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Review

Reframing MASLD Through a Sex-Specific Lens

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Abstract

Background: The transition from non-alcoholic fatty liver disease (NAFLD) to metabolic dysfunction–associated steatotic liver disease (MASLD) marks a major update in the classification of hepatic steatosis. This redefinition emphasizes metabolic dysfunction as the core diagnostic criterion, improving disease characterization and risk assessment. MASLD demonstrates marked variability across sex and age groups, influencing disease onset, progression, and outcomes. Understanding these biological and hormonal differences is essential for optimizing clinical management.

Materials and Methods: A comprehensive literature review was performed using PubMed, ScienceDirect, SpringerLink, and Web of Science to identify studies published between January 2020 and October 2025. Search terms included "MASLD," "MAFLD," "sex differences," "estrogen," "androgen," and "metabolic dysfunction." Clinical, epidemiological, and mechanistic studies were reviewed to summarize evidence related to sex- and age-specific differences in MASLD pathogenesis and outcomes.

Discussion: MASLD occurs more frequently in men during reproductive years but becomes increasingly common in women after menopause due to estrogen decline, visceral fat redistribution, and increased insulin resistance. Estrogen exerts protective hepatic effects by regulating lipid metabolism and inflammatory pathways, whereas androgen deficiency in men contributes to steatohepatitis and fibrosis. Genetic polymorphisms, including PNPLA3, TM6SF2, and MBOAT7, further influence susceptibility and disease severity. With advancing age, both sexes experience accelerated fibrosis and a higher risk of hepatocellular carcinoma (HCC); however, men show greater rates of advanced liver disease, liver transplantation, and mortality.

Conclusion: Metabolic dysfunction–associated steatotic liver disease (MASLD) shows distinct sex-based differences driven by hormonal, metabolic, and genetic factors. Recognizing these variations is essential for personalized diagnosis, prevention, and treatment.

Keywords: MASLD; sexual dimorphism; biological; genetic and lean population

Introduction

The transition from non-alcoholic fatty liver disease (NAFLD) to metabolic dysfunction–associated steatotic liver disease (MASLD) marks a pivotal advancement in the nomenclature of steatotic liver disorders. This updated terminology highlights metabolic dysfunction as the defining criterion, ensuring greater diagnostic precision and improved risk stratification. MASLD expands the clinical spectrum to include individuals with varying metabolic phenotypes, such as lean patients with hepatic steatosis, thereby reflecting the multifactorial nature of this condition. The global acceptance of the MASLD framework fosters consistency in clinical practice and research, facilitating multicentre collaborations and promoting the development of targeted diagnostic and therapeutic strategies.[1]

The conceptual shift toward metabolic dysfunction–based classification originated in 2020 when experts across the Asia-Pacific region proposed the term metabolic dysfunction–associated fatty liver disease (MAFLD) as a replacement for NAFLD. Subsequently, in 2023, an international expert consensus led by major liver societies from Europe and the Americas introduced

the refined terminology metabolic dysfunction–associated steatotic liver disease (MASLD). These rapid nomenclature transitions have attracted global attention, given their implications for clinical management and research in both adult and paediatric populations. Although MAFLD and MASLD differ in some definitional aspects, they share core features that link hepatic steatosis with cardiometabolic risk factors and associated increases in all-cause and liver-related mortality. The MASLD framework integrates several innovative concepts from MAFLD, and while conceptual harmonization continues, global efforts must now focus on advancing understanding of disease pathogenesis, outcomes, prevention, and treatment.[2]

MASLD represents the most prevalent chronic liver disease worldwide and exhibits distinct sex-based biological differences in its onset, progression, and outcomes. The influence of sex chromosomes and sex hormones contributes significantly to this sexual dimorphism: estrogens confer protective effects against MASLD, whereas androgens tend to promote its development. Consequently, sex-specific therapeutic strategies, including estrogen replacement, androgen blockade, and hormone-modulating therapies, have gained attention as personalized approaches. However, the interplay between hormonal regulation and genetic predisposition adds complexity to disease susceptibility, emphasizing the need for more tailored interventions.[3]

Biological sex profoundly influences MASLD progression and outcomes. Males are more likely to develop downstream complications such as hepatocellular carcinoma (HCC), whereas females more commonly progress to metabolic dysfunction–associated steatohepatitis (MASH) and cirrhosis. Beyond biological factors, gender-related sociocultural influences—including dietary habits, physical activity, and alcohol use—further modify disease trajectories. The increasing recognition of gender diversity and fluidity introduces additional dimensions to MASLD pathophysiology and management, underscoring the need for inclusive and personalized care frameworks.[4]

