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Relationship between MASLD and women's health: A review

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD; formerly non-alcoholic fatty liver disease, NAFLD) is a common chronic liver disease strongly linked to obesity, metabolic syndrome (MetS), and type 2 diabetes. It starts as benign hepatic steatosis, but may progress to severe fibrosis, cirrhosis, or hepatocellular carcinoma. Today, MASLD represents one of the leading indications for liver transplantation. This review summarizes current knowledge on MASLD, including its pathogenesis, management strategies, regional disparities, and its specific relevance to women's health. The influence of sex hormones on MASLD has been documented. Polycystic ovary syndrome (PCOS) and the menopause increase MASLD prevalence by more than twofold. Moreover, PCOS increases the risk and severity of MASLD, independent of BMI. The role of menopausal hormone replacement therapy in MASLD remains controversial. However, transdermal estrogen and micronized progesterone or dydrogesterone seem to be more appropriate options. In pregnancy, MASLD is associated with >3-fold increased risk of gestational diabetes and preeclampsia. It may also increase the risk of MASLD development in the offspring—an effect that appears to be mitigated by breastfeeding for longer than six months. Given these findings, it is essential that clinicians involved in women's healthcare are aware of MASLD and its implications across the female lifespan.

Plain language summary

Understanding MASLD: a growing women's health concern

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD), is one of the most common chronic liver conditions today. It is closely linked to obesity, type 2 diabetes, and MetS. MASLD often begins as a simple fat buildup in the liver (steatosis), but over time, it can lead to serious complications such as liver scarring (fibrosis), cirrhosis, or even liver cancer. In fact, MASLD is now a leading reason for liver transplantation. This disease affects both men and women, but recent research highlights its impact on women's health. Female sex hormones appear to influence MASLD risk. Conditions like PCOS and menopause significantly increase a woman's likelihood of developing MASLD. Notably, women with PCOS are at higher risk of developing more severe liver disease, even if they are not overweight. The effect of the use of hormone replacement therapy (HRT) on MASLD is not clear. However, certain forms of HRT, like estrogen patches and progesterone that is chemically identical to the natural one, seem to be safer options for women with this condition who are considering HRT. MASLD can also pose some risks during pregnancy. It increases the risk for gestational diabetes and preeclampsia. Additionally, the presence of MASLD during a pregnancy might increase the child's own risk of developing liver disease later in life. Fortunately, breastfeeding for more than six months may help reduce this risk. There is fast-growing and promising research in the field of MASLD management with medications. However, the most effective interventions still relate to lifestyle change, exercise and a healthy diet. In conclusion, MASLD has wide-reaching effects throughout a woman's life, therefore, health providers who care for women should be aware of this condition and how to manage it effectively.

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently a major cause of chronic liver disorders. It was known as non-alcoholic fatty liver disease (NAFLD) until June 2023, when the new nomenclature was announced to reflect the growing evidence about the disease nature.[1] MASLD is usually linked to obesity, MetS, and insulin resistance (IR), with or without type 2 diabetes mellitus (T2DM). The incidence of these problems is still rising; hence, the prevalence of MASLD is expected to continue to rise in the forthcoming years.[2] A recent meta-analysis estimated its global prevalence to be 30%, a 50% increase over the last three decades.[3] Although the prevalence and severity of MASLD are known to increase with age, there is evidence that the prevalence of MASLD is also rising in children and young adults.[4]

There are certain conditions and periods in a woman's life that significantly increase their risk of developing MASLD. However, many clinicians involved in women's healthcare are not fully aware of the pathogenesis of MASLD and its consequences. Therefore, the aim of our review was to highlight the importance and relevance of this topic to women's health. The first part of this review summarizes current knowledge on MASLD, including: (1) its definition and outcomes, (2) associated risk factors, (3) global patterns and disparities, (4) pathophysiological mechanisms, and (5) treatment approaches. Sections in the second part are focused on the associations between MASLD and women's health, specifically its relationship to (6) polycystic ovary syndrome (PCOS), (7) pregnancy, and (8) menopause and sex hormones. Each of the sections 6–8 concludes with relevant clinical recommendations.

The MASLD spectrum

The term MASLD comprises a spectrum of disease phenotypes connected to steatosis in patients with cardiometabolic risk factors.[1] The mild form is represented by metabolic dysfunction-associated steatotic liver (MASL) (previously non-alcoholic fatty liver, NAFL). The more severe form is termed metabolic dysfunction-associated steatohepatitis (MASH) (previously non-alcoholic steatohepatitis, NASH), which could be present with different degrees of fibrosis, including cirrhosis.[5,6]

MASL manifests as simple steatosis or steatosis with mild lobular inflammation without cellular damage.[5] It is usually harmless, symptomless, and could be diagnosed incidentally, by imaging modalities during examination for reasons other than liver-related symptomatology.

