdominal visceral fat. Consequently, obesity-related metabolic disorders are much lower in premenopausal women than men (15). In addition, estrogens are responsible for body weight homeostasis in women. The prevalence of obesity is particularly high among middle-aged women. Symptoms of the metabolic syndrome, including increased visceral obesity and shifts in body fat distribution, as well as glucose intolerance and insulin resistance begin appearing in many women experiencing menopause and developing estrogen deficiency (16). Even in women who do

not gain weight after menopause, fat shifts from a subcutaneous location into the abdomen. Women are at an increased risk to develop visceral obesity due to the loss of endogenous ovarian hormone production. The increased visceral obesity in menopausal women can be altered by exogenous hormone replacement therapy (17, 18). Researches using animal models have provided important insights into the pathogenesis of human diseases and new therapeutic approaches. Peripheral metabolic signals and hormones are not only involved in regulating adiposity and body fat distribution, but also involved in regulating glucose metabolism and glucose tolerance. In experimental rodent models, reductions in circulating estrogens, which occurs following removal of ovaries (i.e., ovariectomy), results in increased body adiposity. Such increase in body adiposity can be ameliorated by exogenous 17β – estradiol administration (19).

In addition, sex hormones are directly involved in the regulation of glucose tolerance (20, 21). In a prospective study that included over 500 women and men who did not have diabetes upon study entry, development of diabetes was associated with low levels of total testosterone in men and high levels of bioavailable testosterone in women (22). Therefore, differences in the regulation of glucose tolerance may be under the influence of sex hormones indirectly through their influence of body fat content and distribution or directly through their influence in the glucose metabolism and insulin signaling.

This chapter discusses the sex differences in regulation of glucose homeostasis, focusing on the roles of female sex hormone estrogens as determinants mediating body adiposity levels and body fat distribution as well as glucose metabolism and insulin sensitivity. We will use the term “sex difference” instead of “gender difference” throughout this chapter. The term “sex” refers to differences between males and females that result from the chromosomal complement and the effects of hormones; whereas the term “gender” refers to an individual’s identity as a man or a woman, and the cultural and behavioral expectations associated with being a man or a woman. With regard to the regulation of glucose homeostasis and energy metabolism, little is known about gender differences, thus this chapter focuses primarily on sex differences.

2. Sex differences in body adiposity and fat distribution

The prevalence of obesity is higher in women than in men in many areas around the world (www.iaso.org). In addition there is a sex difference in body fat distribution. These sex differences in obesity incidence and fat distribution can be explained in part by the influence of gonadal steroids, as well as behavioral, socio-cultural and genetic factors. Several factors may play important roles to drive greater propensity for excess body fat in females than in males. It has been suggested that evolutionary pressures predispose females to store excess fat for reproduction and lactation. In contrast, evolutionary pressures predispose males to burn stored fuels in gathering and hunting. Adipose tissue plays a major role in the regulation of glucose homeostasis and insulin sensitivity, thus total body adiposity is closely associated with insulin sensitivity. Increased body fat is a risk factor for developing type 2 diabetes mellitus. A line of research has focused on behavioral and social differences between men and women that relate to eating or activity behaviors. Sex differences in body

composition and insulin sensitivity are evident in humans throughout the lifespan. Pregnancy and menopause also have physiological and behavioral consequences on appetite and weight regulation that confer elevated obesity risk in many women. There is a sex difference in the regional fat distribution. Men and premenopausal women differ in their fat distribution. Females have “gynoid” or female-pattern fat distribution with more subcutaneous fat, whereas males have “android” or male-pattern body fat distribution with more abdominal visceral fat (15). Fat deposition in the subcutaneous depot is important for females during lactation. Despite the higher level of body fat, obesity-related metabolic disorders, such as type 2 diabetes, are much lower in premenopausal women and female animals than males. The role of estrogen in mediating body fat distribution and glucose homeostasis will be discussed in this chapter.

2.1. Difference between subcutaneous and abdominal adipose tissues

Body fat distribution is a more appropriate indicator than total adiposity for metabolic disorders, as obesity is not only a condition characterized by homogenous distribution of adipose tissue, but that the regional distribution of adipose tissue is more important in understanding the relationship between obesity and various metabolic diseases. Adipose tissue, which is distributed in the abdominal viscera, carries a greater risk for glucose intolerance and insulin resistance than adipose tissue subcutaneously. Specifically, abdominal adipose tissues contribute to the development of insulin resistance, glucose intolerance, hypertension, dyslipidemia, and atherosclerosis (23). Metabolites and secretions of visceral adipose tissue drain through the hepatic portal system, partially at least, to the liver. Insulin effect is lower and catecholamine effect is higher in visceral than subcutaneous adipose tissue. Specifically, visceral fat have higher rates of catecholamine-induced lipolysis (24, 25), express higher numbers of beta-1, -2 and -3 adrenergic receptors and are more sensitive to catecholamine-induced lipolysis (26, 27), and are less responsive to the cAMP-lowering effects of alpha-adrenergic agonists (28). In addition, visceral fat cells express higher levels of glucocorticoid receptor (29, 30) and have greater glucocorticoid response with lipoprotein lipase activation (31), produce more angiotensinogen (32, 33), and secrete more interleukin-6 and plasminogen activator inhibitor-1 (34) than subcutaneous adipose tissue. Accumulation of intra-abdominal/visceral adipose tissue carries a much greater risk for metabolic disorders than does adipose tissue distributed subcutaneously (35-37). In contrast, subcutaneous fat distribution is poorly correlated with risks for these metabolic disorders (23). Therefore, the elevated health risks in diabetes associated with obesity depend on the localization of the adipose tissue in the body, as the distribution of fat is more directly associated with glucose tolerance and insulin sensitivity than the total body adiposity. Consequently, there is a sex-based difference in the prevalence and incidence of metabolic complications associated with obesity. Males have an increased incidence of obesity-related metabolic diseases than females aged 12 to 18 years (38, 39). In premenopausal women, there is a lower incidence of metabolic disorders associated with obesity (38). The prevalence of the metabolic syndrome increases with age, and the prevalence of the metabolic syndrome is similar in middle-aged men and women (40).