Understanding the sex disparities in MASLD pathogenesis and outcomes is essential for developing effective, personalized management strategies. Addressing these sex-specific pathways through dedicated clinical research and tailored interventions will be central to optimizing MASLD management and improving long-term outcomes.[3]

Material and Methods

This narrative review was conducted to synthesize current evidence on metabolic dysfunction–associated steatotic liver disease (MASLD) with emphasis on sex-based biological, hormonal, and genetic factors. Relevant literature published between January 2020 and October 2025 was identified through PubMed, ScienceDirect, SpringerLink, and Web of Science using the keywords: “MASLD”, “MAFLD”, “sex differences”, “sexual dimorphism”, “estrogen”, “androgen”, and “menopause”. Articles were included if they discussed biological or hormonal influences on MASLD.

Discussion

Sex-Based and Age-Related Differences in MASLD Prevalence

Metabolic dysfunction–associated steatotic liver disease (MASLD) demonstrates pronounced sexual dimorphism, with a consistently higher prevalence in men than in women. Women of reproductive age generally exhibit a lower risk of MASLD than age-matched men; however, this protection diminishes after menopause, when prevalence becomes comparable or even higher among women. This variation reflects a complex interplay of sex hormones, adipose tissue distribution, and metabolic regulation.[3]

Epidemiological data shows variability in MASLD prevalence across populations and methodologies. A recent meta-analysis confirmed a lower overall prevalence in women, though no significant sex difference was observed in metabolic dysfunction–associated steatohepatitis (MASH). Advanced liver fibrosis is more frequent in women, particularly post-menopause, whereas hormone replacement therapy has been linked to reduced MASLD incidence. In a multinational cohort with histologically confirmed MASLD and advanced fibrosis, older age and male sex correlated with poorer survival and higher hepatocellular carcinoma (HCC) incidence, underscoring estrogen’s protective role in disease progression.[5] Consistent epidemiological findings indicate that premenopausal women have lower MASLD rates than men, but this difference narrows or reverses following menopause.[6]

MASLD is one of the most common causes of chronic liver disease in India, with a reported prevalence ranging from 9% to 32% in the general population and a higher occurrence among obese and diabetic individuals. A large multicentric study involving 924 non-alcoholic type 2 diabetes mellitus (T2DM) patients (355 females and 569 males), aged 25–84 years, enrolled from 189 centres across 101 cities, reported that 522 (56.5%) participants had MASLD based on elevated

aminotransferase levels as per NHANES III criteria. Notably, the disease was more prevalent among females (60%) than males (54.3%), with regional variation ranging from 44.1% in western India to 72.4% in northern India.[8]

A systematic review by Shalimar et al. analysed 16 datasets (n = 10,282) providing gender-specific estimates. The pooled prevalence of MASLD was 39.4% among males and 35.4% among females, showing no significant difference between sexes. The overall pooled prevalence of MASLD in India was 38.6% among adults and 35.4% among children. Despite these findings, the available data remains limited. Most studies lack comprehensive demographic and clinical details, such as stratification by age, BMI category (lean versus obese), comorbidities (diabetes, hypertension, metabolic syndrome, or polycystic ovary disease), and regional or lifestyle variations.[9]

Aging and Metabolic Dysfunction in MASLD Pathogenesis

Age is a key determinant of hepatic health and MASLD progression. With increasing global life expectancy, steatotic liver disease poses a growing public health concern. Approximately one-ninth of the global population is aged ≥60 years, a proportion projected to rise to one-fifth by 2050, reflecting the expanding clinical burden of age-related hepatic dysfunction.[7]

MASLD diagnosis requires evidence of hepatic steatosis accompanied by at least one cardiometabolic risk factor. While early hepatic steatosis may be reversible, persistent metabolic stress contributes to lipid accumulation, mitochondrial dysfunction, oxidative stress, and inflammation, collectively driving progression to MASH.[7]

At the cellular level, aging promotes senescence-associated lipid accumulation and fibrosis. The classical "two-hit" hypothesis proposed that metabolic dysregulation triggers hepatic fat accumulation ("first hit"), followed by oxidative stress and inflammation ("second hit") that accelerate fibrosis and hepatocarcinogenesis. The updated "multiple-hit" model integrates the influence of gut microbiota, insulin resistance, and adipokine signalling through the gut–liver axis as synergistic contributors to disease progression.[7]

The prevalence of MASLD increases progressively with age, beginning from childhood and extending through adulthood. Findings from the Study of Child and Adolescent Liver Epidemiology (SCALE), which assessed liver histology in children aged 2–19 years who underwent autopsy in San Diego County (1993–2003), revealed an overall prevalence of 9.6%, with a distinct age-related rise: 0.7% in children aged 2–4 years, 3.3% in those aged 5–9 years, 11.3% in children aged 10–14 years, and 17.3% among adolescents aged 15–19 years. Complementing these data, a systematic review and meta-analysis of global studies estimated a MASLD prevalence of 7.6% in the general pediatric population.[10]

