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Sex-Specific Differences in Lipid Metabolism in Obesity: Implications for Cardiometabolic Risk

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ABSTRACT

Sex-specific differences in lipid metabolism play a critical role in the pathophysiology of obesity and its related cardiometabolic risks. Men and women exhibit distinct patterns of fat distribution, lipid handling, and hormonal regulation, contributing to varying susceptibilities to conditions like dyslipidemia, insulin resistance, cardiovascular diseases (CVD), and metabolic syndrome. In women, subcutaneous fat deposition is more prominent, whereas men tend to accumulate visceral fat, which is associated with greater cardiometabolic risk. These differences are influenced by sex hormones, particularly estrogen, which has protective effects on lipid profiles in premenopausal women, but diminishes post-menopause, increasing CVD risk. Furthermore, genetic, epigenetic, and lifestyle factors modulate these sex-specific lipid metabolic processes. Understanding these differences is crucial for developing targeted therapeutic strategies aimed at reducing the burden of obesity-associated cardiometabolic disorders. This review explores the mechanisms underlying sex differences in lipid metabolism, their implications for cardiometabolic risk, and potential interventions to address sex-specific metabolic dysfunction in obesity.

Keywords: Sex differences, lipid metabolism, obesity, cardiometabolic risk, estrogen, visceral fat, metabolic syndrome

INTRODUCTION

Obesity is a major global health issue, closely associated with an increased risk of cardiometabolic diseases such as dyslipidemia, type 2 diabetes (T2D), hypertension, and cardiovascular diseases (CVD). Despite the similarities in overall obesity prevalence between men and women, significant sex-specific differences in lipid metabolism and fat distribution have been reported, which contribute to disparities in cardiometabolic risk profiles[1–3]. Understanding these sex-specific variations is essential to effectively address the growing burden of obesity-related health complications. Fat distribution between men and women varies significantly due to hormonal, genetic, and environmental factors[4]. This difference plays a crucial role in influencing overall health, particularly cardiometabolic risk. Men generally accumulate more visceral fat—found around internal organs—which is metabolically active and strongly associated with an elevated risk of cardiovascular disease (CVD), insulin resistance, and metabolic syndrome[5, 6]. In contrast, women, particularly during their reproductive years, tend to store fat subcutaneously, particularly in the gluteal, femoral, and thigh regions. This subcutaneous fat is considered to be metabolically less harmful compared to visceral fat and is associated with a lower risk of metabolic complications. Visceral fat, the deeper fat surrounding the internal organs, is predominantly found in men. This type of adipose tissue is strongly linked to several adverse metabolic conditions, including insulin resistance, dyslipidemia, chronic inflammation, and increased risk for CVD. It is metabolically active, releasing more free fatty acids and inflammatory markers into the bloodstream, contributing to a higher risk of developing type 2 diabetes and heart disease. On the other hand, subcutaneous fat is stored just beneath the skin and is more common in women, particularly in premenopausal women. It is concentrated in areas such as the hips, thighs, and buttocks, regions less associated with severe metabolic issues. Subcutaneous fat is considered less harmful because it does not contribute as aggressively to insulin resistance and systemic inflammation[7]. However, this protective effect diminishes after menopause, when

hormonal changes, particularly the reduction in estrogen levels, lead to an increase in visceral fat in women. As visceral fat increases in postmenopausal women, their cardiometabolic risk begins to resemble that of men, resulting in a heightened susceptibility to heart disease, hypertension, and metabolic disorders. This shift in fat distribution post-menopause highlights the complex role that sex hormones, particularly estrogen, play in regulating fat storage and distribution, as well as the subsequent impact on cardiometabolic health[4].

Role of Sex Hormones in Lipid Metabolism

Sex hormones, particularly estrogen and testosterone, play a significant role in regulating lipid metabolism. Estrogen is associated with favorable lipid profiles, promoting higher levels of high-density lipoprotein cholesterol (HDL-C) and lower levels of low-density lipoprotein cholesterol (LDL-C) in premenopausal women[8].

Estrogen and Lipid Regulation: Estrogen plays a significant role in regulating lipid metabolism, particularly in women. It enhances the clearance of triglycerides from the bloodstream by promoting the activity of lipoprotein lipase, an enzyme involved in breaking down triglycerides. Additionally, estrogen increases the synthesis of high-density lipoprotein cholesterol (HDL-C), often referred to as "good" cholesterol, which is essential for transporting excess cholesterol to the liver for excretion[9]. This mechanism contributes to the cardioprotective effects seen in premenopausal women, as higher levels of HDL-C are associated with a lower risk of atherosclerosis and cardiovascular disease (CVD). However, following menopause, estrogen levels significantly decline, which reduces these protective effects. As a result, postmenopausal women experience a rise in triglyceride levels, a decrease in HDL-C, and an overall increased risk of developing dyslipidemia and CVD[10].

In contrast, men, who naturally have higher levels of testosterone, tend to have lower HDL-C levels compared to women. Testosterone has been shown to suppress the production of HDL-C, which reduces the cardioprotective effect seen with higher HDL-C levels. Additionally, men are more prone to visceral fat accumulation due to the influence of testosterone. Visceral fat, which surrounds the internal organs, is metabolically active and contributes to insulin resistance, inflammation, and dyslipidemia, all of which elevate the risk of developing cardiometabolic diseases, including CVD and type 2 diabetes.[11, 12] This difference in fat distribution and lipid profile partly explains why men generally have a higher predisposition to cardiovascular conditions compared to premenopausal women. However, as estrogen levels decline in women after menopause, their cardiometabolic risk converges with that of men.