There are noted functional differences between subcutaneous and abdominal adipose tissues. Subcutaneous tissue is poorly innervated compared to the abdominal adipose tissue (35). Consequently, subcutaneous adipose tissue takes up free fatty acids and stores the excess calories more readily than abdominal adipose tissue in both males and females. Lipoprotein lipase (LPL) is the major enzyme involved in the fatty acid uptake and is the key regulator of fat accumulation in adipose tissues. Estrogens decrease adipose tissue LPL activity (41-43), and thus males have a higher level of LPL activity and thus fat accumulation than females with higher levels of estrogens. The lipolytic pathway involves the breakdown of energy stored in the form of triglycerides and is initiated when the energy supply from the metabolic fuels is depleted. The lipolytic activity of the abdominal fat is higher compared to the lipolytic activity of the subcutaneous fat in premenopausal women; a phenomenon not observed in post-menopausal women lacking endogenous estrogen (24, 44, 45).

Recent evidence suggests that great subcutaneous fat accumulation may be protective against development of metabolic disorders. First, epidemiological studies indicate association of a high waist-to-hip ratio, instead of a large waist circumference alone, with the incidence of type 2 diabetes and other metabolic diseases (46-48). Indeed, a larger hip circumference has been shown to be protective against metabolic risk in multiple ethnic groups, independent of waist circumference or abdominal fat accumulation (49). Second, several animal studies reported that mice with transplantation of subcutaneous fat from the inguinal region of male donors into the intra-abdominal compartment of male recipient mice resulted in significantly protective effects on adiposity, insulin sensitivity and glucose tolerance (50-53). Since protective effect of a large hip circumference with regard to cardiovascular disease morbidity and mortality is significant in women but not in men (54), it would be expected that transplanting female subcutaneous adipose tissue might have greater protective effects.

2.2. Sex hormone estrogens and estrogen receptors regulate adiposity

Obesity development is accelerated after menopause in women; factors such as loss of estrogens, the ageing process and changes in lifestyle may all be contributors (Shi & Clegg 2009, Barton 2010). The effect of menopause is supported by animal models showing that a reduction in circulating estrogen levels following ovariectomy results in increased body adiposity (55). Body fat increases in several conditions associated with estrogen deficiency such as ovariectomy, polycystic ovary syndrome (PCOS), and the lack of a functional aromatase gene; all can be corrected and reversed by exogenous administration of 17 β -estradiol, the active form of estrogens (56-61).

The classical nuclear estrogen receptors (ER) include estrogen receptor alpha (ER α) and estrogen receptor beta (ER β). Genomic activation of ERs results from estrogens binding to estrogen response elements (EREs) in promoter regions of target genes (62, 63). Increased visceral adiposity is associated with the XbaI polymorphism of the human ER α gene when guanidine is substituted for adenine in exon one (64). Additionally, pre-menopausal women with increased visceral adiposity, indicated by higher waist-hip ratios, have the XbaI polymorphism compared to the control cohort of women with the normal genotype (64).

Interestingly such polymorphism does not affect adiposity in postmenopausal women or in men (64). ER α gene expression in subcutaneous adipose tissue is reduced in obese premenopausal women, but increases after weight reduction (65). Furthermore several ER α single nucleotide polymorphisms have been associated with obesity phenotypes in women and men (64, 66, 67). Thus, polymorphisms of the human ER α gene may impair estrogen signaling and lead to increased visceral adiposity and its attendant health risks. In humans, polymorphisms in the ER β gene have been associated with lower BMI although other investigators found no correlations (68, 69).

Utilizing targeted deletions in the ER α gene or both ER α and ER β genes of male and female mice indicate increase in adiposity (70, 71). ER β inhibits food intake and reduces body weight through effects in the central nervous system in rats (72). In addition, one study investigated the effect of estrogens on adipose tissue development using ER α knockout mice. Loss of estrogen following ovariectomy in ER α knockout mice resulted in decreased body fat and adipocyte size, which was reversed by 17 β -estradiol treatment (73), suggesting that regulation of body adiposity is mediated by an ER other than ER α , possibly by ER β . In contrast, mice lacking both ER α and ER β develop obesity but increased adiposity is not observed in ER β -knockout mice (71), questioning a role for ER β and suggesting that the obesity-promoting effect of estrogen deficiency is mediated specifically through ER α . These findings support a substantial physiological role for ER α in mediating the effects of estrogens in the control of body adiposity. Replacement of 17 β -estradiol prevents ovariectomized wild-type mice from developing obesity, such protective effects are not observed in ovariectomized ER α deficient mice (74). Therefore, estrogens, together with its ER α , play important roles to regulate total adiposity.

To summarize, the metabolic effects of estrogens appear to be largely mediated by ER α whereas the role of ER β and possible cross-talk with other ERs is currently unclear. Indeed, ER β inhibits ER α -mediated gene expression in certain cell types and often opposes the action of ER α (75), an interaction that might be also important for the regulation of body fat. Finally, it should be noted that compensatory developmental changes in both animal models and humans may alter hormone responsiveness in ways that are different from the inherent biology in healthy individuals or wild-type animals respectively.