Although MASLD is most commonly diagnosed during the peripubertal period, increasing evidence indicates that hepatic steatosis can develop even in early childhood. The Viva La Familia study, using elevated ALT as a surrogate marker, identified suspected MASLD in 15% of children aged 4–5 years, 21% in those aged 6–11 years, and 30% among adolescents aged 12–19 years. Similarly, a Canadian review of CT scans and an Israeli study of children with obesity demonstrated the early onset of MASLD, with cases increasingly detected in children under 6 years of age presenting with elevated ALT and increased adiposity.[10]

In the general pediatric population, MASLD affects approximately 11% of males and 7% of females, with this gap widening during adolescence. This sex difference is largely due to variations in fat distribution — males tend to accumulate more visceral fat, a major contributor to hepatic steatosis, while females generally have higher levels of subcutaneous fat, which poses a lower risk. Hormonal changes during puberty further amplify these disparities. MRI-based proton density fat fraction analyses in children with obesity show MASLD prevalence rates of 29% in males compared with 22% in females.[10]

Sex hormones, particularly estrogens, exert protective effects against MASLD by enhancing fatty acid oxidation, reducing hepatic lipogenesis, and limiting inflammation. Consequently, premenopausal women exhibit lower MASLD prevalence, whereas its incidence rises sharply after menopause, peaking around 70 years of age. In contrast, younger and middle-aged men display higher rates of MASLD due to increased visceral adiposity and altered fatty acid metabolism.[11] The loss of estrogen's protective role post-menopause contributes to higher MASLD prevalence in older women. Studies consistently show that MASLD is more common in men during reproductive years but becomes more prevalent in women after menopause. Estradiol regulates fatty acid synthase expression in hepatic and adipose tissues, while saturated fatty acids induce endoplasmic reticulum stress and mitochondrial free radical generation, leading to hepatocellular injury and steatosis.[12]

Sex- and age-specific variations in MASLD prevalence have also been documented across populations. A 12-year Japanese study reported a fatty liver prevalence of 26% in men, about twice that observed in women (13%). Although men

showed relatively stable prevalence across age groups, women exhibited a progressive increase with age, surpassing men in the 70–79-year category. Similarly, a South China study reported higher MASLD prevalence in men than women below 50 years (22.4% vs. 7.1%), but this trend reversed beyond 50 years (20.6% vs. 27.6%).[20] Overall, MASLD incidence rises with advancing age in both sexes, reaching its peak between 70 and 79 years.[12] Liu et al. further observed that MASLD was most prevalent in individuals aged 50–59 years, with the highest rates in men aged 40–49 years and in women aged 50–59 years, likely reflecting hormonal changes associated with menopause. Younger men, conversely, tend to exhibit earlier disease onset, potentially due to the coexistence of metabolic and cardiovascular comorbidities.[12]

At the global level, the burden of MASLD continues to rise in parallel with aging and metabolic disorders. In a large-scale meta-analysis encompassing 8,515,431 samples from 22 countries, Younossi et al. reported a global MASLD prevalence of 25.24%, with the highest rates in the Middle East and South America and the lowest in Africa. The disease prevalence strongly correlated with obesity, diabetes, and dyslipidaemia. In the United States, the median age of MASLD patients increased from 50 years in 2015 to a projected 55 years by 2030, underscoring the impact of an aging population on disease burden.[7]

Menopause and Ethnic Variations in MASLD Outcomes

Ethnicity, genetic susceptibility, and cardiometabolic factors substantially influence MASLD prevalence and fibrosis progression. Multiple studies report higher MASLD incidence in men and postmenopausal women than in premenopausal women. Estrogen confers metabolic protection by reducing hepatic fat deposition and cardiometabolic risk, whereas menopause—marked by estrogen decline—induces insulin resistance, dyslipidaemia, weight gain, and hepatic fibrosis.[13] Consequently, MASLD prevalence rises sharply in women after menopause, often matching or exceeding that in men around age 50, particularly among those with obesity.[14]

Ethnic disparities are well established. Nguyen et al. found that Black patients with MASLD had the highest all-cause and non-liver-related mortality, followed by Hispanic patients, while Asian patients had the lowest risk compared with White counterparts. Despite lower overall prevalence, Black individuals exhibit worse outcomes, reflecting higher rates of obesity, diabetes, dyslipidaemia, and limited healthcare access. Conversely, Hispanic populations show the highest MASLD prevalence, largely attributed to obesity, diabetes, and diets rich in carbohydrates and fats. Culturally tailored dietary interventions may therefore mitigate MASLD burden in these groups.[15]