In contrast, steatosis must be accompanied by lobular inflammation and cellular damage in the form of hepatocyte ballooning in MASH. Additional histological features, for example, Mallory–Denk bodies, apoptotic bodies, lymphocyte infiltrates, portal inflammation, and fibrosis, could be present.[5] Definitive diagnosis of MASH and its grade could only be confirmed by liver biopsy. However, this tends to be reserved for patients deemed to be at high-risk of having advanced disease, who would benefit from a biopsy.[6]

The degree of fibrosis is the primary prognostic marker for MASLD because it increases the risk of developing cirrhosis, hepatocellular carcinoma, and mortality.[7] Fibrosis severity can be graded using several scoring systems; a commonly used system is presented in Table 1. Using this grading system, it was demonstrated that compared to MASLD patients without fibrosis, all-cause mortality is increased by 1.5, 2, and 3.7-fold if stage F2, F3, and F4 are present, respectively.[8] The leading causes of death in patients with MASLD are cardiovascular diseases, followed by extrahepatic cancer-related and liver-related events.[3] MASLD is currently one of the leading indications for liver transplantation.[9,10]

Factors affecting MASLD development

Development and progression of MASLD seems to be driven by the synergistic effect of multiple factors, including eating habits, lifestyle, genetic susceptibility, age, and sex. These factors trigger the development of IR, obesity, intestinal dysbiosis, and hyperlipidemia, and activate inflammatory processes in the adipose tissue and liver.[11] This impairs the balance between lipid storage and its removal. In healthy conditions, lipids in the bloodstream originate mainly from adipose tissue lipolysis, and to a lesser extent, from dietary lipids and *de novo* lipogenesis from excessive carbohydrates. It was shown that *de novo* lipogenesis is increased up to 5-fold in MASLD patients, indicating the importance of diet in the pathogenesis of the disease.[12,13] The main risk factors and complications of MASLD are summarized in Figure 1.

Diet

Although high-caloric intake, leading to obesity and IR, is the key dietary factor in MASLD development, nutrients'

Table 1. Mortality outcomes by fibrosis stage as published by Ng et al.[8]

Score	Stage [a]	All-cause mortality [b]	Liver-related mortality [b]	Cumulative incidence of mortality	
				5 years	10 years
0	No fibrosis	Reference	Reference	3.3%	7.7%
1	Mild	NS	NS		
2	Moderate	1.46	4.07		
3	Severe	1.96	7.59	14.9%	32.2%
4	Cirrhosis	3.66	15.1		

NS: nonsignificant.
[a]Description of stages according to the International Association for the Study of the Liver.
[b]Hazard ratios compared to score 0.