2.3. Sex hormone estrogens regulate fat distribution

Because there are differential effects on health risk between subcutaneous and abdominal adipose tissues, it is important to understand mechanisms that determine not only total fat accumulation but also where fat is accumulated, and how fat distribution is regulated in males and females. Recent research using molecular approaches and animal models has provided greater understanding of the role of sex hormones and other molecules on fat partitioning.

The question of sex differences in fat distribution have been examined using animal models. Several animal species, including pigs and rodents, show sex-specific differences in fat distribution, with males having more abdominal fat and less subcutaneous fat than females.

Ovarian hormone estrogen appears to be a key regulator in mediating the sex-specific adipose tissue distribution pattern. Estrogens promote the accumulation of subcutaneous fat (76). In contrast, abdominal fat varies inversely with levels of estrogens (77). During the peri-menopausal period, depletion of ovarian follicles leads to a steady decline in 17β -estradiol production in post-menopausal women (78). Loss of estrogens with menopause is associated with an increase in abdominal fat accrual (36). Indeed, changes in body fat mass are positively correlated with serum 17β -estradiol concentration in post-menopausal women (79-81), although this association varies with time from the onset of menopause and may take up to 6 years to develop (81). In premenopausal women, there is a lower incidence of metabolic disorders associated with obesity. However, after menopause when there is a very low level of estrogen in the circulation, an increased risk of obesity-related metabolic disorders is reported (38). Therefore ovarian hormones might play a vital role in protecting the body against metabolic diseases via the sex-based differences seen in adipose tissue deposition.

The sexual dimorphism in adipose tissue distribution may partially explain the greater risk for the metabolic syndrome in men compared with premenopausal women. Estrogens are known to regulate body fat distribution in animals and humans. As being discussed earlier in this chapter, females tend to accumulate more fat in their subcutaneous depots whereas males tend to accumulate more fat in their visceral depots (82). Additionally, after the loss of endogenous estrogens as a result of menopause, a shift towards visceral adiposity occurs, which is sensitive to estrogen therapy (55).

Studies in ovariectomized rodent models have elucidated possible mechanisms by which changes in estrogen levels may impact fat distribution. Ovariectomized female rats gain fat, specifically visceral fat with a loss of subcutaneous fat (19, 83). Additionally peripheral or central administration of 17β -estradiol to OVX rats changes their body fat distribution to mirror that of intact females with normal estrous cycles. administration of exogenous estradiol reverses this increased visceral fat distribution pattern (19). Furthermore, altering the sex hormone milieu in males with exogenous 17β -estradiol administration to male rats decreases visceral fat and increases subcutaneous fat relative to males not given estrogen (19). An important implication from these findings is that estrogens are critical determinates of body fat distribution. Estrogen may influence fat distribution centrally by modulating leptin responsiveness, as leptin not only influences total body fat in rodents but also favors loss of visceral fat via Stat3 signaling in the hypothalamus (84). Female mice are more responsive than male mice to the effects of centrally administered leptin to decrease food intake and body weight and to increase c-fos and Stat3 expression in the arcuate nucleus (85). In addition, research has shown that both male and female aromatase-knockout mice, which are estrogen-deficient and have elevated testosterone, accumulate more abdominal adipose tissue with increased adipocyte size in the gonadal and intra-renal fat depots (57). Male aromatase-knockout mice also develop fatty liver, as do aromatase-deficient men, and this is reversible with estradiol treatment (86).

Sex hormones play important roles in adipose tissue lipolysis and fat uptake. Sex differences exist for regulation of lipolysis by alpha-2 adrenergic receptor(87). Estrogen treatment

increases lipolysis in abdominal fat cells in mice(88). Lactation and menopausal status also impact the lipolytic responsiveness and lipoprotein lipase activity of fat cells. Higher adipose tissue lipoprotein lipase activity (promoting fat storage) occurs in subcutaneous femoral adipocytes compared with abdominal adipocytes in premenopausal women but not in postmenopausal, estrogen-deficient women(89). Additionally lipolysis increases in subcutaneous femoral fat during lactation but not in abdominal fat(89). Furthermore, estrogen treatment in postmenopausal women restores the lipoprotein lipase activity of the femoral adipocytes and attenuates lipolytic response in subcutaneous adipocytes but not in abdominal adipocytes (90). Subcutaneous gluteal adipocytes from premenopausal women are more sensitive to the antilipolytic effects of insulin than abdominal adipocytes (91).

Testosterone, male androgens also impact body fat distribution. Testosterone deficiency aggravates the development of obesity and hyperinsulinemia, which in turn will suppress testicular androgen synthesis even further and result in a vicious cycle (92). In 'andropause' men, gradual decline in circulating androgens with aging is accompanied by increased total and abdominal fat (93). Administration of aromatizable androgens such as testosterone (94, 95), but not nonaromatizable dihydrotestosterone (94), reduces total and abdominal fat in older men. In contrast, androgen administration to ovariectomized female mice significantly increases body adiposity and abdominal fat (96). Such obesity development is associated with reduced fatty acid oxidation, indicated by decreased phosphorylation of adenosine monophosphate (AMP)-activated protein kinase and acetyl-CoA carboxylase in abdominal visceral fat (96). In humans, women with higher circulating androgen levels (97) or exogenous androgen administration (98, 99) increase abdominal fat. These findings raise significant clinical concern about the use of testosterone as a hormone replacement therapy in postmenopausal women.

