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Nonalcoholic fatty liver disease shows significant sex dimorphism

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Abstract

Nonalcoholic fatty liver disease (NAFLD), which has been renamed metabolic dysfunction-associated fatty liver disease, is a growing global medical problem. The incidence of NAFLD and its associated end-stage liver disease is increasing each year, and many research advancements have been achieved to date. This review focuses on the current knowledge of the sex differences in NAFLD and does not elaborate on areas without differences. Studies have revealed significant sex differences in the prevalence, influencing factors, pathophysiology, complications and therapies of NAFLD. Men have a higher incidence than women. Compared with women, men exhibit increased visceral fat deposition, are more susceptible to leptin resistance, lack estrogen receptors, and tend to synthesize fatty acids into fat storage. Male patients will experience more severe hepatic fibrosis and a higher incidence of liver cancer. However, once NAFLD occurs, women show a faster progression of liver fibrosis, higher levels of liver cell damage and inflammation and are less likely to undergo liver transplantation than men. In general, men have more risk factors and more severe pathophysiological reactions than women, whereas the development of NAFLD is faster in women, and the treatments for women are more limited than those for men. Thus, whether sex differences should be considered in the individualized prevention and treatment of NAFLD in the future is worth considering.

Key Words: Nonalcoholic fatty liver disease; Metabolic dysfunction-associated fatty liver disease; Sex differences; Estrogen; Steatosis; Cirrhosis

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Core Tip: Nonalcoholic fatty liver disease (NAFLD) is a sexual dimorphic disease, and its prevalence worldwide is increasing each year. However, our understanding of sex differences in NAFLD remains insufficient. The incidence in males is significantly higher than that in females, and studies have also revealed significant sex differences in

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influencing factors, pathophysiology, complications and therapies. This review summarizes the current research progress on sex differences in NAFLD and indicates that whether sex differences in NAFLD can be considered in future research, treatment and prevention is worth exploring.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD), which has been renamed metabolic dysfunction-associated fatty liver disease, affects approximately a quarter of adults worldwide[1]. In the past, NAFLD was considered a Western disease, but with improvements in living standards, the prevalence of this disease in Asia is increasing each year, particularly in China[2], where the incidence has exceeded that in Europe and North America. NAFLD should be regarded as a global disease. Moreover, NAFLD, which manifests as nonalcoholic fatty liver or nonalcoholic steatohepatitis (NASH), is a growing worldwide cause of chronic liver disease, which may gradually lead to severe liver disease, such as liver cirrhosis, hepatocellular carcinoma, and even death. The increasing prevalence of this disease and the serious complications it may cause pose a substantial medical and economic burden to the whole world[3]. With the development of research on NAFLD, an increasing number of findings have revealed significant sex differences regarding this disease. This review focuses on the current knowledge of sex differences in NAFLD and does not elaborate on the areas without differences. The review mainly focuses on the following aspects: Epidemiology, influencing factors, pathophysiology, complications and treatments.

EPIDEMIOLOGY

The prevalence of NAFLD is increasing annually and has exceeded 25% of the global population. The increasing trend of NAFLD is closely related to the increasing standard of life and the increasing prevalence of obesity[4]. A large number of studies have proven that obesity is an important risk factor for hepatic steatosis and promotes the formation of NAFLD[5-7]. Considering the continuing increase in NAFLD, this disease will be the main cause of cirrhosis and hepatocellular carcinoma (HCC) and is the fastest growing cause of orthotopic liver transplantation[8].

