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Sex differences in metabolism and cardiometabolic disorders

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Abstract

Purpose of review—Sex differences are pervasive in metabolic and cardiovascular traits, yet they have often been ignored in human and animal model research. Sex differences can arise from reversible hormonal effects, from irreversible organizational (developmental) processes, and from gene expression differences from the X and Y chromosomes. We briefly review our current understanding of the impact of these factors in metabolic traits and disorders, with an emphasis on the recent literature.

Recent findings—Novel sex differences continue to be identified for metabolic and cardiovascular traits. For example, it is now clear that gut microbiota tend to differ between men and women, with potentially large implications for disease susceptibility. Also, tissue-specific gene regulation differs between men and women, contributing to differential metabolism. These new insights will open up personalized therapeutic avenues for cardiometabolic diseases.

Summary—Sex differences in body fat distribution, glucose homeostasis, insulin signaling, ectopic fat accumulation, and lipid metabolism during normal growth and in response to hormonal or nutritional imbalance are mediated partly through sex hormones and the sex chromosome complement. Most of these differences are mediated in a tissue-specific manner. Important future goals are to better understand the interactions between genetic variation and sex differences, and to bring an understanding of sex differences into clinical practice.

Keywords

genetic interactions; gonadal hormones; mitochondria; mouse models; sex chromosomes

INTRODUCTION

Sex differences in metabolic traits such as obesity, diabetes, and cardiovascular disease have been amply described in mice, humans, and other species, with females generally exhibiting more beneficial metabolic profiles [1–6,7■■,8]. While originally those differences were

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Conflicts of interest

There are no conflicts of interest.

attributed to the effect of sex hormones, recent studies suggest that both hormones and sex chromosome complement play a role [9,10■■]. The effects of sex hormones can be either reversible or irreversible (‘organizational’). Sex differences may be dependent upon the genetic background, environmental factors and the gut microbiome [11,12■]. Gene expression studies show a large proportion of genes differentially expressed in adipose, liver, brain, and other tissues [6,13■], and that sex hormones and also chromosome complement play a major role in modulation of gene expression [6,14–17]. It is important to understand sex differences for practical reasons. First, because sex affects the prevalence of most chronic diseases, in some cases as much as 10-fold, there is much to be learned about disease mechanisms. Second, as discussed below, disease symptoms and treatments will also differ between sexes, and sex differences are probably the most accessible target of the current Precision Medicine effort. An ultimate goal will be to understand sex differences at the level of biologic networks (the ‘sexome’) [18].

BODY COMPOSITION, ADIPOSE DISTRIBUTION AND OBESITY

Adipose tissue is now recognized as more than a mere fat storage organ. Through their secretion of several adipokines and cytokines such as leptin, adiponectin, tumor necrosisfactor (TNF)-α and interleukin (IL)-6, adipose tissue plays a major role in regulating metabolic and energy homeostasis [19]. The major form of adipose tissue in adult mammals is the white adipose tissue, and it occurs either under the skin as subcutaneous adipose tissue (SAT) or in the deep abdominal region as visceral adipose tissue (VAT). Understanding how normal adipose physiology differs between men and women will be key to deciphering how sex differences affect the pathology of disrupted metabolic homeostasis. Under normal physiological conditions, premenopausal women have higher overall fat mass percentage, whereas men have higher lean mass percentage [20]. However, premenopausal women store more fat in their SAT depots surrounding hips and thighs (also known as gynoid fat distribution), whereas men store fat in their VAT depots in the deep abdominal region (also known as android fat distribution) [20]. Increasing evidence shows that higher VAT in men is significantly associated with cardio-metabolic risk, whereas higher SAT in women might be involved in cardiometabolic protection [21–24]. Postmenopausal women lose this protection, as there will be a shift from gynoid fat to android fat accompanied by increased cardiometabolic risk compared to men [25–27]. This signifies that increased VAT confers more cardiometabolic risk in women compared to men.