In summary, sex differences in body fat distribution appear to be largely a result of differences in sex hormones between men and women. Estrogens reduce visceral fat in men and women, an effect that is likely mediated by both central and peripheral mechanisms. In contrast, opposite effects of androgens on fat distribution in men and women are seen, with aromatizable androgens decreasing visceral fat in men but increasing it in women.

2.4. Estrogen receptors regulate fat distribution

Gonadal hormones, including estrogen, progesterone and androgen, have their receptors expressed in the visceral and the subcutaneous adipose tissue depots (100). Subcutaneous adipose tissues have higher concentrations of estrogen receptors and progesterone receptors than androgen receptors in females, and estrogens down-regulates AR expression in subcutaneous fat (101). In contrast, visceral adipose tissue has higher concentrations of androgen receptors (102, 103). In visceral adipose tissue, there is an increase in the expression of androgen receptors in males relative to estrogen receptors. The development of knockout animals has provided a powerful tool to examine the role of individual receptors for estrogen, progesterone and androgen in the regulation of adipose tissue. Adipose tissue-specific androgen receptor knockout mice have increased intra-adipose

tissue estradiol levels, which precedes increased subcutaneous obesity and hyperleptinemia (104). Additionally, androgens can be converted to estrogens through activation of the aromatase enzyme. Aromatase knockout mice have elevated testosterone and accumulate more abdominal adipose tissue with increased adipocyte size in the visceral fat depot. Hence, in adipose tissue, there is a counteracting effect between estrogen and androgen, which may lead to differences in fat distribution.

Estradiol regulates body fat distribution either directly at the level of the adipocyte or through augmenting the efficacy of the adiposity signals in the CNS. Subcutaneous and abdominal adipose tissues express both ER α and ER β , but ER α is predominantly expressed in abdominal adipose tissue (105) and ER β are higher in subcutaneous adipose tissue (106). ER α gene polymorphisms predict abdominal obesity in women, but not in men, suggesting a possible sexual dimorphism in the ER α effects (64). Female and male mice lacking ER α develop central obesity with increases in abdominal adipose tissue, which is reflected by increased adipocyte number and size (70). ER α is ubiquitously expressed in rodent brains, but the physiologically relevant sites of ER α in the regulation of food intake and energy expenditure have not been identified. ER α is expressed in the ventrolateral portion of the VMN, the ARC, the medial preoptic area (MPOA), and the paraventricular nuclei (PVN) (107-109). ER β is found in the same hypothalamic nuclei as ER α , but ER β expression is significantly reduced relative to ER α . Site-specific knock-down of ER α in bilateral ventromedial nucleus of the hypothalamus in mice using siRNA result in increased adiposity, no change in food intake, and suppression of energy expenditure, increased visceral adiposity, and decreased leptin sensitivity, implicating ventromedial hypothalamic ER α in energy homeostasis (110).

Both short-term and long-term castration in males resulted in increased insulin sensitivity and increased lipogenesis in both abdominal and subcutaneous adipose tissues, an event that is independent of changes in the fat pad weights (102). Thus, in contrast to the preferential effect of estrogen in females on the abdominal adipocytes, testosterone exerts an inhibitory effect on lipogenesis and insulin sensitivity in both abdominal and subcutaneous adipocytes.

3. Sex difference in glucose metabolism

Glucose challenge test is important in terms of understanding the pathophysiology of individuals at risk of progressing to type 2 diabetes. As recommended by the World Health Organization, the standardized, 75-g oral glucose tolerance test is used for diagnosis of impaired fasting glucose and impaired glucose tolerance. Plasma glucose at fasting and 2 hours after oral glucose tolerance test are measured to indicate glucose tolerance in individuals. Fasting glucose is the glucose concentration after an overnight fast and mostly reflects endogenous glucose production, whereas glucose level 2 hours after oral glucose tolerance test, *i.e.* post-load hyperglycemia, reflects the acute increase in blood glucose after a glucose challenge.

Several epidemiological investigations from European countries (111-113), Australia (114-116), Asian countries (117), and Mauritius (118) report that men have higher fasting plasma

glucose levels and plasma glucose levels during the early course of the oral glucose tests than women, indicating that the prevalence of impaired fasting glycaemia is higher in men than in women; and women have higher plasma glucose levels 2 hours after oral glucose tolerance tests than men, suggesting that the prevalence of impaired glucose tolerance is higher in women than in men. The pre-diabetic condition of impaired fasting glycaemia is characterized by hepatic insulin resistance, elevated hepatic glucose production and beta cell dysfunction.

3.1. Sex difference in glucose tolerance

Men and women are given the same amount of glucose during a standard oral glucose tolerance test. In all ethnic groups throughout the world, women are on average shorter by approximately 15 cm and thus have smaller body sizes than men (119). Additionally, women generally have less absolute amount of fat-free muscle mass than men, which is the major metabolically active tissue involved in glucose uptake, and thus women are less able to metabolize the fixed amount of glucose (111, 115, 118). The higher prevalence of impaired glucose tolerance in women may be an artifact caused by the fact that individuals of different body sizes and lean muscle masses receive the same amount of glucose during glucose challenge test. This notion is supported by the observation that the increments of glucose, insulin and the incretin hormones glucagon-like peptide-1 and glucose-dependent insulintropic polypeptide after an glucose challenge test are significantly higher in women than in men (120), indicating that the same amount of glucose represents a larger stimulus in women than in men when seen in relation to their body sizes.