Previous epidemiological studies revealed a significant sex difference in the incidence rate of NAFLD, which is strongly related to age. Overall, the prevalence of NAFLD in men is higher than that in women[7,9-11]. Interestingly, studies in pediatric populations have also found that the prevalence of NAFLD is higher in boys than in girls[12]. A study performed in Korea using data from 6648 subjects found that the prevalence of NAFLD in women increased with age, and the prevalence increased sharply with age among women older than 50 years, particularly after the perimenopausal period. However, the prevalence in men shows minimal differences according to age. The prevalence among men under 50 years of age is significantly higher than that among women (22.6% *vs* 6.8%), whereas the sex difference is not significant among participants over 50 years of age (23.6% *vs* 24.2%)[7]. Similar conclusions have been reached by studies conducted in Shanghai and Japan[10,11]. Compared with men and postmenopausal women, premenopausal women are at a significantly lower risk for NAFLD. Moreover, hormone replacement therapy can reduce the prevalence of NAFLD in postmenopausal women, which suggests that estrogen is protective against NAFLD[13]. Men are more susceptible to NAFLD at a younger age than women, which is a problem worthy of attention. Men are exposed to high metabolic risk for a longer period of time.

INFLUENCING FACTORS

Adipose distribution, adipocytokines and lipid metabolism

The main sex differences in adipose distribution are well recognized: Men store more adipose tissue in their intra-abdominal depots, whereas women tend to have enlarged peripheral adipose tissue, and these differences are associated with the deleterious metabolic consequences of men and the lower cardiometabolic risk of women[14]. Estrogen promotes and maintains typical female fat by reducing the lipolysis of subcutaneous fat without affecting visceral fat[15]. Peripheral adipocytes exhibit a lower lipolytic response[16]. Heine *et al*[17] found that estrogen regulates the amount of adipose tissue. The absence of estrogen receptor α (ER α) causes adipocyte hyperplasia and hypertrophy. Postmenopausal women exhibit increased central fat deposition[18]. For a given waist circumference or body mass index, women have higher levels of subcutaneous adipose tissue than men[19]. Sex also influences lipid storage within the liver and muscle. Fat can be stored in adipose tissue, liver and skeletal muscle as triglycerides (TGs). Excessive liver TG storage leads to NAFLD. Studies have found that men have higher levels of TGs stored in the liver than women, and women store more intramyocellular lipids than men, which explains the higher prevalence of NAFLD in men[20,21]. Skeletal muscle is one of the major organs responsible for peripheral glucose disposal, and a higher intramyocellular lipid content is associated with insulin resistance, which decreases the skeletal muscle glucose uptake[22]. However, the increased levels of intramyocellular lipids in women are not related to a higher risk of diabetes, which may be related to the mechanism through which lipids are stored and metabolized in muscles[20].

Adipose tissue releases a multitude of secretory products, which are collectively called adipocytokines. The related sex differences are mainly reflected by the levels of leptin, adiponectin and prohibitin. Leptin is a metabolic regulator that can reduce food intake and inhibit the synthesis of lipids, and its secretion is proportional to the fat mass. However, in some cases, hyperleptinemia can lead to insulin resistance and participates in hepatic steatosis. Studies have repeatedly shown that adiponectin enhances insulin sensitivity and increases lipolysis, which is inversely correlated with the fat mass[23-25]. Many studies have proven that the levels of leptin and adiponectin in males are lower than those in females[26,27]. The serum leptin levels in men and women with NAFLD are higher than those in individuals without NAFLD, whereas the opposite trend has been found for adiponectin. A previous study showed that the leptin level is correlated with the severity of steatosis in men and women, whereas the serum adiponectin level is inversely correlated with the severity of steatosis in men ($P < 0.01$) but not in women ($P = 0.4$)[26]. Prohibitin plays a sex-dimorphic role in adipose tissue functions[28]. Its overexpression induces the upregulation of mitochondrial organisms, which leads to obesity and impairments in glucose homeostasis and insulin sensitivity, but this issue is specific to males.