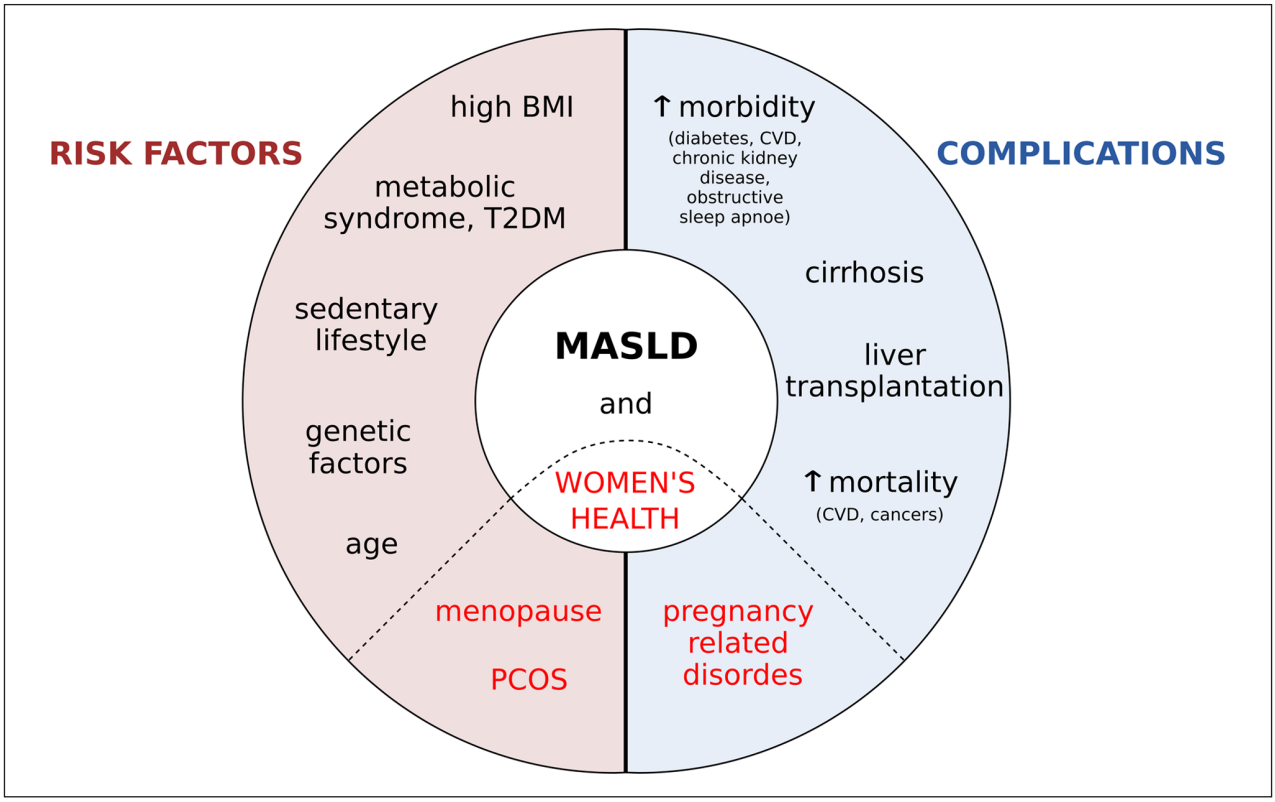

Figure 1. Summary of MASLD important risk factors and complications, and their relation to women's health.
CVD: cardiovascular disease; MASLD: metabolic-dysfunction-associated steatotic liver disease; PCOS: polycystic ovary syndrome; T2DM: type 2 diabetes mellitus.

composition is also important. Large amounts of highly processed food rich in fructose and saturated fatty acids, or the so-called "Western diet," have negative effects favoring MASLD development.[14] This type of diet was found to affect lipolysis, plasma lipid profile, insulin sensitivity, production of adipokines, and microbiota composition.[15]

Physical activity

Physical activity affects lipid metabolism and enhances insulin sensitivity.[16] It also results in improving cardiorespiratory fitness (tissue oxygen uptake), which is connected to a lower risk of developing MASLD.[17] Physical activity is helpful in preventing MASLD development in a dose-dependent manner.[18] Activity ⩾150 min/week of moderate-intensity or ⩾75 min/week of vigorous-intensity has been shown to reduce the risk of MASLD development. Even less vigorous activity has a beneficial effect compared to none.[18,19]

Comorbidities

Obesity is the most connected metabolic co-morbidity with MASLD. Prevalence of MASLD increases from 30% in the general population to >90% in obese people undergoing weight reduction procedures.[3,5] Obesity contributes

to MASLD development via adipose tissue dysregulation, systemic inflammation, IR, dysbiosis, and increased gut permeability.[20]

MASLD is also bi-directionally associated with T2DM and MetS, where patients with T2DM and MetS often develop MASLD and *vice versa*.[21] Both conditions share some predisposing dietary and lifestyle factors and consequences with MASLD, where IR is the main link between all these conditions.[20]

Furthermore, MASLD has been associated with some endocrinopathies, such as PCOS, hypothyroidism, hypogonadism, and growth hormone deficiency.[22] The mechanisms by which these diseases contribute to MASLD development are probably linked to IR, modulation of adipokine production, and deficiency or excess of hormones that influence lipid and glucose metabolism.[22]

Genetic predispositions

Finally, several genetic variants predisposing to MASLD development were identified. Although previously overseen, these are now believed to be crucial modifiers of disease progression. Patatin-like phospholipase domain-containing 3 (PNPLA3) is the most associated gene with MASLD development.[23] PNPLA3 encodes adiponutrin lipase, which is involved in the release of triacylglycerols from lipid droplets. Its variant I148M loses its enzymatic activity, resulting in increased liver fat content, worsening the disease's histological severity.[24] Interestingly, MASLD patients with this genetic background are less likely to have MetS features compared to patients without the variant.[20]

Global perspective on MASLD

There is global geographical variability in MASLD prevalence. In a meta-analysis covering data up to 2019, the highest pooled prevalence was estimated in Latin America (44%), followed by the Middle East and North Africa (MENA) (37%), South Asia (34%), South-East Asia (33%), North America and Australia (31%), East Asia (30%), Asia Pacific (28%) and Western Europe (25%).[3] These findings are consistent with data from the Global Burden of Disease 2019 database.[25] It was reported that MASLD prevalence across all age groups has increased in >80% of countries. Asian countries accounted for 56% of MASLD cases and showed the highest annual increase in prevalence (2.8% per year in East Asia), whereas the MENA region had the highest all-age and adult prevalence (27% and 41%), and Latin America had the highest all-age MASLD liver-related crude death rate (5.9 per 100 000).[25]

These geographical disproportions could be partly attributed to ethnic and genetic factors. The prevalence of the PNPLA3 risk allele was reported to be increased in the South Asia population, while in Latin America, a higher prevalence of the TM6SF2 risk allele and lower prevalence of the HSD17B13 protective allele were identified.[26] In contrast, the highest prevalence of this protective allele was found in East Asia.[26] Impact of ethnicity was evaluated mainly in the US population, where the highest prevalence and severity of MASLD was reported in Hispanic populations, followed by non-Hispanic White, and the lowest in non-Hispanic black populations.[26]

While many of the studies addressing disparities related to MASLD have addressed the role of ethnicity, surprisingly few have considered the impact of socioeconomic factors, although they seem to be important.[27] For example, Rieman-Klinger et al. reported that the PNPLA3 risk allele was more frequent in the Hispanic population and that its presence was associated with increased MASLD severity regardless of ethnicity; however, this association diminished after adjustment for education level.[28] Several other studies have also shown that lower educational level, food insecurity, and poor dietary quality are associated with MASLD prevalence.[29–34] These socioeconomic variables may disproportionately influence disease burden in regions where ultra-processed food is both inexpensive and widely available, and where public awareness of its health impact remains limited.