Further analysis using anthropometric measures (*e.g.*, weights, heights and waist-hip circumferences) indicated that the differences in plasma glucose levels 2 hours after oral glucose tolerance tests, but not fasting plasma glucose levels, could be explained by differences in body size and/or body composition between men and women (113, 115, 118, 121). Consequently, women are more commonly diagnosed with diabetes on the basis of glucose level 2-hour post glucose tolerance test compared with fasting plasma glucose levels (112, 115). The risk of gestational diabetes is also higher in shorter compared with taller women (122). Women do not have higher glucose levels following glucose test than men when differences in height and high-waist circumference (113) or absolute amount of fat-free mass (121) are taken into account. This notion is supported by the observation that there is a higher risk of developing type 2 diabetes in men than in women with impaired glucose tolerance (123), suggesting that women with impaired glucose tolerance may be healthier than their male counterparts. In summary, sex difference in glucose tolerance without taking into account of body size is probably not related to sex-specific differences in the physiology of glucose regulation.

3.2. Sex difference in fasting plasma glucose

In contrast to the sex difference in glucose tolerance, sex difference in fasting plasma glucose levels is not related to differences in anthropometry and could not be explained by

differences in body size and/or body composition between men and women. Indeed, higher fasting plasma glucose in men compared with women reflects differences in insulin sensitivity and pancreatic β cell function between men and women (113), suggesting that the sex difference in fasting plasma glucose has a true physiological basis.

During fasting females have decreased liver enzymes, lower creatinine and uric acid concentrations with a trend toward reduced triglycerides, but higher HDL cholesterol and body fat mass, which are generally seen as gender-related differences because of the direct effects by sex hormones (124, 125). There is an association between elevated FFA and increased endogenous glucose production (126). Interestingly, females displayed lower fasting endogenous glucose production than males, despite higher fasting plasma FFA concentrations (116). Study using laboratory rodent models indicate that there is no direct effect by FFA on hepatic glucose production in isolated perfused rat liver (127).

The possible physiological mechanism that is responsible for the higher fasting plasma glucose levels observed in men compared with women could be related to large waist circumference in men (128), suggesting that sex differences in body fat distribution contribute to the sex difference in fasting plasma glucose levels. Indeed, high waist circumference and hip circumference are associated with impaired glucose tolerance in both men and women (113), suggesting that obesity contributes and is related to disturbances of glucose metabolism. Visceral component of abdominal fat is strongly associated with insulin resistance (129). Abdominal adipose tissue has a reduced ability to metabolize the glucose load of a glucose challenge test (102). Homeostasis model assessment of insulin resistance (HOMA-IR), predominantly reflecting hepatic insulin resistance, is lower in men than in women in general (113). Homeostasis model assessment of β cell function (HOMA- β) is also slightly lower in men than in women.

In summary, sex differences in fasting plasma glucose levels are caused by underlying physiological differences in both insulin sensitivity and β cell function.

3.3. Sex difference in glucose absorption

Sex difference in carbohydrate metabolism may contribute to sex-specific glucose regulation. A glucose infusion at fasting and during hyperinsulinemia is used to measure whole-body insulin sensitivity and endogenous glucose production using hyperinsulinemic clamp technique. Healthy glucose-tolerant women have slower glucose absorption rates and slower liquid emptying from the stomach (130), and thus longer gut glucose half-life compared with glucose-tolerant men (116). Furthermore, there is an association between glucose absorption velocity and body size, with body tallness having strong influence on the glucose absorption velocity. This notion is supported by a recent study showing that, for both sexes, although people with different heights have similar fasting glucose levels, those in the shortest height quartile do have significantly higher 2 h glucose levels following oral glucose tolerance test compared with those in the tallest height quartile (115). As it is mentioned earlier in this section, women are on average shorter by approximately 15 cm

than men (119). Consequently, women generally have lower glucose absorption rates and have higher plasma glucose levels 2 hours after oral glucose tolerance test than men (115).

Glucose absorption rates are higher in males in the initial phase and elevate in females in the end of the of the oral glucose tolerance tests three hours after oral glucose intake (116). The best-suited value to describe of glucose absorption velocity is glucose half-life in the gut. In all participants, glucose half-life is negatively related to body height and fat-free mass (116, 131), thus glucose half-life is prolonged in females in comparison with males. When adjusted for total fat-free body mass, females with similar gut absorption as males are slightly more insulin sensitive than males(116). The alterations of plasma glucose concentrations during glucose tolerance test in females and males are not only due to different glucose clearance rates but also due to different absorption rates from the gastrointestinal tract between sexes (116), which could serve to explain higher glucose concentrations at the end of the glucose challenge test in females. Additionally, postprandial insulin secretion affects glucose disappearance rate and glucose concentrations. One study has reported that females have greater peripheral insulin release and thus higher concentration during the first hour of oral glucose tolerance test (132). A separate study has reported that insulin secretion is comparable between young males and females following a high-carbohydrate mixed meal (133). Therefore, these available data from previous human studies suggest that the disturbance in insulin secretion does not contribute to the higher postprandial glucose concentrations in women. This notion is supported by animal studies using rodents, which have reported no sex associated difference in glucose-stimulated insulin secretion (134).

To summarize, sex difference in glucose absorption and concomitant effect of insulin release, but not insulin-induced glucose uptake or glucose metabolism, contributes to the higher prevalence of glucose intolerance in females diagnosed from oral glucose tolerance tests as observed in several epidemiological studies worldwide.