Sex differences in adipose distribution are attributed partly to adipose depot-specific differences in lipoprotein lipase (LPL) activity, and also adrenergic receptor and estrogen receptor distribution. LPL plays a key role in fat accumulation in adipose. Although LPL is highly active in SAT of women compared to VAT, the converse is true in men [28]. Apart from this, testosterone also suppresses LPL activity in SAT of men [29]. Adipose tissues express both lipolytic β1–2-adrenergic receptor and antilipolytic α2-adrenergic receptor, thereby regulating balance between lipolysis and lipogenesis leading to fat storage. However, in premenopausal women, estradiol increases α2-adrenergic receptor only in SAT, thereby shifting the balance toward gynoid fat accumulation [30–32]. In contrast, men have higher α2-adrenergic receptor in their VAT contributing to android fat [31]. Animal studies revealed that women are resistant to diet-induced obesity, whereas ovariectomy reverses this

protective effect [33,34]. Nevertheless, estrogens can rescue ovariectomized women from obesity in an estrogen receptor α-dependent manner [35–37]. Women have lower estrogen receptor α distribution in SAT, whereas men have lower estrogen receptor α in VAT, thereby partly contributing to their differential fat depot accumulation. Adipose-specific estrogen receptor α deletion increases diet-induced adiposity in both men and women, specifically increasing VAT deposition [38]. Estrogens mediate their antiobese effect by decreasing food intake and increasing energy expenditure in women [39–43].

Apart from these mechanisms, adipose-mediated sex hormone metabolism also contributes in dimorphic adipose distribution. For instance, compared to VAT, SAT has higher levels of aromatase enzyme that converts androgens to estrogens [44,45]. In contrast, VAT has higher levels of 17β-hydroxysteroid dehydrogenase (17βHSD) that converts less active hormones to their more active counterparts, for example, androstenedione to testosterone [44,45]. As a consequence, higher VAT results in higher 17βHSD-mediated local androgen production [44,45]. Furthermore, aromatase deletion in animal models leads to metabolic dysfunction such as increased adiposity, hyperinsulinemia and hepatic steatosis that can be partly rescued by estradiol treatment [46–48].

Genetic tools available in mouse models such as the four core genotypes (FCGs) enable better understanding of the role of sex chromosome complement in regulating obesity independent of sex hormones [49]. FCGs dissociate sex chromosome complement from sex hormones, and include XX men or women and XY men or women [49]. Studies on FCG mouse model revealed that X chromosome complement is positively associated with increased adiposity in a dose-dependent manner [50]. Comparing their observations with the most common human chromosomal anomaly (~1/600 live births), namely Klinefelter syndrome (XXY), revealed that compared to XY men, XXY men had higher incidence of visceral adiposity-associated metabolic abnormalities [51]. Genes that escape X inactivation, genes on Y chromosome and distinct epigenetic imprinting inherited from maternal or paternal parents are hypothesized to contribute to these differential chromosomal effects [9].

GLUCOSE HOMEOSTASIS, INSULIN RESISTANCE AND DIABETES

Glucose homeostasis is primarily regulated by skeletal muscle through basal and insulin-stimulated glucose uptake. Men have more muscle mass compared to women [52,53]; however, premenopausal women show similar insulin sensitivity compared to men. This difference was attributed to enhanced skeletal muscle-mediated glucose uptake in women compared to men [54]. Moreover, women tend to have increased insulin secretion compared to men as measured by postprandial insulin and C-peptide levels [55]. It is proposed that estradiol may partly mediate this mechanism [56■■]. On the contrary, sex differences also affect prediabetic conditions such as impaired fasting glucose and impaired glucose tolerance. Population studies have shown that women have lower fasting glucose, but impaired glucose tolerance compared to men [57–60]. Estrogen therapy in menopausal women decreases fasting glucose, but impairs glucose tolerance [56■■,59]. Sex differences also exist in diabetic prevalence. Population studies have shown that both type 1 and 2 diabetes have a male predominance [61–63]. Global survey on diabetic populations revealed that sex-specific diabetic prevalence reverses depending on the reproductive stages [64].

Specifically, more men have diabetes prepuberty, whereas more women have diabetes postmenopause [64].