Sex Hormone Influence on Hepatic Metabolism and MASLD Risk Across Genders

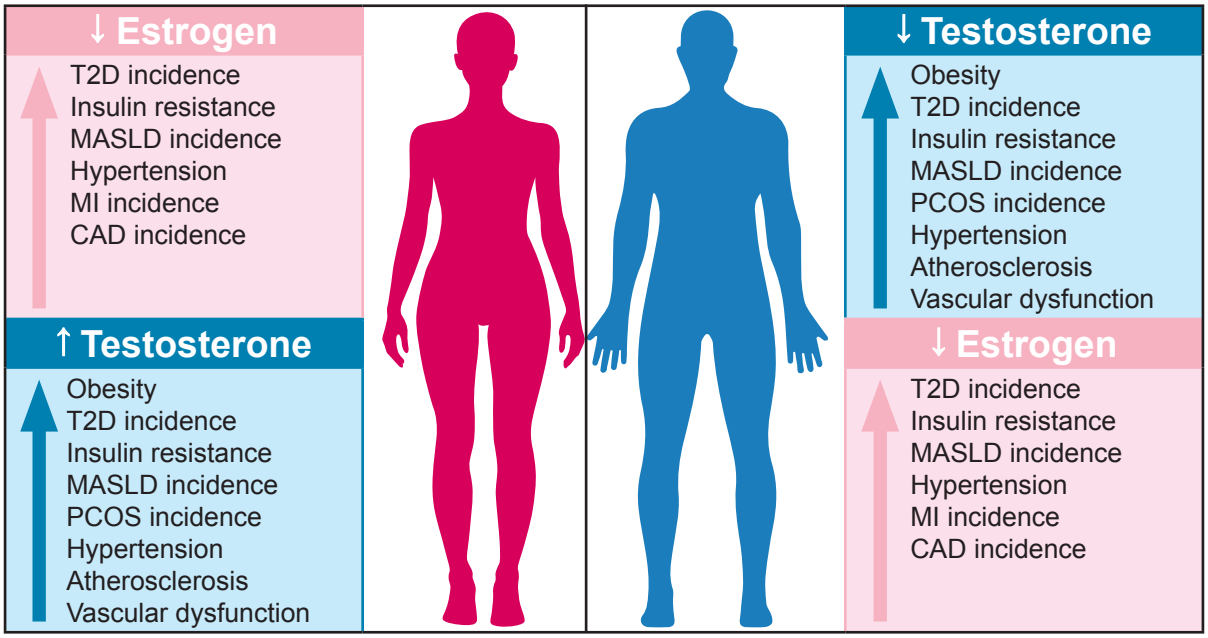

Fig. 1. Impact of sex hormones on the development of MASLD and CVD.[16]

Premenopausal women exhibit a metabolically favorable profile compared to both men and postmenopausal women, emphasizing the hepatoprotective role of estrogen. Estrogen mitigates lipolysis, limits the influx of free fatty acids to the liver, suppresses de novo lipogenesis, and enhances fatty acid oxidation—mechanisms that collectively prevent hepatic lipid accumulation. Furthermore, it reduces the risk of metabolic syndrome and cardiovascular disease. Estrogen deficiency, irrespective of age or adiposity, is associated with increased risk of MASH and hepatic fibrosis. Several studies report comparable MASLD and MASH prevalence between men and postmenopausal women, though fibrosis severity tends to be greater in the latter.[17]

The hepatic actions of estrogen are primarily mediated through estrogen receptor alpha (ERα), which orchestrates metabolic homeostasis and sex-specific transcriptional regulation. Experimental studies indicate that estrogen deficiency, such as following ovariectomy, induces hepatic transcriptomic remodeling, characterized by upregulation of lipid storage genes and downregulation of amino acid metabolism genes. These effects are further intensified in liver-specific ERα knockout models. ERα also influences PPARα-regulated genes involved in fatty acid oxidation. Loss of ERα results in partial masculinization of hepatic gene expression through STAT5B-dependent pathways. Clinical observations in obese postmenopausal women with MASLD demonstrate similar molecular patterns, reinforcing ERα's pivotal role in maintaining hepatic metabolic balance in females.[18]

Androgens exert sex-specific effects on hepatic metabolism. Both androgen excess in women and androgen deficiency in men predispose individuals to central obesity, insulin resistance, and MASLD. Physiological androgen concentrations are essential for metabolic equilibrium. However, certain metabolites, including dehydroepiandrosterone (DHEA) and its sulfate form (DHEAS), have been associated with insulin resistance and histologic alterations characteristic of MASLD. In women, androgen excess, commonly observed in polycystic ovary syndrome (PCOS), correlates with MASLD prevalence ranging from 15% to 55%. Notably, approximately 77% of women with MASLD present with PCOS, underscoring the mechanistic link between hyperandrogenism and hepatic steatosis.[17]