4. Sex differences in insulin sensitivity

Glucose homeostasis is maintained in a narrow range via glucose output by the liver and glucose uptake by tissues. Insulin, secreted by the pancreatic β cells in response to increased circulating levels of glucose, is the major anabolic hormone whose action is essential for maintenance of glucose homeostasis. Insulin regulates glucose homeostasis by reducing hepatic glucose production via decreased gluconeogenesis (de novo glucose synthesis) and glycogenolysis (glycogen breakdown), and increasing the rate of glucose uptake, primarily into skeletal muscle and adipose tissue (135). Insulin's actions are brought about by intracellular events following the binding of insulin to insulin receptor and the activation of its tyrosine kinase, which phosphorylates tyrosine residues of target proteins such as insulin receptor substrates (136). The phosphatidylinositol 3-kinase (PI3K)/Akt signaling cascade is activated by the IRS proteins to trigger the stimulation of glucose uptake (135). Insulin resistance, defined as a state of decreased responsiveness of target tissues to insulin, plays a major role in the development of type 2 diabetes. Increased plasma free fatty acid

concentrations due to high-fat diet feeding are typically associated with many insulin-resistant states (135). Abnormalities in fatty acid metabolism result in inappropriate accumulation of lipids in myocytes and hepatocytes, thus impairing their function and leading to insulin resistance (135).

4.1. Female human and animals are more insulin sensitive

There is evidence indicating that insulin sensitivity differs between males and females (137). Premenopausal women have better glucose tolerance and insulin sensitivity compared with men in general. Despite having lower fat mass, the prevalence of diabetes and early abnormalities of glucose metabolism is three times higher in men than in women (138). Moreover, women have decreased susceptibility to fatty acid-induced peripheral insulin resistance (124, 139, 140). Female humans and rodents are more insulin-sensitive than their male counterparts.

In many different laboratory rodent models of glucose intolerance, insulin resistance, and diabetes, the different insulin sensitivity of female versus male mice can be detected by glucose tolerance tests and insulin tolerance tests. When various strains of mice are subjected to glucose tolerance tests, female mice have lower glucose levels than male mice at different time point throughout the tests (141-143). Additionally, female mice show a greater fall in blood glucose in response to insulin as compared with male mice during insulin tolerance tests (141-143). These data from our lab suggest that female animals are more insulin sensitive than males. Furthermore, female rodents are less prone to diet-induced insulin resistance, and many genetically induced forms of insulin resistance have a milder phenotype in females compared with males (141, 142, 144, 145).

4.2. Female fat cells are more insulin sensitive

Adipocytes in different fat depots appear to have a distinct impact in insulin sensitivity. As it is mentioned previously in this chapter, accumulation of visceral fat, but not subcutaneous fat, is linked to the development of metabolic complications. Fat accumulation in different depots is sexually dimorphic, i.e., men accumulate more visceral fat, whereas women accumulate more subcutaneous fat and have a higher percentage of body fat compared with men. These sex-related differences in insulin sensitivity and adipose tissue development and function could be attributable in part to actions of estrogen and testosterone. For example, decreases in estrogen and increases in testosterone levels that occur during menopause are associated with loss of subcutaneous and gain of visceral fat and increase in insulin resistance (146).

Female adipocytes have increased insulin sensitivity compared with male adipocytes, which is particularly true for abdominal adipocytes (102, 147). A recent study analyzed insulin sensitivity and glucose metabolism of adipocytes from abdominal and subcutaneous adipose tissue from normal, castrated, or steroid-implanted mice (102). The authors reported that both abdominal and subcutaneous adipocytes of females have greater lipogenic rates than those from males. Additionally, female abdominal adipocytes are more insulin

sensitive than subcutaneous adipocytes and more insulin-sensitive than male adipocytes from either depot, with female abdominal adipocytes showing a robust increase in insulin-induced lipogenesis and insulin signaling, including downstream targets Akt and extracellular signal-related kinase phosphorylation, when stimulated by low physiological concentrations of insulin. In contrast, male adipocytes show activation only at much higher insulin concentrations (102). Furthermore, adipocytes from females have higher mRNA and protein levels of several genes involved in glucose and lipid metabolism, including glucose transporters and key lipogenic enzymes fatty acid synthase and acetyl CoA carboxylase (102), suggesting that the sex difference in insulin sensitivity at adipocyte level is attributable at least partially to increased glucose transporters and lipogenic enzyme levels. In summary, sex-specific differences in insulin action in adipocytes may contribute to the sexual dimorphism of insulin resistance.

Despite a higher lipogenic rates female adipocytes are smaller than male adipocytes, especially those from the abdominal adipose depot. This is because adipocytes of females also has a higher lipolytic capacity than those of males (148, 149), suggesting a higher metabolic turnover of female abdominal adipocytes leading to decreased fat accumulation in visceral depots in females compared with males. As a result, in humans, females have higher serum levels of free fatty acid than males (124, 139) but appear to be protected against insulin resistance induced by elevated free fatty acid (139).

Sex steroids are known to play a role in the regulation of adipose tissue development and function as well as whole body insulin sensitivity (146). These sex differences in insulin sensitivity in adipose tissue are regulated by physiological levels of sex steroids. Adipocytes of castrated male mice have increased insulin sensitivity and increased lipogenic rates, whereas adipocytes of ovariectomized females have lowered insulin sensitivity and reduced lipogenic capacity (102). The increased sensitivity to insulin and lipogenesis observed in adipocytes from females may account for their lower level of insulin resistance and diabetes risk despite similar or higher fat content than in male mice (102), indicating a positive role of estrogen in insulin sensitivity and lipogenesis in females. Therefore, gonadal hormones estrogen and testosterone contribute to the sexual dimorphism of lipogenesis and insulin sensitivity, lipogenic capacity of adipocytes.