Low socioeconomic status is typical for developing countries, where MASLD is now rapidly emerging, as illustrated by the data above. This likely reflects a combination of increasing urbanization, lifestyle changes, and limited access to early diagnosis and appropriate healthcare. Notably, the MENA region has one of the highest global rates of obesity and physical inactivity, and both MASLD risk factors are more prominent in women in this region.[35]

Cellular mechanisms involved in MASLD pathogenesis

The development and progression of MASLD involves a complex interplay between various liver cell types, which, together with intestinal and adipose tissue signaling, mediate cellular damage, inflammation, and fibrosis (Figure 2).

Lipid droplets, *per se*, are not hepatotoxic. Indeed, MASL is benign because the total amount of stored lipids is not a determining factor of toxicity—only some lipid species are harmful. Whereas triacylglycerols seem to be well tolerated, cholesterol, long saturated free fatty acids (e.g. palmitic acid, stearic acid), and their metabolites are strongly hepatotoxic.[36] Their accumulation in the hepatocytes leads to multiple organelle dysfunction, oxidative stress, impaired autophagy, activation of apoptotic pathways, and extracellular vesicle release. Subsequently, non-parenchymal liver cells are also affected.[36,37]

Although lipotoxicity could result in apoptosis and other types of cell death, the cellular damage is often sublethal, resulting in degenerated cells, known as ballooned hepatocytes. These are enlarged cells characterized by impaired functions, damaged cytoskeleton, and cytoplasmic accumulation of ubiquitinylated proteins, often in the form of