In men, physiological androgen levels exert a protective effect against hepatic lipid accumulation, while androgen deficiency contributes to steatosis. Testosterone and dihydrotestosterone interact with androgen receptors to modulate lipid metabolism, protein synthesis, and muscle mass. Low testosterone levels—documented in approximately 26% of men with MASLD—are associated with higher rates of MASH (88% vs. 67%) and fibrosis (27% vs. 14%). Testosterone deficiency enhances SREBP-1 expression and reduces AMPK activity, thereby decreasing fatty acid oxidation and promoting hepatic fat deposition. Low testosterone and reduced sex hormone-binding globulin (SHBG) independently predict metabolic syndrome, highlighting hypogonadism as a key risk factor for MASLD.[19]

Androgens play a multifaceted role in hepatic metabolism. In men, reduced testosterone concentrations are linked to an increased risk of MASLD. Testosterone and dihydrotestosterone, the principal androgens, act via the androgen receptor (AR), which is expressed at levels nearly 20 times higher in men than in women.[11] A study in Taiwanese men demonstrated that MAFLD is associated with an elevated risk of testosterone deficiency (TD), particularly in the absence of metabolic syndrome (MetS), suggesting MAFLD may serve as an early indicator of TD.[20] Testosterone deficiency promotes MASLD development, either directly or through increased insulin resistance and total body fat accumulation.[20] Androgen deficiency may further enhance hepatic steatosis by stimulating de novo lipogenesis.[21]

Men with MASLD typically exhibit lower testosterone concentrations than those without the condition, and a proportional relationship exists between decreasing testosterone levels and increasing MASLD risk. However, findings from a longitudinal cohort of 1,944 Korean men revealed that baseline testosterone levels, when adjusted for percent weight change, did not independently influence MASLD progression. Similarly, a multiethnic cross-sectional study of men with type 2 diabetes and biopsy-confirmed data found that testosterone levels correlated with hepatic triglyceride content but not with other histological features of MASH. Cross-sectional evidence also suggests that testosterone inversely associates with hepatic steatosis index but not with non-invasive fibrosis risk indices. Collectively, these results imply that the link between low testosterone and MASLD may arise from associated metabolic risk factors such as obesity and insulin resistance, or through a direct influence of testosterone on intrahepatic triglyceride metabolism.[21]

Parallel trends have been observed for SHBG levels, which are lower in men with MASLD than in controls and independently correlate with increased MASLD risk after adjusting for age, BMI, and waist circumference. Furthermore, lower sperm concentration, total sperm count, and motility have been reported in men with MASLD.[21] Testosterone levels also demonstrate a significant association with body fat distribution.[20]

In a study of 631 Taiwanese men aged 40–80 years, individuals with MAFLD showed significantly higher prevalence of total testosterone (TT) levels below 300 ng/dL, TD, and MetS compared with those without MAFLD. They also exhibited

elevated serum leptin and RBP-4 levels and decreased serum adiponectin concentrations, suggesting a link with insulin resistance. Among men without MetS, those with MAFLD had a greater prevalence of TT levels below 300 ng/dL and TD. After adjusting for confounders, MAFLD remained significantly associated with increased risk of both low TT and TD, highlighting a potential role of MAFLD in TD development in individuals without MetS.[20]

Hypogonadism is a prevalent condition among men, particularly in older, obese, and diabetic populations. It is estimated to affect approximately 35% of men over 45 years of age and 30–50% of men with obesity or type 2 diabetes.[22]

Female-Specific Endocrine Conditions and MASLD Risk

Menopause marks a pivotal transition in MASLD pathogenesis, with estrogen loss driving hepatic lipid deposition, insulin resistance, and fibrosis.[7,23] Hormone therapy may confer hepatic and systemic benefits in this setting.