4.3. Estrogens regulate insulin sensitivity

Gonadal hormones play critical roles in the regulation of glucose metabolism and maintenance of insulin sensitivity. Disturbances and changes in the relationship between estrogens and androgen metabolism seem to adversely affect fat metabolism and insulin sensitivity independent of sex (see below). Deficiency of estrogen leads to development of insulin resistance. Animals and humans lacking endogenous estrogen synthesis exhibit insulin resistance, which can be treated by estrogen supplementation (57, 61, 150). In humans, postmenopausal women with deficiency in endogenous estrogen have increased risk of insulin resistance and developing type 2 diabetes (4), while hormone replacement therapy or treatment with estradiol, the major bioactive form of estrogen, improves insulin sensitivity and lowers blood glucose levels (151, 152) and reduce incidence of diabetes (153,

154). Insulin resistance in a man with a homozygous inactivating mutation of the aromatase gene has been reported (60, 155). Estrogen deficiency also contributes to the development of insulin resistance and type 2 diabetes in rodent models (Louet et al 2004). Ovariectomized rodents with low level of endogenous estrogen have elevated basal glucose levels and impaired glucose tolerance (Bailey et al 1980). Aromatase knockout mice with a genetic impairment in endogenous estrogen synthesis exhibit decreased glucose tolerance and insulin resistance (Jones et al 2000; Takeda et al 2003).

The mechanism of regulation of estrogens on insulin sensitivity is not clear. Estrogens may increase hepatic insulin sensitivity by decreasing gluconeogenesis and glycogenolysis and increasing insulin release in islets of Langerhans (156). Estrogens also prevent β -cell apoptosis (157). Additionally, estrogens reduce pro-inflammatory adipokines and their signaling and therefore decrease inflammation (158, 159). Changes in the level of sex steroids had variable effects on levels of circulating adipokines, as ovariectomized females have lower level of adiponectin and females implanted with estradiol have higher adiponectin levels (102). It is increasingly evident that chronic activation of pro-inflammatory pathways may be at least partly responsible for obesity-induced insulin resistance and diabetes (25, 160). ERs are expressed in monocytes and macrophages, and estrogens activate these cells (161, 162). Female rats and mice are relatively protected from high-fat diet induced obesity, insulin resistance and inflammatory responses (141-143, 163-165). Recent studies have shown that 17β -estradiol may play a role in reducing the inflammatory response in adipose, cardiovascular, and neural systems (146). Suppression of pro-inflammatory responses with estrogens may represent a promising strategy to combat obesity and associated metabolic disorders. Furthermore estrogens may improve insulin action (166). Therefore, the greater amount of abdominal visceral adipose tissue in conjunction with lower endogenous estrogen levels found in men may be related to the higher insulin resistance when compared with pre-menopausal women.

4.4. Estrogen receptor regulates insulin sensitivity

Estrogen's action is via its classic nuclear receptors and non-classic membrane receptors (63, 167-172). Both ER α and ER β are expressed in the liver, muscle, and adipose tissue, as well as in several key regions of the hypothalamus of the central nervous system that have been linked to the control of peripheral glucose homeostasis. In particular, recent evidence points to neurons in the arcuate nucleus as critical regulators of glucose homeostasis (173). ER subtype-specific ligands have been used to clarify the specific roles of ER α and ER β , such as the selective ER α ligand propyl pyrazoletriol (PPT) and the selective ER β agonist (2,3-bis(4-hydroxyphenyl)-propionitrile (DPN). PPT has similar effects as estradiol, including increase of uterine weight, and prevention of increased body weight following ovariectomy (174). In addition, estrogen acts through other extranuclear pathways after ligands bind to the ER α or ER β associated to the plasma membrane, as well as to ERs located at the plasma membrane, in the cytosol, or in the mitochondria (167, 171, 175) to regulate energy balance and glucose homeostasis (167). Estrogen may trigger its actions after binding to membrane ERs, such as GPR30 (176, 177), binding to receptors for other ligands, or binding to ion channels (167, 178,

179). The membrane ERs are characterized by a completely different pharmacological profile when compared to nuclear ER α and ER β . They do not bind the antiestrogen ICI182,780 (167). These extranuclear actions of estrogen are the rapid activation of signaling cascades resulting in the activation of transcription factors and therefore in the regulation of gene expression.

Both animal and human studies suggest that ER α may play a critical role to regulate glucose tolerance and insulin sensitivity (see below). Impaired insulin sensitivity, glucose intolerance, and hyperinsulinemia in a man with a mutation of ER α and thus lacking functional ER α has been reported (180). Estrogen-dependent effects on glucose homeostasis through both ER α and ER β , whereas glucose tolerance is normal in ER β -knockout mice (70, 73, 181, 182). Additionally, ER α deficiency increases fasting insulin levels, impairs glucose tolerance, and results in skeletal muscle insulin resistance (182), suggesting that ER α may have a direct anti-diabetic role. Insulin sensitivity is preserved in mice lacking ER β although these animals become obese following a high-fat diet (183). In addition, ER β acts as an inhibitor of peroxisome proliferators-activated receptor gamma activity, a major inhibitory regulator of glucose and lipid metabolism (183). Therefore, previous studies argue in favor of an estrogen-dependent regulation of glucose tolerance and insulin sensitivity by ER α .

Several mechanisms of metabolic function of ERs involved in the regulation of estrogen-mediated insulin sensitivity have been suggested by animal studies.