The retention of TGs within the liver is a prerequisite for the development of NAFLD. The synthesis of fatty acids (FAs) in the liver is an important determinant of the development of hepatic steatosis[29]. The oxidation of FAs removes TGs from the liver[30]. To some extent, the occurrence of NAFLD depends on the imbalance between liver FA synthesis and oxidation. Individuals with a similar age, BMI, and liver fat content were assessed using metabolic substrates labeled with stable isotope tracers, and the results revealed clear differences in hepatic FA partitioning. Specifically, females tended to favor oxidation pathways, and increased levels of ^{13}C in breath CO_2 and plasma 3-hydroxybutyrate are found in females, whereas males tend to favor synthetic pathways. In both men ($r_s = 0.75$, $P < 0.05$) and women ($r_s = 0.79$, $P < 0.01$), de novo lipogenesis (DNL) is positively correlated with the plasma very low-density lipoprotein (VLDL) cholesterol concentration[31]. As many studies have revealed, premenopausal women have better lipid profiles than men, as demonstrated by higher high-density lipoprotein cholesterol levels and lower low-density lipoprotein cholesterol, VLDL cholesterol and total plasma TG levels[32,33]. The disposal of FAs *via* the oxidation pathway may play an important role in preventing the accumulation of TG in the liver, which may partially explain the sex difference in the prevalence of NAFLD.

In addition, glucocorticoids exert certain effects on the human body during the process of lipid metabolism. Excessive glucocorticoids are related to the pathogenesis of NAFLD, which can cause the decomposition of adipose tissue, hyperlipidemia, visceral fat generation and insulin resistance[34]. One study found hepatic steatosis in 20% of patients with Cushing's syndrome[35]. It is important to note that gender differences remain during the process. Among mice administered high levels of cortisol, male mice exhibit more severe insulin resistance, and female mice show more

protective adaptations to adipose tissue, such as increased adiponectin levels[36].

Estrogen and hepatic ER α

Based on the abovementioned differences in prevalence between men and women and the findings that women of postmenopausal age are at increased risk of developing NAFLD, that hormone replacement therapy is protective against NAFLD after menopause[13], and that women are at increased risk of developing NAFLD after using an anti-estrogen drug or undergoing surgical ovariectomy[37,38], we can assume that the resistance to NAFLD in premenopausal women depends on estrogen. A large number of studies have shown that estrogen regulates almost all steps of lipid metabolism. Estrogen reduces the lipolysis of subcutaneous adipocytes by upregulating α_2A -adrenergic receptors[15] and thereby reduce the delivery of FAs to the liver. Estrogen regulates liver lipid metabolism through ER α . Estrogen signaling reduces DNL to prevent hepatic steatosis. The lack of estrogen signaling will reduce the VLDL output, promote the accumulation of TGs in the liver, and lead to hepatic insulin resistance[39]. In female mammals, estrogen receptor is highly expressed in the liver, but this finding has rarely been observed in males. This receptor plays an important role in the regulation of the synthesis of receptors for cholesterol uptake, cholesterol transport proteins, and enzymes for lipoprotein remodeling[40]. A recent study found that hepatic ER α shows opposite lipid metabolism regulation in men and women that consume diets high in lipids: the male liver exceeds its compensatory capacity, and liver ER α promotes the accumulation of liver lipids by stimulating the input and synthesis of lipids. While the female liver can handle the excess lipids, and the ER α in the female liver is able to reduce lipid synthesis and absorption and promote FA oxidation[41]. In general, hepatic ER α plays an important role in the sex difference in NAFLD.

Androgen

Polycystic ovary syndrome (PCOS) is a female endocrine disease characterized by hyperandrogenemia. Many studies have documented a higher incidence of NAFLD in women with PCOS. However, only patients with PCOS and high androgen levels are associated with a higher risk of NAFLD[42]. It can be inferred that high androgen levels play an important role in this process. Biological studies have shown that androgen can induce cell cycle arrest and initiate hepatocyte apoptosis[43]. High androgen levels can promote inflammation by activating mononuclear cells[44]. Increased androgen levels increase the visceral fat mass by decreasing the activation of adenosine 5' and monophosphate-activated protein kinase and increasing the expression of lipogenic genes in visceral fat[45]. In men, however, decreased androgen levels are independently associated with NAFLD[46]. Low serum testosterone levels increase visceral fat accumulation and inflammation, and these effects lead to insulin resistance and hepatic steatosis[47-49]. Therefore, further studies may be needed to clarify the mechanism related to androgen and NAFLD.