Sex-specific adipose distribution is partly attributed to the observed differential glucose homeostasis between men and women. For instance, insulin resistance is associated with increased VAT through pro-inflammatory cytokines. Apart from this, increased VAT lipolysis results in higher free fatty acid flux delivered to liver leading to hepatic insulin resistance such as hyperinsulinemia and increased glucose production [65]. Moreover, insulin resistance and diabetes are improved by surgical removal of VAT in both animals and humans [66,67]. In contrast, selective SAT removal is associated with worse metabolic profiles in both animals and humans, indicating that SAT acts as a metabolic sink and protects against metabolic syndrome [68,69]. This is further exemplified by adipose redistribution from SAT to VAT following liposuction [70]. Studies in premenopausal women show that SAT through its highly active LPL takes up most of the fatty acids from circulation and meals, acting as a metabolic sink preventing ectopic fat accumulation in liver and muscle [71]. As a consequence, SAT adipocytes are larger, yet remain insulin-sensitive [72].

Studies have also shown that deregulated adipose expansion and their inability to store lipids lead to ectopic fat accumulation followed by insulin resistance [65]. Normal adipose tissue expansion happens through either increased cell number by recruitment of new adipocytes (hyperplasia) or increased cell size in pre-existing adipocytes (hyper-trophy). Hyperplastic expansion results in improved metabolic health, whereas hypertrophic expansion leads to systemic metabolic dysfunction [73,74]. Animal studies have shown that SAT expands predominantly via hyperplasia, whereas VAT expands primarily through hypertrophy following high-fat feeding [75,76]. A similar trend was observed in women as well [77]. It was proposed that estrogens play a role in this, but the precise mechanism for this differential fat expansion is unknown. Apart from this, vascular supply influences both hyperplasia and hypertrophy. Human samples have shown that SAT has increased capillary density and angiogenic growth compared to VAT [78]. Reduced vascular supply during fat expansion leads to hypoxia and activation of hypoxia inducible factor (HIF) that enhances adipose inflammation and fibrosis, leading to insulin resistance [79]. In contrast, estrogen through estrogen receptor a promotes HIF ubiquiti-nation and degradation through transcriptional up-regulation of prolyl hydroxylase enzyme, thereby reducing adipose inflammation and fibrosis [80]. Apart from this, adipocyte-specific deletion of estrogen receptor α in mice has demonstrated its protective role against adipose inflammation, fibrosis, and insulin resistance in animal models [38].

Apart from these mechanisms, mouse population studies revealed extensive gene-by-sex regulation in insulin resistance [3]. Furthermore, studies on FCG mice revealed that high fat/high carbohydrate feeding resulted in similar fasting glucose levels in all four genotypes; however, XX mice produced nearly twice as much insulin to maintain normal glucose levels compared to XY mice [50]. This suggests that, similar to adiposity, X chromo-some complement contribute to insulin resistance and can lead to type 2 diabetes. Likewise, human studies have revealed that compared to XY men, XXY men have higher incidences of insulin resistance and type 2 diabetes [81–84].

HEPATIC STEATOSIS

Another major obesity complication is nonalcoholic fatty liver disease (NAFLD). NAFLD is the most common chronic liver disorder, which comprises of a spectrum of hepatic abnormalities ranging from simple steatosis (intrahepatic triglyceride accumulation) to steatohepatitis (NASH), fibrosis, and cirrhosis, in the absence of excessive alcohol consumption [85–87]. Population studies revealed that NAFLD is more prevalent in men than women, with men exhibiting more severe NAFLD symptoms [86,88–92]. Also, NAFLD was found to be more prevalent in postmenopausal compared to premenopausal women, suggesting hormonal regulation [93]. In addition, mouse population studies also revealed that, in response to high fat/high sucrose feeding, male mice generally had higher hepatic steatosis, and that genetic variation played a major role in sex differences [94■]. Additionally, the FCG mice revealed that, similar to obesity and insulin resistance, X chromosome complement increased hepatic triglyceride accumulation in a dose-dependent manner [50]. The observed sex differences in both humans and animals were attributed partly due to genes escaping X inactivation and differences in genetic regulation, differential body fat distribution, and sex hormone metabolism between men and women. Nevertheless, the mechanisms underlying these sex differences in NAFLD prevalence are poorly understood.

Intrahepatic ceramide accumulation was implicated as one of the causal mechanisms for sex-specific differences observed in hepatic steatosis and insulin resistance. Using a mouse reference population, we observed that different ceramide species were prevalent between sexes, thereby differentially regulating hepatic steatosis and/or insulin resistance [95■]. Follow-up gonadectomy studies on three different common inbred mouse strains revealed that these differences were partly due to testosterone-mediated inhibition of ceramide synthase 6 in the liver [95■].