PCOS affects 6–15% of reproductive-age women and doubles MASLD risk.[19,24] Mechanisms include hyperandrogenism and insulin resistance: hyperinsulinemia stimulates androgen synthesis, reduces hepatic SHBG, and increases free androgen levels. Two PCOS phenotypes, reproductive (high SHBG, low BMI/insulin) and metabolic (low SHBG, high BMI/insulin), illustrate the heterogeneity of disease mechanisms. Androgen-mediated activation of SREBP1 enhances hepatic lipogenesis and inflammatory cytokine production, worsening liver injury.[19]

During pregnancy, MASLD is linked to a threefold higher risk of gestational diabetes and preeclampsia, with possible transgenerational effects on metabolic and hepatic health. Extended breastfeeding (>6 months) may offer protection.[24]

Although MASLD is more prevalent in men, disease severity increases markedly after menopause. Estrogen remains protective, while testosterone exerts sex-specific metabolic effects. Innate immune cells also display sexual dimorphism, with male immune cells demonstrating a more pro-inflammatory phenotype that may exacerbate disease progression.[25]

Genetic Determinants of MASLD and Sex-Specific Interactions

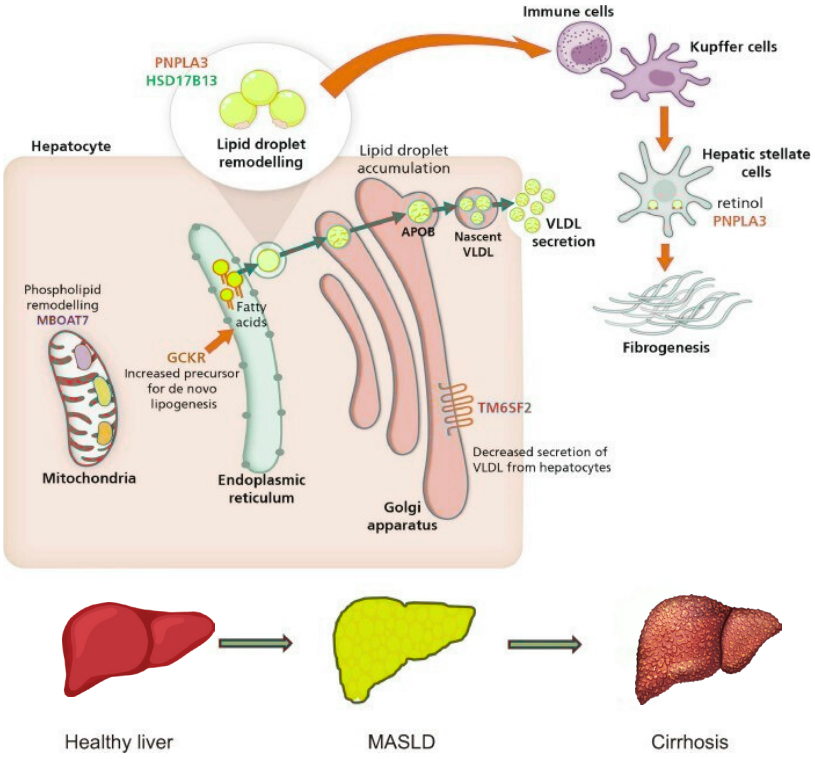

Fig 2. Genetic loci involved in the susceptibility and pathophysiology of fatty liver disease.[26]

Abbreviations: PNPLA3, patatin-like phospholipase domain-containing protein 3; HSD17B13, hydroxysteroid 17-beta dehydrogenase 13; VLDL, very low-density lipoprotein; APOB, apolipoprotein B; MBOAT7, membrane bound O-acyltransferase domain-containing 7; GCKR, glucokinase regulator; TM6SF2, transmembrane 6 superfamily member 2; MASLD, metabolic dysfunction-associated steatotic liver

MASLD outcomes differ across racial and ethnic groups due to combined genetic, environmental, and socioeconomic influences. Variants such as PNPLA3, TM6SF2, and MBOAT7 significantly affect MASLD susceptibility and progression. The PNPLA3 I148M variant, more prevalent among Hispanics, contributes to their higher disease risk relative to non-Hispanic Whites and Blacks.[15]

Genetic variants including PNPLA3, TM6SF2, GCKR, MBOAT7, and HSD17B13 show strong associations with MASLD onset and progression, influencing lipid remodelling, VLDL secretion, and de novo lipogenesis.[26] Environmental modifiers, diet, physical activity, and healthcare access, can amplify or mitigate these genetic risks. Adverse social determinants of health (SDOH), including low income and limited education, further intensify MASLD severity, particularly among Hispanic populations.[15]

Familial aggregation studies indicate that first-degree relatives of MASLD patients have up to a 12-fold increased risk compared with the general population. In one study, MASLD prevalence reached 59% in siblings and 78% in parents of affected children, independent of age, sex, race, and BMI. Twin studies estimate heritability between 35% and 61%. A Swedish multigenerational cohort of 38,000 adults with biopsy-confirmed MASLD reported 1.8-, 1.52-, and 2.14-fold higher rates of hepatocellular carcinoma, major liver events, and liver-related mortality, respectively, among first-degree relatives versus controls.[26]