Molecular Mechanisms of Sex-Specific Lipid Metabolism

The molecular regulation of lipid metabolism differs between sexes due to variations in gene expression, hormone receptor activity, and metabolic enzymes. Key molecular players, including peroxisome proliferator-activated receptors (PPARs), lipoprotein lipase (LPL), and hormone-sensitive lipase (HSL), exhibit sex-specific activity patterns that influence fat storage and lipid oxidation[13–16].

PPARs and Fatty Acid Metabolism: PPARs are nuclear receptors involved in lipid metabolism, with PPAR-α promoting fatty acid oxidation and PPAR-γ involved in adipogenesis. The expression of these receptors is modulated by sex hormones, with estrogen enhancing PPAR-γ activity in women, promoting healthier lipid storage in subcutaneous fat, while testosterone's effect in men favors visceral fat deposition and reduced fatty acid oxidation.

Lipoprotein Lipase (LPL) Activity:LPL is responsible for hydrolyzing triglycerides in lipoproteins to release free fatty acids for storage or energy use. In women, LPL activity is higher in subcutaneous fat, favoring fat storage in these depots. In contrast, men exhibit greater LPL activity in visceral fat, contributing to an unfavorable metabolic profile with higher cardiometabolic risk.

Genetic and Epigenetic Influences on Sex-Specific Lipid Metabolism

Genetic predisposition to obesity and cardiometabolic disorders exhibits sex-specific patterns, with several loci influencing fat distribution and lipid metabolism differently in men and women. Moreover, epigenetic modifications, such as DNA methylation and histone modifications, can modulate gene expression in a sex-dependent manner, further contributing to differences in lipid metabolism [17–19].

Epigenetics and Hormonal Regulation

Epigenetic regulation of hormone receptor genes, such as those for estrogen (ER) and androgen (AR), plays a pivotal role in determining how these hormones influence lipid metabolism differently in males and females. Estrogen and androgen receptors are critical regulators of lipid homeostasis, with estrogen generally promoting lipid oxidation and lowering cholesterol levels, while androgens are associated with anabolic processes that can increase lipid synthesis. Epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNA interactions, can alter the expression of ER and AR genes, leading to variations in lipid metabolism across sexes[20]. In women, estrogen plays a protective role by enhancing lipid metabolism and reducing the risk of dyslipidemia, which is often disrupted during menopause when estrogen

levels decline. Epigenetic silencing of estrogen receptor genes may exacerbate lipid disorders in postmenopausal women, increasing their risk of cardiovascular diseases. In men, androgen signaling has been linked to more aggressive lipid metabolism, with alterations in AR gene expression contributing to lipid accumulation and a higher prevalence of dyslipidemia. Epigenetic changes that downregulate AR expression may mitigate this effect, but also lead to other metabolic complications[21].

Environmental factors such as diet, physical activity, and stress are potent drivers of epigenetic changes in these hormone receptor genes. High-fat diets can increase DNA methylation of hormone receptor genes, reducing their expression and altering lipid metabolism. Sedentary behavior may also promote histone modifications that impair the function of ER and AR, while chronic stress can trigger the release of stress hormones like cortisol, which interacts with epigenetic mechanisms to modify receptor gene expression. These changes exacerbate sex-specific cardiometabolic risks in obese individuals, with women more prone to increased fat accumulation and men to higher lipid production, thus elevating the risk of cardiovascular diseases in both sexes. Ultimately, epigenetic regulation of hormone receptors serves as a crucial link between environmental factors and sex-specific vulnerabilities to lipid metabolism disorders, contributing to the differential cardiometabolic risks seen in obese individuals.

Implications for Cardiometabolic Risk

The sex-specific differences in lipid metabolism contribute to distinct patterns of cardiometabolic risk in men and women. Men are more likely to develop metabolic syndrome, characterized by abdominal obesity, dyslipidemia, and insulin resistance, due to their propensity for visceral fat accumulation. In contrast, premenopausal women are somewhat protected from these risks, but their susceptibility increases significantly after menopause[22, 23].

Dyslipidemia and Cardiovascular Disease

Dyslipidemia, characterized by elevated triglycerides, LDL-C, and reduced HDL-C levels, is a major risk factor for CVD. While men generally have worse lipid profiles from a younger age, postmenopausal women experience a sharp increase in dyslipidemia and associated cardiovascular risks, necessitating gender-specific interventions[24].

Therapeutic Interventions and Future Directions

Addressing sex-specific lipid metabolism differences requires targeted therapeutic approaches. Hormone replacement therapy (HRT) in postmenopausal women has been explored to mitigate the loss of estrogen's protective effects on lipid profiles. Additionally, lifestyle interventions, including diet and physical activity, need to be tailored to optimize lipid metabolism differently in men and women. Pharmacological treatments, such as lipid-lowering agents (e.g., statins, fibrates), may need to consider sex-specific efficacy and side-effect profiles. Personalized medicine approaches, including the use of pharmacogenomics, could enhance the effectiveness of these treatments based on individual genetic and sex differences in lipid metabolism.

CONCLUSION

Sex-specific differences in lipid metabolism profoundly impact the risk of obesity-related cardiometabolic disorders. Understanding these variations is critical for developing effective, personalized interventions aimed at reducing the burden of cardiometabolic diseases in both men and women. Future research should focus on the mechanisms driving these differences and explore novel therapeutic strategies that address the unique needs of each sex.

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