Mitochondria and liver pyruvate kinase

Mitochondrial dysfunction contributes to the development of NAFLD, which predates insulin dysfunction and hepatic steatosis[50]. Exercise enhances mitochondrial function[51]. In general, females exhibited an improved mitochondrial quality than males. Men often need to exercise to maintain a stronger mitochondrial respiratory function, whereas women can maintain this function even without exercise[52]. A recent study reported a close relationship between liver pyruvate kinase (LPK) and NAFLD. As demonstrated by mouse experiments, LPK affects liver lipids, mitochondrial respiration, glucose metabolism and insulin sensitivity. LPK expression is increased in men under the influence of testosterone. LPK overexpression aggravates insulin resistance, increases the plasma cholesterol levels and exacerbates liver steatosis by changing liver mitochondrial respiration, whereas LPK silencing attenuates these effects. Studies have also found a positive correlation between hepatic LPK expression and the liver TG levels in males but not in females, which shows that LPK is only slightly involved in the development of steatosis in females. Researchers have performed liver biopsies in patients with NASH and observed a strong positive correlation between liver LPK expression and the NAFLD activity score in men but no correlation in women[53]. LPK overexpression exerts a male-specific effect on NAFLD.

Vitamin D deficiency

Vitamin D deficiency can increase hepatic fat accumulation and mildly reduce insulin sensitivity[54]. Studies have found that low serum levels of 25-hydroxyvitamin D are

associated with dyslipidemia and cardiovascular disease[55,56]. Vitamin D increases intestinal calcium absorption, and this finding is more obvious in males than in females[57]. Calcium supplements can improve blood lipids[58]. Estrogen can also affect calcium absorption[59]. A sex disparity has been found for the association of vitamin D deficiency with NAFLD. A cross-sectional study revealed that vitamin D deficiency is positively associated with NAFLD in men, whereas no significant interaction has been observed in women. Vitamin D deficiency is an independent risk factor for NAFLD in men and may be associated with testosterone levels[60]. Women may respond differently to vitamin D supplementation than men, and women show improvements in blood lipids in response to this supplementation[61].

Serum uric acid

Elevated serum uric acid (SUA) is a risk factor for NAFLD[62,63]. The mechanism may be related to the insulin resistance induced by high SUA levels[64]. According to basic studies, SUA can directly induce and regulate hepatic steatosis and stimulate hepatic fat accumulation[65-67]. Many population-based studies have revealed a sex difference in the association between SUA and NAFLD: The correlation between SUA and NAFLD is significantly higher in women than in men[68,69]. However, a study of patients with type 2 diabetes mellitus (T2DM) revealed that although SUA is associated with NAFLD, an increase in the SUA level is independently associated with a higher risk of NAFLD only in male patients[70]. Therefore, whether diabetes is one of the causes of the inconsistent results is worth further study.

Fructose and dietary intake, sleep quality and the gut microbiota

Regarding food choices, women tend to eat more fruits, vegetables and grains, whereas men tend to choose more meat products, eggs and certain types of poultry [71]. Studies have shown that women tend to eat better-quality diets. The negative correlation between diet quality and obesity is similar in both men and women[72]. However, the diet-induced increases in serum TGs are more significant in females[73]. With a high consumption of fructose, the role of fructose in inducing NAFLD has become increasingly important. Fructose can increase insulin resistance and induce an increase in plasma TGs. In a study of a high-fructose diet, female mice that were fed this diet for a long time showed extensive steatosis and ballooning, whereas males showed only a slight increase in hepatic steatosis[73]. These findings suggest that after the long-term consumption of high-fructose foods, women are more likely than men to develop NAFLD/NASH.