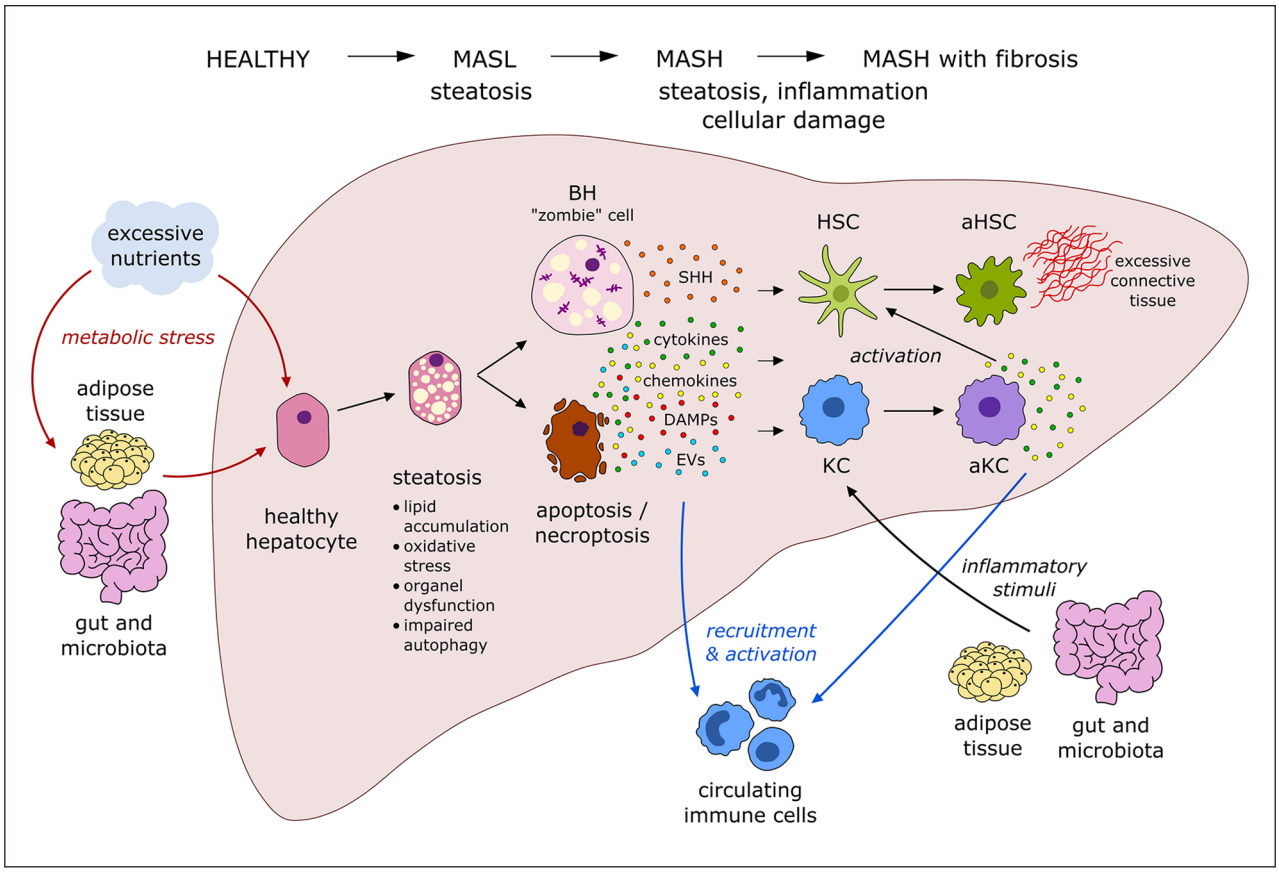

Figure 2. Metabolic dysfunction-associated steatotic liver disease—Complex interplay between hepatic and extrahepatic cells. In MASLD development, hepatocytes are triggered by metabolic stress (e.g. excessive nutrients, insulin resistance, altered adipokines, dysbiosis). This results in hepatic steatosis, a benign form of MASLD termed metabolic dysfunction-associated steatotic liver (MASL). However, lipids could become toxic, leading to either programmed cell death (apoptosis, necroptosis) or sublethally injured cells termed ballooned hepatocytes (BH). These cells produce a variety of proinflammatory and profibrotic molecules that stimulate hepatic stellate cells (HSC) and Kupfer cells (KC)–liver resident macrophages. Activated HSC, activated KC, and extrahepatic cells further exacerbate the proinflammatory environment. Circulating immune cells are also recruited. This severe stage of MASLD is termed metabolic dysfunction-associated steatohepatitis (MASH). Moreover, BH cannot be cleared from the liver; however, the reasons for this are not fully understood. Their long-term production of sonic hedgehog (SHH) protein overstimulates HSC, resulting in the production of excessive connective tissue and, thus, fibrosis.
BH: ballooned hepatocyte; DAMPs: damage-associated molecular patterns; EVs: extracellular vesicles; HSC: hepatic stellate cell; KC: Kupffer cell; MASL: metabolic dysfunction-associated steatotic liver; MASH: metabolic dysfunction-associated steatohepatitis; SHH: sonic hedgehog.

Mallory–Denk bodies.[38] Ballooned hepatocytes persist in the liver and contribute to fibrosis by producing sonic hedgehog protein, a signaling molecule involved in the regulation of liver healing processes.[39] The long-term presence of sonic hedgehog protein overstimulates the neighboring hepatic stellate cells, which respond by activation and production of fibrotic tissue components.[40]

Macrophages represent another crucial cell type in MASLD progression. Kupffer cells (liver-resident macrophages) recruit monocyte-derived macrophages, and both types are activated into the proinflammatory state by several stimuli. These stimuli include cytokines, damage-associated molecules, and extracellular vesicles released by damaged hepatocytes, lipid species, and intestinal microbiota secondary to overnutrition.[41,42] Activated macrophages in the liver then secrete molecules enhancing inflammation (TNFα, IL1β, IL8, CCL2) and fibrosis (TGFβ).[41] Adipose tissue macrophages also influence MASLD development, especially in obese people, because they contribute to both local and systemic low-grade inflammation, IR, and increased lipolysis.[43]

Treatment

Recently, resmetirom was approved by the Food and Drug Administration as the first pharmaceutical agent specifically targeting MASH. Subject to country-specific approvals, resmetirom may be considered for adults with non-cirrhotic MASH and fibrosis stage $\geqslant$2.[5,44] However, the cornerstone of MASLD management remains non-pharmacological therapy, primarily focused on lifestyle modification, with weight loss being the most critical

factor. A meta-analysis demonstrated that greater weight loss leads to greater improvements in MASLD.[45] A weight reduction of ⩾5% is recommended for improving steatosis, while ⩾7–10% is advised for reducing MASH and fibrosis in overweight and obese patients.[5] In lean individuals with MASLD, a weight loss of 3–5% was suggested.[5,46] All types of diet leading to caloric restriction are advisable; however, a "Mediterranean diet" is particularly recommended due to its additional cardiovascular benefits.[5,6] Although the type and amount of physical activity need to be individualized, the general recommendation is at least 150 min/week of moderate activity or 75 min/week of vigorous-intensity activity.[5] Regular monitoring of possible disease progression is necessary, as well as screening for T2DM and cardiovascular disease.[6] Furthermore, screening for chronic kidney disease, PCOS, and obstructive sleep is recommended, and age-appropriate cancer screening is advised, as non-hepatic malignancies are a common cause of death in MASLD patients.[5,6] Regarding women's health, a meta-analysis associated MASLD with a 40% increased risk of developing breast cancer and a 60% increased risk of gynecological cancers.[47]

