Review Article

Sex differences in metabolic dysfunction-associated steatotic liver disease: a narrative review

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Abstract

Understanding the effects of sex and sex differences on liver health and disease is crucial for individualized healthcare and informed decision-making for patients with liver disease. The impact of sex on liver disease varies according to its etiology. Women have a lower prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) than men. However, postmenopausal women face a higher risk of advanced liver fibrosis due to hormonal influences. Sex differences affect the pathogenesis of MASLD, which involves a complex process involving several factors such as hormones, obesity, and the gut microbiome. Furthermore, sex-related differences in the development of MASLD-related hepatocellular carcinoma have been observed. The sex-specific characteristics of MASLD necessitate an individualized management approach based on scientific evidence. However, research in this area has been lacking. This article reviews the current understanding of sex differences in MASLD.

Keywords: Gastrointestinal microbiome; Hepatocellular carcinoma; Liver cirrhosis; Postmenopause; Sex characteristics

Introduction

Background

There has been growing interest in sex differences in medical conditions both in Korea and around the world [1,2]. Additionally, Korea has established its first institute focusing on sex differences in medicine, mirroring a global trend towards increased awareness of these differences.

Sex-specific medicine strives to deliver optimal personalized care for both men and women, grounded in scientific evidence. Physiological differences between the sexes, including hormone levels and fat distribution, along with variations in social and cultural factors such as dietary habits and physical activity, can affect the onset and progression of liver disease. Consequently, it is crucial for systematic research to concentrate on exploring the sex-specific differences in disease development.

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a significant health concern, affecting roughly one-third of the global population. Its prevalence differs by sex and reproductive status [3-5]. The nature of MASLD as a sex-differentiated disease necessitates an individualized management approach based on scientific evidence. However, research on this topic has been limited.

Objectives

This article aimed to review sex differences in the epidemiology and pathophysiology of MASLD.

Methods

Ethics statement

Neither approval by the institutional review board nor obtainment of informed consent was required, since this was a literature-based study.

Identifying the literature

A comprehensive literature search was conducted in March 2024 using the PubMed databases to identify relevant studies. The search keywords included "sex differences," "sex characteristics," "estrogen," "postmenopause," "gastrointestinal microbiome," "gut-liver axis," "hepatocellular carcinoma," "liver cirrhosis," "nonalcoholic fatty liver disease," "metabolic dysfunction-associated steatotic disease," "nonalcoholic steatohepatitis," and "metabolic dysfunction-associated steatohepatitis." These keywords were used individually or in combination. The initial search yielded published reports from 2012 to August 2023. From this extensive list of search results, studies that met the following criteria were included in this review: published after 2015, review articles, and articles on MASLD or MASLD-related epidemiology and pathophysiology. Initially, the type of study was reviewed, followed by a screening of abstracts to identify suitable studies. Ultimately, ten studies were included in this review and subjected to a comprehensive evaluation in terms of the epidemiology and pathophysiology of MASLD (Supplement 1).

Epidemiology

MASLD is caused by the excessive accumulation of fat in the liver. Differences in the distribution of adipose tissue and various associated mechanisms between sexes are linked to variations in MASLD, which subsequently influence its epidemiology, risk factors,

complications, and treatment [6]. The prevalence of MASLD varies among studies [4]. Studies have shown that MASLD is more prevalent in men than in women during the premenopausal stage; however, its prevalence is higher in postmenopausal women [7-11]. A recent meta-analysis revealed a lower prevalence of MASLD among women; however, no significant sex differences were observed in metabolic dysfunction-associated steatohepatitis (MASH) [12]. Advanced liver fibrosis is more prevalent in women, particularly those in the postmenopausal stage [6,13,14]. The lower incidence of MASLD in postmenopausal women has been associated with the use of hormone replacement therapy [15]. Furthermore, a multinational study of histologically confirmed MASLD and advanced liver fibrosis reported poorer survival and a higher incidence of hepatocellular carcinoma (HCC) among older individuals and men, suggesting that estrogen may have a protective effect against MASLD progression.

Pathophysiology, adiposity, and estrogen

Obesity manifests differently in men and women. Men generally accumulate more visceral fat within the abdominal cavity, leading to upper body or apple-shaped obesity. Visceral fat is known for its high lipolysis rate and an inflammatory adipokine profile. Anatomically, this type of fat drains directly into the hepatic portal vein, which results in the liver being exposed to elevated levels of lipids and inflammatory adipokines. In contrast, premenopausal women tend to accumulate more subcutaneous fat around the lower body and hips, resulting in lower body or pear-shaped obesity [6]. This subcutaneous fat is characterized by a lower rate of lipolysis, a higher capacity for fat storage, and increased potential for fat browning, and it is associated with the release of adiponectin, which protects against metabolic syndrome and MASLD [16]. However, the redistribution of fat following

menopause heightens the risk of MASLD [7,17]. Moreover, metabolic syndrome is more common among both men and women in the postmenopausal stage than in premenopausal women [18].