First, estrogen's action helps to sustain insulin production. In the absence of ER α , 17 β -estradiol only partially protects pancreatic β -cells from apoptosis in diabetic male and female mice (157), suggesting that this effect is at least in part ER α dependent. A recent study from the same group of investigators has demonstrated that estradiol stimulates islet insulin synthesis in an ER α independent manner, through interactions between non-classic extranuclear / membrane ER α and the tyrosine kinase Src, which activates ERK1/2 MAPK (184).

Second, estrogen's action facilitates insulin release. Glucose- and arginine-stimulated insulin release in pancreatic islets is similar in mice lacking either ER α or ER β when compared with control animals (181). 17 β -estradiol does not increase insulin levels in isolated islets from ER α knockout animals compared to controls or to ER β -knockout mice (156).

Third, estrogen's action regulates insulin sensitivity in liver and muscle. The development of ER α and ER β knockout mice (185) has demonstrated the participation of these receptors in the regulation of many processes related to glucose metabolism, including insulin sensitivity in the liver and muscle. Impaired insulin sensitivity and glucose tolerance as determined by the hyperinsulinemic clamp technique in ER α deficient animals is attributed to either inadequate suppression of hepatic glucose production by insulin or impaired insulin action in skeletal muscle (181, 182). Furthermore, insulin-stimulated glucose uptake in skeletal muscle, mediated by the glucose transporter isoform GLUT4, is suppressed in the absence of ER α (181), however GLUT4 expression is not affected in mice lacking ER β (186).

Fourth, estrogen's action mediates inflammation associated with insulin resistance. In both healthy and diabetic mice lacking ER β , 17 β -estradiol reduces inflammatory nitric oxide synthase expression in the aorta. This inhibitory effect is absent in ER α knockout animals

(187), indicating that the protective effects of estrogens on inflammatory responses in the vessel wall are mediated by ER α (187). In addition, adiponectin, an adipokine associated with suppression of insulin resistance and inflammation, is decreased in the absence of ER α whereas plasminogen activator inhibitor-1, a surrogate marker of systemic inflammation is increased (182). Increased inflammation-associated changes following streptozotocin-induced injury of pancreatic islets have been described in ER α -deficient mice (Le May et al. 2006). Moreover, enhanced inflammatory signaling and impaired fatty acid oxidation are found in the skeletal muscle of ER α -knockout mice (182), further indicating an ER α dependent regulation in inflammation which affects insulin resistance. In vitro studies have demonstrated 17 β -estradiol-activated ER α decreases the number of pro-inflammatory cytokines (161). The anti-inflammatory properties of 17 β -estradiol can be partially explained by the ability of ERs to act as transcriptional repressors by inhibiting the activity of nuclear factor kappa B (NF κ B) through protein–protein interactions between agonist-bound ERs and activated NF κ B subunits (188-190). Estrogens' inhibitory effect on NF κ B function is not fully understood and may be target selective (189, 191). The PI3K pathway is also implicated in the anti-inflammatory effects of estrogens. For example, 17 β -estradiol blocks LPS-induced NF κ B nuclear translocation in macrophages, an effect that involves the activation of PI3K (188). Similarly, estradiol-17 β decreases vascular leukocyte accumulation after an ischemia–reperfusion injury, and these effects are blocked by PI3K inhibitors (192).

In summary, previous studies not only support that estrogens and their cellular targets are important for the maintenance of glucose homeostasis, but also indicate an important role of ER α in the regulation of insulin sensitivity.

5. Conclusion

Sex differences and the role of gonadal hormones in modulating insulin sensitivity and glucose tolerance are of increasing interest and importance because of the increasing prevalence of type 2 diabetes mellitus and the metabolic abnormalities. Body composition is closely associated with insulin sensitivity, and increased body fat, particularly in the visceral compartment, is a risk factor for developing type 2 diabetes mellitus. Sex differences in body composition and/or insulin sensitivity are evident in humans and many non-human animal models.

Gonadal hormones estrogens and androgens are important, sex-independent regulators of body weight, body fat distribution, glucose metabolism and insulin resistance. When women enter menopause, they have a dramatically increased risk for developing obesity, type 2 diabetes and the metabolic syndrome. Although conventional hormone replacement therapy might beneficially affect adiposity and to reduce diabetes risk, its previous use in women is associated with adverse effects including an increased risk for breast cancer and heart disease (i.e. thromboembolism). This increased risk may partly due to non-selective activation of ERs, which are ubiquitously expressed in the human body, especially in peripheral tissues, and due to complex intracellular events coupled to ERs genomic and non-genomic actions.

Future basic science investigations should therefore lead to a better understanding of the molecular mechanisms whereby different ERs regulate body weight, body fat, and insulin sensitivity in both females and males. Important gaps in the research need to be identified. In particular, potential interactions and cross-talk between ER α and G-protein-coupled estrogen receptor, which seem to mediate most beneficial effects, critical brain sites where ERs regulate glucose homeostasis, and intracellular signaling pathways that are required for estrogens' actions, need to be identified. Consequently only the ERs involved in energy homeostasis and glucose metabolism will be targeted. This identification would help to define novel pharmacological targets selectively associated with fat metabolism and glucose homeostasis and help to develop estrogen-like drugs that only initiate intracellular events that produce metabolically beneficial actions without deleterious side effects. Such an approach would also imply a therapeutic potential in men bypassing the unwanted effects of estrogens.

Author details

Haifei Shi and Shiva Priya Dharshan Senthil Kumar

Cellular, Molecular and Structural Biology, Miami University, Oxford, Ohio, USA

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