MASLD and PCOS

Prevalence of MASLD in PCOS

Evidence about PCOS association with MASLD has been growing in the last decade. Several meta-analyses showed that patients with PCOS have a 2–2.5-fold risk for developing MASLD compared to their age- and BMI-matched non-PCOS controls.[48–50] The largest meta-analysis to date indicated that MASLD prevalence in PCOS patients is significantly influenced by ethnicity (particularly South America and the Middle East) and body weight, independent of IR and MetS.[49] Other meta-analyses found that MASLD is more prevalent in PCOS patients with hyperandrogenism,[48,50] even after correction for age, BMI, and IR.[48] This effect may be particularly relevant in non-obese individuals.[51] Indeed, increased MASLD prevalence was described in patients with PCOS and normal BMI across different ethnicities.[51–54] It is suggested that hyperinsulinemia and elevated androgen levels impair lipid metabolism and lower adiponectin production, promoting hepatic steatosis. Low adiponectin may also reduce hepatic sex hormone-binding globulin production, further exacerbating IR and hyperandrogenism.[55]

Consequences of PCOS and MASLD coexistence

Several studies showed that the coexistence of PCOS and MASLD might increase the severity of one or both conditions. It was reported that severe fibrosis and cirrhosis occurred more frequently in MASLD patients with PCOS compared to those without.[56] Similarly, severe steatosis was reported in >50% of patients with associated PCOS compared to <5% of controls.[54] A higher prevalence of severe fibrosis and hepatocyte ballooning was also observed in women with both MASLD and PCOS compared to women with MASLD only.[57] Additionally, it was suggested that PCOS patients with MASLD could be at higher risk for cardiovascular morbidity than those without.[58]

The relationship between MASLD and subfertility in patients with PCOS is not clearly understood. It has been reported that the prevalence of MASLD is higher in women seeking fertility treatment who have PCOS compared to non-PCOS patients.[56] In general, advanced liver diseases can cause anovulation, amenorrhea, and subfertility.[59] Further research is required to understand if the relationship between MASLD and infertility in PCOS is one of causation or mere correlation.

Recommendations

Lifestyle modification of diet and activity, especially in obese and overweight patients, is an important part of both MASLD and PCOS management.[6,60] Specific recommendations on weight loss in MASLD patients are stated above in section Treatment. Regarding pharmaceuticals, metformin is the most commonly used drug for improving the metabolic outcome in PCOS patients.[60] Although metformin was studied in MASLD treatment, a meta-analysis did not find any beneficial effects on histological scores and MASH.[61] In contrast, liraglutide was associated with MASLD improvement in PCOS patients, where they achieved greater weight loss and a decrease in liver steatosis compared to the placebo group.[62] Moreover, both liraglutide and semaglutide have been shown to improve steatosis and trigger MASH resolution in a recent meta-analysis.[63] In the recent clinical guidelines, neither metformin, liraglutide, nor semaglutide was recommended for MASLD management; however, they were stated as safe to use in MASLD patients to target metabolic comorbidities.[5,6]

Hyperandrogenism in PCOS is usually treated by oral contraceptives and anti-androgens.[60] One study has shown the beneficial effect of anti-androgen spironolactone in combination with vitamin E on steatosis and IR in MASLD patients.[64] However, more studies and additional evidence on MASH are needed. Similarly, there is a need for further evaluation of how oral contraceptives affect MASLD in PCOS women. There has been conflicting evidence suggesting both benefit[57,65] and harm.[66,67]

MASLD in pregnancy

Acute fatty liver of pregnancy is a rare, acute, and serious condition that can complicate pregnancy, but it has a different etiology and consequences in comparison to

MASLD,[68] and hence, is not covered in this review. However, MASLD in pregnancy is quite common. Along with the rising prevalence of MASLD in the general population, pregnancies with MASLD have almost tripled in the period between 2007 and 2015.[69]

Pregnancy outcomes

The association of MASLD and pregnancy brings certain risks for both mother and child. In a study by Sarkar et al., gestational diabetes mellitus (GDM), gestational hypertension, hypertensive complications, cesarean section, postpartum hemorrhage, and preterm birth were more prevalent in pregnant women with MASLD compared to healthy controls or even women with other chronic liver diseases.[69] According to a meta-analysis of 22 studies, there was >3-fold increase in the risk for GDM and pre-eclampsia, and there was a 2-fold increase in the risk of premature birth and large for gestational age in MASLD women.[70]

Lee and associates showed that the prevalence of GDM was not only higher in MASLD women, but it also correlated with steatosis severity, low serum adiponectin, and high serum selenoprotein P.[71] Decreased serum adiponectin and increased selenoprotein P were also associated with large for gestational birth weight,[72] gestational hypertension, and pre-eclampsia in MASLD pregnancies.[73]

Similar to T2DM, the association of MASLD and GDM is bidirectional. A meta-analysis reported that women with prior GDM had a 2.6-fold higher risk of MASLD development later in life.[74] Of note, the MASLD-associated increased risk of GDM seems to happen even in women with a normal pre-pregnancy weight.[75,76]