Sex Differences in Body Composition and Fat Distribution

Sex-specific variations in adipose distribution significantly affect metabolic risk. Men accumulate more visceral adipose tissue (“apple-shaped”), which is metabolically active and directly exposes the liver to free fatty acids and adipokines. In contrast, premenopausal women predominantly store subcutaneous fat (“pear-shaped”), which is metabolically protective and associated with higher adiponectin levels. After menopause, fat redistributes toward visceral depots, increasing metabolic syndrome and MASLD risk.[6] Elevated body fat percentage in MASLD patients with normal BMI underscores adiposity as a stronger predictor of hepatic risk than BMI alone. Waist circumference and central fat accumulation independently correlate with hepatic steatosis, emphasizing the pathogenic role of visceral adiposity.[27]

Sarcopenia also contributes to MASLD progression, independent of obesity or insulin resistance.[27] Reduced skeletal muscle mass correlates with increased BMI and fat mass, with sex-specific differences largely driven by hormonal regulation. Estrogen enhances hepatic–adipose communication and promotes metabolic resilience via increased adiponectin and PPAR signalling, whereas men exhibit greater JNK activation, predisposing to insulin resistance and hepatocyte injury.[6]

Microbiome and Bile Acid Modulation in MASLD

Alterations in gut microbiota and bile acid metabolism play critical roles in MASLD pathogenesis. Dysbiosis compromises intestinal integrity, allowing bacterial metabolites and endotoxins to enter the portal circulation, triggering hepatic inflammation, steatosis, and fibrosis. The farnesoid X receptor (FXR) pathway regulates bile acid synthesis and lipid, glucose metabolism through FGF15/19 signalling. Gut microbial composition varies with age, sex, and menopausal status, linking estrogen levels and microbial diversity to metabolic outcomes. Further research is needed to elucidate how gut–liver–sex interactions influence MASLD progression.[6]

Gender Differences in Immune and Inflammatory Responses in MASLD

Hepatic sexual dimorphism has been recognized since the 1960s; however, mechanistic understanding of its molecular and physiological basis has evolved considerably in the past two decades with advancements in technology. One of the earliest studies by Bond (1960) identified a male-specific cytoplasmic liver protein, termed the “mystery protein”, using chromatography, later shown to be under sex hormone regulation. Early histological analyses using hematoxylin and eosin (H&E) staining and immunohistochemistry revealed structural differences in hepatocyte morphology, nuclear size, and Kupffer cell distribution. More recently, integrated liver and serum proteomic studies have provided deeper insights into sex-based variations in immune response proteins.[11]

Growth hormone (GH) signalling serves as a crucial modulator of hepatic dimorphism and interacts closely with estrogen and androgen pathways. These hormonal interactions contribute to the greater visceral fat accumulation, lower adiponectin levels, and enhanced inflammatory response observed in men compared with premenopausal women. GH also regulates

hepatic circadian gene expression, influencing overall metabolic homeostasis. Sex-specific differences in GH-regulated transcriptional activity may partly explain the variation in MASLD susceptibility and severity between men and women.[11]

MASLD demonstrates clear gender-based disparities, reflecting hormonal modulation of immune and inflammatory pathways. Sex hormones regulate both innate and adaptive immune responses, shaping hepatic inflammation and fibrogenesis. Ballooned hepatocytes release pro-inflammatory mediators that activate macrophages, stellate cells, and T cells, perpetuating hepatic injury. PU.1 and EF-hand domain family member D2 (EFHD2) have been identified as immune regulators upregulated in hepatic macrophages during MASH; inhibition of these mediators has been shown to alleviate metabolic dysfunction and hepatic inflammation in preclinical models.[25] Targeting Th17-related pathways, such as modulation of secreted phosphoprotein 1 (SPP1) through ursolic acid, has also shown therapeutic potential in attenuating MASLD-associated immune activation.[28]

Innate immune cells exhibit notable sex-related functional differences in MASLD. Male immune cells display a more migratory and pro-inflammatory phenotype compared to female cells. Molecular data further demonstrate that sex significantly influences innate immune mechanisms involved in MASLD pathogenesis. Despite this, research on innate immune sexual dimorphism remains limited, and most drug discovery programs do not consider gender-specific immune regulation.[25]

Animal studies further support these findings. In a model employing male and female Balb/c and CD1d–/– mice (deficient in NKT cells) fed a high-fat, choline-deficient diet, female mice exhibited less severe steatohepatitis than males. In males, absence of NKT cells aggravated hepatic injury, inflammation, and fibrosis, indicating a protective role of NKT cells. In contrast, in females, NKT cells appeared to play a minimal role in early disease progression, possibly due to their lower hepatic abundance.[29]