With no available pharmacological treatment, it is imperative that we need to understand the underlying sex-specific mechanisms modulating hepatic steatosis as it will lead to improved personalized therapeutics for NAFLD treatment and prevention.

CARDIOVASCULAR TRAITS

The prevalence of coronary heart disease (CHD) and myocardial infarction increases with age in both sexes, but is delayed by about 10 years in women as compared to men. Moreover, the symptoms, treatment, and outcomes of CHD differ between sexes [96■■,97]. The underlying causes of these differences are unclear. Blood lipoprotein levels are strongly associated with CHD, with LDL-cholesterol and triglyceride levels directly correlated, and disease and HDL-cholesterol levels inversely correlated. Men and women have similar levels of LDL-cholesterol, but women have about 20% higher HDL-cholesterol and about 15% lower triglyceride levels. Lp(a) is an LDL-like lipoprotein that is highly proatherogenic. A relatively small but potentially interesting recent epidemiologic study suggests that Lp(a) concentrations are correlated with angio-graphic scores in men but not women [98]. There are also sex differences in hypertension and thrombosis risk, two other CHD risk factors. The sex differences in hypertension are complex and age-dependent, being more prevalent in

men below 45 years of age, but more prevalent in women above 55 years of age. Women have elevated thrombosis risk as compared to men, which may be related to the fact that strokes comprise a larger fraction of cardiovascular events in women than men [99].

Differences in endogenous gonadal hormones have been hypothesized to play a role in CHD sex differences. In particular, the cardioprotection in women is lost once menopause occurs. Female sex hormones have been intensively investigated in the context of hormone replacement therapy, whereas male sex hormones have received less attention. Glisic *et al.* [100■] recently examined the relationship of gonadal hormones with carotid plaque composition in 2100 older men and women. Men exhibited increased carotid atherosclerosis and increased likelihood of lipid cores and intraplaque hemorrhage. Both estrogen and testosterone levels were associated with carotid plaque composition. Increased estradiol was associated with a lipid core in both sexes, whereas testosterone was associated with reduced lipid cores in women, but was unrelated in men. Increased estradiol levels were also associated with stroke in women.

It has been hypothesized that some of the differences in metabolic and cardiovascular disorders could involve gut microbiota (collectively termed the ‘microbiome’). Studies over the last two decades have convincingly shown that gut microbiota play a significant role in many disorders, including obesity, inflammatory bowel disease, and cardiovascular disease. There are significant sex differences in gastrointestinal permeability and susceptibility to intestinal injury, and recent studies have also shown that the gut microbiome differs between sexes. In addition to intestinal properties, potential mechanisms include sex differences in bile acid metabolism and gut microbe effects on the levels and potency of estrogen metabolites [101■■].

CONCLUSION

In reviewing the current literature, we find that there are many reports of sex differences in cardiovascular and metabolic traits, but relatively few basic studies directed at understanding the underlying mechanisms. For example, as yet very little is known about the epigenetic differences in men and women, and few genome-wide association studies examine the sexes separately. Such basic studies will be critical for the implementation of Precision Medicine. We summarize some important questions for the future in Table 1. Also, quite surprising, given the attention that has been raised about sex differences in recent years, is that many animal model studies include only one sex, most often males.

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KEY POINTS

- Sex differences contribute to majority of cardiometabolic traits and are mediated mostly in a tissue-specific manner.
- Sex differences are mediated through reversible sex hormones, irreversible developmental processes, and sex chromosome complement.
- Gene-by-sex interactions must be understood for a better understanding of sex differences and development of personalized treatment.

Table 1.

Key questions in understanding sex differences in metabolic and cardiovascular traits

1. How do different tissues and cell types differ in hormonal responses between sexes?
2. What genes on the X or Y chromosomes are involved in sex differences?
3. How do tissues differ in epigenetic organization during sexual development?
4. Are sex-specific differences well conserved between humans and animal models?
5. How do men and women differ in drug responses? For example, statin use is associated with diabetes, but more so in women than men.
6. How prevalent are gene-by-sex interactions?