MASLD in the offspring

In utero exposure to maternal obesity, hyperinsulinemia, and overnutrition has been associated with increased susceptibility to MASLD in the offspring. Such a maternal environment could influence transplacental transfer and placental function, resulting in modifications to the fetal epigenome and long-term consequences.[77] Several studies showed that maternal obesity, before and during pregnancy, increases the prevalence of MASLD in the offspring during their adolescent and young adult life.[78–81] Maternal high BMI was associated with high BMI in their children before their fourth year of life, which further increased their risk of staying overweight/obese into their adolescence and adult life. Moreover, both mother's and offspring's BMI was associated with MASLD in the offspring.[81] GDM or glycosuria, independent of maternal BMI, has also been associated with MASLD prevalence in the offspring.[78] Similarly, high levels of maternal triglycerides and fatty acids in pregnancy were linked to childhood susceptibility to steatosis.[82]

Recommendations

Pre-conception counseling for women with MASLD should include recommendations for weight loss to decrease the impact of the disease on the pregnancy and the newborn.[59,83] Specific recommendations on weight loss in MASLD patients are stated above in section Treatment. Breastfeeding should also be encouraged.[59,83] Indeed, lactation for ⩾6 months seems to have a protective role on the risk of developing MASLD later in the mother's life,[84,85] where it has been demonstrated to reduce the risk by 37%.[86] In addition, breastfeeding for ⩾6 months was associated with a 0.6-fold reduction in the prevalence of MASLD in adolescents, even after adjustment for maternal and offspring obesity and dietary patterns during adolescence. Moreover, adolescents with MASLD who were breastfed for ⩾6 months had a less severe metabolic profile.[79] This is consistent with the findings of a study evaluating MASLD in children aged 3–18 years, where breastfeeding was protective against MASH and fibrosis regardless of several MASLD risk factors, and this protective effect on disease progression correlated with the duration of breastfeeding.[87] However, some studies were not able to demonstrate the protective effect of breastfeeding on MASLD in the offspring.[81,88] It has been suggested that breastfeeding mediates its effects on the offspring through metabolically active particles in the milk and the development of healthy intestinal microbiota. While on the mother's side, lactation increases energy expenditure and consumption of circulating glucose and lipids for milk production, and thus, improves cardiometabolic health.[89]

MASLD, menopause, and sex hormones

Menopause

It was shown that the prevalence of MASLD is higher in men compared to premenopausal women. However, the prevalence seems to be comparable between both sexes around the age of 50 and higher in women after the age of 60.[90] According to a meta-analysis, women have a 2.4-fold higher risk of MASLD development after menopause.[91] It was also reported that premenopausal women without MASLD had higher levels of estradiol than premenopausal women diagnosed with MASLD.[92] The aforementioned evidence suggests that estrogens might have a protective role in MASLD development.

The risk of MASLD progression also seems to be hormone dependent. Balakrishnan et al. reported that the presence of MASH and severe fibrosis was more prevalent in older women (age >50) than in men, but similar in younger women and men.[93] Furthermore, when categorizing women by menopausal status, postmenopausal women had the greatest risk of severe fibrosis.[66] In a study by Klair et al., premature menopause and menopause duration were

associated with the risk of severe fibrosis.[94] In contrast, in the same study, the risk of hepatocyte damage and inflammation was decreased in men compared to women, independent of menopausal status. Therefore, it is plausible that estrogens have a protective role in fibrosis development, but do not protect from other MASH markers. Moreover, several gene polymorphisms seem to have distinct effects on fibrosis severity depending on sex and/or menopausal status.[95]

Effect of estrogens

The role of estrogens on lipid metabolism is relatively well known. Estrogens reduce *de novo* lipogenesis in the liver and lipolysis in adipocytes, and conversely, they support beta-oxidation of fatty acids in the liver and skeletal muscles.[96] Furthermore, estrogens influence adipose tissue distribution. Adipose tissue of premenopausal women is preferentially stored subcutaneously, promoting insulin sensitivity and limiting lipolysis. In men and postmenopausal women, visceral storage of fat predominantly leads to increased risks of inflammation and IR.[97] Although subcutaneous fat probably has some impact on MASLD development, more inflammatory cytokines are produced by macrophages in visceral adipose tissue in obese people.[98,99]

In addition to their effect on lipids and metabolism, estrogens, in general, affect the activity of almost all immune cells, including macrophages.[100] This immunomodulatory effect is a potential mechanism of how estrogen can affect the degree of immune response in MASLD. Estrogens also influence the production of adipokines. Women tend to have higher serum adiponectin,[101,102] which has anti-steatotic, anti-fibrotic, and anti-inflammatory effects on the liver.[103] The production of adiponectin decreases with the amount of adipose tissue, and its low levels are typical in patients with MASLD.[101,103,104]

Moreover, there is a known impact of estrogens on hepatic stellate cells. Experimental studies on various animal and *in vitro* models have shown that estradiol or estrogen agonists inhibit the proliferation and activation of hepatic stellate cells, resulting in reduced collagen production and thus, reduced hepatic fibrosis.[105–107]

Estrogens could also be partly responsible for the observed sex-specific differences in genetic susceptibility to MASLD. Cherubini et al. observed that women with PNPLA3 risk variant I148M have more severe histological features of MASLD than men.[108] Subsequent *in vitro* and *in vivo* experiments revealed that expression of PNPLA3 is enhanced through estrogen receptor α signalization; therefore, estrogen levels influence the I148M effect on MASLD.[108] However, the relationship of these findings to the menopause needs further investigation.