Adipose tissue also contributes significantly to sexual dimorphism in liver disease. Premenopausal women tend to accumulate more subcutaneous fat and secrete higher levels of adiponectin, enhancing insulin sensitivity and providing anti-inflammatory benefits. In contrast, men predominantly store visceral fat, which is metabolically active and pro-inflammatory. These fat depots release cytokines and free fatty acids into the portal circulation, promoting hepatic steatosis and inflammation.[29]

Sex-Specific Patterns in Fibrosis Progression, Cirrhosis, and Hepatocellular Carcinoma (HCC)

Sex exerts a substantial influence on the severity and progression of chronic liver diseases. Women generally experience a more favorable disease course in the early stages, showing higher spontaneous clearance rates of HCV infection and slower fibrosis progression from viral or metabolic causes, particularly before menopause. However, findings in advanced liver disease remain inconsistent. While several studies have reported higher cirrhosis-related mortality among men, others have shown no significant difference once disease stage and etiology are matched.[30]

In hepatocellular carcinoma (HCC), androgens function as tumour promoters. Overexpression of the androgen receptor (AR) has been identified in approximately one-third of HCCs and is closely associated with tumour progression and poorer prognosis.[11] Mechanistically, AR activation stimulates oncogenic pathways and alters non-coding RNA expression, thereby enhancing tumour growth. Conversely, oestrogens demonstrate anti-tumorigenic effects by modulating immune responses, suppressing inflammatory signalling, and potentially reducing oxidative stress. These protective hormonal effects contribute to a lower incidence of HCC, better therapeutic response, and longer survival in women, whereas male sex remains an independent predictor of early recurrence and overall mortality in HCC.[11]

A large U.S.-based cohort study involving privately insured patients with cirrhosis revealed that men had a more than twofold higher risk of developing HCC, a 63% greater risk of undergoing liver transplantation (LT), and a 16% higher risk of decompensated cirrhosis (DC) compared with women, despite similar population sizes. The disparity was more pronounced in non-viral liver diseases, reflecting the increasing contribution of metabolic etiologies. Parallel findings from inpatient and outpatient databases indicated lower rates of hepatic decompensation and portal hypertension–related complications among women.[30]

Sex-related differences were most evident in HCC, with men showing a 110% higher risk. These disparities are attributed to both biological and behavioural factors, including androgen-driven tumour promotion, estrogen-mediated protection, and lifestyle influences such as alcohol consumption, smoking, and central obesity. Additionally, men exhibit lower adherence to surveillance programs, often leading to delayed HCC diagnosis and poorer outcomes.[30]

Although women have lower cirrhosis-related mortality, liver transplantation rates remain disproportionately lower among them. Potential explanations include a lower frequency of LT indications (owing to fewer DC and HCC cases), sex

bias in the MELD score due to creatinine-based underestimation of renal dysfunction in women, and challenges in organ size matching. The LT disparity appears more pronounced in HCC-related cirrhosis, possibly because women undergo earlier surgical resections, thereby reducing the need for transplantation.[30]

An Indian population-based study demonstrated that severe hepatic steatosis was significantly more prevalent among individuals with abdominal obesity, defined as waist circumference ≥100 cm in men and ≥90 cm in women. Severe fibrosis was also more frequent in participants with abdominal obesity in both sexes; however, statistical significance was achieved only in men. Interestingly, women with abdominal obesity displayed higher frequencies of both severe steatosis and fibrosis compared with men. Consistent with these findings, our study observed that a greater proportion of women with abdominal obesity presented with advanced grades of steatosis and fibrosis than men. Furthermore, a systematic review and meta-analysis reported that although women generally have a lower overall risk of developing MASLD, once established, the likelihood of progression to advanced fibrosis is higher in women, particularly those above 50 years of age.[31]

Collectively, these findings underscore that severe steatosis and fibrosis occur more frequently in women with increased waist circumference than in men with comparable degrees of abdominal obesity, highlighting a distinct sex-specific trajectory in MASLD progression within the Indian population.[31]

Conclusion

Metabolic dysfunction–associated steatotic liver disease (MASLD) exhibits marked sex- and gender-based differences driven by hormonal, genetic, metabolic, and immunological factors. Estrogen confers hepatoprotective effects through enhanced lipid metabolism, reduced inflammation, and improved insulin sensitivity, whereas androgen imbalance, either deficiency in men or excess in women, predisposes to hepatic steatosis and fibrosis. Postmenopausal estrogen loss, central adiposity, and immune dysregulation further amplify disease risk in women, while men experience earlier onset and greater progression to hepatocellular carcinoma (HCC). These biological differences are compounded by sociocultural influences, body composition, and ethnic variation. Recognizing and integrating sex-specific mechanisms into clinical practice, preventive strategies, and therapeutic development is crucial for advancing precision medicine in MASLD management.

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