Estrogen influences the interactions between the liver and adipose tissue; consequently, women generally have a higher percentage of body fat than men. However, women tend to accumulate a lower ratio of visceral fat to subcutaneous fat. Research indicates that the expandability and browning capacity of adipose tissue are more pronounced in women than in men, which helps to reduce the metabolic load on the liver. Women exhibit higher blood levels of adiponectin and leptin, along with increased expression and activation of downstream adiponectin signaling elements such as AMP-activated protein kinase, peroxisome proliferator-activated receptor-α, and peroxisome proliferator-activated receptor-γ coactivator-1α. Additionally, women are shielded from intrahepatic fat accumulation due to enhanced mitochondrial biosynthesis and heightened fatty acid oxidation. Moreover, women have higher expression of antioxidant enzymes compared to men, leading to reduced oxidative stress and preventing the continuous activation of c-Jun N-terminal kinase in response to various stimuli, including fatty acids and pro-inflammatory cytokines. In contrast, men are more prone to sustained activation of c-Jun N-terminal kinase, which can lead to insulin resistance and liver damage through apoptotic necrosis. Although the expression of fibroblast growth factor 21 (FGF 21) is stimulated by peroxisome proliferator-activated receptor-γ, no differences in blood levels have been noted between sexes in humans. FGF 21 primarily affects adipose tissue, promoting glucose uptake, fat browning, and adiponectin expression. Levels of intrahepatic cytokines, such as retinol-binding protein 4 and certain angiopoietin-like isoforms, are elevated in men [16].

Additionally, estrogen plays a role in the development of MASLD in premenopausal women by suppressing the expression of adipogenesis-related genes in hepatocytes, inhibiting the release of inflammatory cytokines from Kupffer cells, and reducing the expression of fibrosis-related genes in hepatic stellate cells [19]. Summarizing these findings, the epidemiology and pathophysiology of MASLD are influenced by age and hormonal changes during the premenopausal and postmenopausal stages [20]. For example, early menarche may heighten the risk of MASLD in adulthood, a risk partially mediated by excessive obesity. Ovarian aging, due to estrogen deficiency, eventually leads to the progression of hepatic steatosis and liver fibrosis through metabolic dysregulation. This metabolic dysregulation also leads to type 2 diabetes, hypertriglyceridemia, and visceral obesity, which are commonly observed post-menopause. Thus, sex-based differences in adiposity and other metabolic risk factors contribute to variations in disease progression based on sex.

Microbiome and bile acids

It is well established that alterations in gut microbiota and bile acids contribute to the development of MASLD, MASH, and HCC [21,22]. In a healthy gut, the microbiome provides nutrients and energy, protects against cancer, inhibits pathogens, and supports normal gastrointestinal immune functions and bowel movements [23]. However, when the gut microbiota is disrupted, bacterial metabolites and commensal components compromise intestinal epithelial integrity and facilitate access to the liver via the portal vein [24]. These byproducts of the microbiome contribute to inflammation, intrahepatic steatosis, liver injury, and, ultimately, MASLD and MASH [25].

The gut microbiota regulates the gut-liver axis via farnesoid X receptor signaling. This

signaling pathway releases fibroblast growth factor 15 and fibroblast growth factor 19, which modulate bile acid synthesis, lipid metabolism, and glucose metabolism. Bile acids, products of cholesterol metabolism, are secreted into the intestine through the biliary tree and regulate energy homeostasis through hepatic and extrahepatic metabolism [26].

Scientific evidence indicates that various factors, including age, hormones, ethnicity, diet, antibiotics, stress, and physical activity, influence the diversity and composition of the gut microbiota [27]. The gut microbiome evolves in response to age-related changes in sex hormones. Clinical studies have shown body mass index-specific sex differences and dimorphism in the gut microbiota associated with the menopausal stage, highlighting a strong connection between the gut microbiota and sex hormones [28-30]. However, further research is needed to explore the effects of the gut microbiome and bile acids on MASLD related to sex differences.

MASLD with HCC

HCC is more prevalent in men than in women, regardless of its etiology [31]. A large study of patients with MASH and cirrhosis revealed that the incidence of HCC in men was two to seven times higher than in women [32,33]. Women have a higher survival rate associated with HCC until the age of 55 years; after this age, the trend reverses [34]. Chronic injury and inflammation are well-known precursors to HCC. Additionally, the incidence of HCC in patients with MASH increases alongside the incidence of liver fibrosis. A cross-sectional study involving 87 patients with MASH indicated that men are more likely to develop HCC at earlier stages of liver fibrosis compared to women [35]. Therefore, this study suggests that there are sex differences in the development of MASH-related HCC.

Suggestions for future research

Sex and sex hormones play crucial roles in biological differences in MASLD. Despite evident sex differences in the mechanisms of MASLD, the development of tailored treatments is hindered by a lack of sufficient evidence. Therefore, it is vital to consider potential sex or hormonal influences in population-level analyses. Additional research, encompassing preclinical studies, epidemiological surveys, and clinical trials, is necessary to investigate how sex differences and reproductive status influence disease risk in women with MASLD.

Conclusion

The prevalence of MASLD is rapidly increasing worldwide. Furthermore, MASLD can progress to MASH and cirrhosis, with a rising incidence of MASLD-associated HCC. MASLD has clinical significance due to its association with cardiovascular disease and the development of malignant neoplasms. The complex and multifactorial mechanisms underlying MASLD involve factors such as female hormones, adipose tissue distribution, gut microbiota, and bile acids. However, the development of tailored treatments is contingent upon the availability of sufficient evidence. Consequently, studies that take into account variables such as sex, age, and hormonal status could pave the way for evidence-based and personalized clinical treatments that alleviate the burden of MASLD.

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Data availability

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Supplementary material

Supplement 1. List of studies finally included in this review for a comprehensive evaluation in terms of the epidemiology and pathophysiology of metabolic dysfunction-associated

steatotic liver disease (MASLD).

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