Effect of testosterone

Male sex hormones could also impact MASLD in women. It was shown that the risk of MASLD development is increased by low levels of testosterone in men, compared to high levels in women.[109] Park et al. further specified this relation, where, in their study, only premenopausal women with high levels of testosterone (but still within normal range) had an increased risk of MASLD development.[110] According to another study, high levels of testosterone in premenopausal women were also associated with a higher risk of MASH development and more severe fibrosis.[111] Interestingly, this association was stronger the younger the women were and persisted even after exclusion of women with PCOS, to mitigate the confounding effect of their hyperandrogenic status.[111]

Hormone replacement therapy

Results from animal studies have shown that HRT administered after the cessation of ovarian function may be protective against the development of MASLD.[112] However, evidence from clinical studies is limited and presents conflicting results. It was reported that postmenopausal women receiving HRT had a lower prevalence of MASLD, MetS, and IR.[113] In contrast, other studies have associated HRT use with increased MASLD prevalence[67] and severity.[66] While other authors reported no significant difference in one-year MASLD incidence between menopausal women who used HRT and those who did not.[114]

However, it is important to emphasize that most of these studies were observational, in which the HRT type, route, and regimen were neither standardized nor specified. This is particularly relevant, as some studies suggest that the effect of HRT on MASLD is multifactorial. Indeed, Yang et al. suggested that the harmful effect of HRT on MASLD was associated with progesterone rather than estrogen intake.[66] In the study by Wang et al., the risk of developing MASLD was linked to prolonged use of HRT, especially when estrogen monotherapy lasted for $\geqslant$5 years.[67] Similarly, Miao et al. reported an association between prolonged HRT use and increased MASLD incidence. Furthermore, they also observed an increased MASLD incidence in women who experienced an earlier onset of menopause ($\leqslant$45 years), regardless of HRT use.[115] The route of HRT administration also appears to be important. While one year of transdermal therapy was associated with a reduction in MASLD prevalence from 24% to 17%, oral administration was linked to an increase in prevalence from 25% to 29%.[116] In the same study, oral HRT—but not transdermal—led to an increase in plasma triglyceride levels, which may partially explain how oral HRT contributes to MASLD development.

In view of the above, there is a need for well-designed clinical studies that specifically investigate the effect of HRT on MASLD. These studies should include detailed information on the type and duration of HRT, the route of administration, and the age at menopause onset. It has been suggested that, ideally, MASLD presence and its severity should be assessed before, during, and after HRT use, preferably by means of a liver biopsy. Alternatively, the use of fibrosis scores, such as FIB-4, or imaging by liver elastography, has been proposed as non-invasive options.[5]

Recommendations

Postmenopausal women are recognized as being at increased risk of progressive fibrosis, development of cirrhosis, and other MASLD complications by European hepatology, obesity, and diabetes societies.[5] These risks are also increased if one or multiple cardiometabolic risk factors, such as hypertension, dyslipidemia, T2DM, and obesity, are present. Hence, these societies recommend fibrosis screening using non-invasive scores such as FIB-4 for individuals within these risk groups.[5] American and Asia-Pacific hepatology societies have also acknowledged the association between menopause and MASLD; however, they have not yet included specific management recommendations in their guidelines.[6,117]

Based on current evidence, the use of HRT for the treatment of MASLD in postmenopausal women is not recommended. However, if HRT is indicated for other clinical reasons, a more appropriate option for women with MASLD is transdermal estrogen therapy and, if required, micronized progesterone or dydrogesterone.[112]

Limitations

We appreciate that our review has some limitations, including its non-systematic nature, the heterogeneity of the study populations included, and the quality of the primary studies. Nevertheless, the thorough search we have undertaken, which was updated several times throughout the course of the preparation for this review, the focus of our review on the impact of the condition throughout a woman's life span are major strengths of our work.

Conclusions

In this review, we presented the current knowledge on MASLD phenotypes, pathogenesis, and available treatment options. Although it is a common chronic liver disease with potentially severe complications and a rising prevalence in over 80% of countries, it remains underrecognized outside the fields of gastroenterology and hepatology. MASLD prevalence and severity are notably increased in women with PCOS and after menopause. Furthermore, women with MASLD seem to be at higher risk for several pregnancy disorders and complications. Some of these complications have been linked to the offspring and their risk of developing diseases later on in life. Therefore, it is prudent that health professionals delivering different aspects of women's healthcare are aware of this condition, its risk factors, and implications on women's and their children's health in the short and long term. Finally, further clinical research is needed to clarify the impact of PCOS-related pharmaceuticals, oral contraceptives, and HRT on MASLD to facilitate the generation of evidence-based recommendations for the management of women with this condition.

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