Poor sleep affects the production of hormones and increases the risk of metabolic syndrome. However, poor sleep quality can be more detrimental to women than men by increasing the risk of T2DM and cardiovascular disease, and this finding may be related to the higher testosterone levels in men and sex differences in peroxisome proliferator-activated receptor- α [74]. The sex differences in gut microbes may be influenced by age, race, and diet. Intestinal microbiota-dependent metabolites, such as short-chain fatty acids and trimethylamine *N*-oxide, are involved in the regulation of cholesterol metabolism and insulin sensitivity. Women are more vulnerable to adverse effects[75]. Bile acids are important signaling molecules that activate receptors such as farnesoid X receptor, and these receptors have been shown to promote hepatic steatosis[76]. Intestinal microorganisms can mediate the metabolism of bile acids. The gut microbiota differs according to sex, which leads to differences in the synthesis and metabolism of bile acids and other metabolites between males and females and thus affects the metabolism of liver fat[77].

PATHOPHYSIOLOGY

Hepatic fibrosis

NAFLD includes a spectrum of liver disorders consisting of nonalcoholic fatty liver and NASH, which range from simple hepatic steatosis to inflammation and fibrosis and even progress to cirrhosis. Hepatic stellate cells are one of the primary target cells of hepatic inflammatory stimulation and play a major role during liver repair reactions, including fibrosis[78]. In mice, estrogen inhibits the activation of stellate cells and suppresses the induction of hepatic fibrosis through estrogen receptors[79]. A cross-sectional study revealed that postmenopausal women and men are at a higher risk (60% to 70%) of developing severe fibrosis than premenopausal women. In postmenopausal women, estrogen replacement treatment appears to reduce the risk of advanced fibrosis[80]. A recent systematic review and meta-analysis of 62239

individuals also found that women have a lower risk of developing NAFLD than men pooled risk ratio (RR), 0.81; 95%CI, 0.68-0.97; $I^2 = 97.5\%$. However, after the development of NAFLD, women face a higher risk of developing advanced fibrosis than men (RR, 1.56; 95%CI, 1.36-1.80; $I^2 = 0$), and this finding is particularly obvious among individuals older than 50 years[81]. This finding suggests the protective effect of estrogen on hepatic fibrosis in patients with NASH, and the effect is more pronounced in patients with hepatitis C virus[82]. However, the severity of hepatocyte injury and inflammation in NAFLD shows the opposite trend. Premenopausal women exhibit increased levels of lobular inflammation, hepatocyte ballooning and Mallory-Denk bodies than men and postmenopausal women. Hormone replacement therapy is related to a risk of more severe hepatocyte inflammation in postmenopausal women [83]. This association may be related to an increase in the progesterone levels, but this hypothesis needs further study.

Branched-chain amino acids

Branched-chain amino acids (BCAAs) are amino acids with nonlinear aliphatic side chains and include the essential amino acids leucine, valine and isoleucine. High plasma BCAA levels may contribute to insulin resistance and increase the risks of metabolic syndrome and T2DM[84,85]. Intestinal microorganisms are also related to the synthesis of BCAAs[86]. The level of plasma BCAAs in patients with NAFLD is increased, and its changes show sex dimorphism. Studies have shown that the plasma BCAA concentration is positively correlated with the severity of NAFLD[87]. However, a recent study found that only the female BCAA concentration is positively associated with the level of steatosis and fibrosis in NAFLD, whereas no correlation has been detected in males, as demonstrated by a moderate negative correlation between the plasma valine level and lobular inflammation. Additionally, menopause alone has no significant effect on the plasma BCAA concentration in NAFLD[88]. The mechanism of BCAAs involved in NAFLD remains unclear. BCAAs are associated with activation of the mammalian target of rapamycin pathway and liver injury in mice[89-91]. However, BCAA supplementing can reduce further liver injury in patients with liver cirrhosis[92].

Macrophages and inflammation

A large number of experimental and clinical studies have shown that macrophages play a critical role in the development and progression of NAFLD. Liver-resident macrophages, which are also known as Kupffer cells, are important participants in liver metabolism disorders and inflammation. These cells activate the inflammatory response, recruit monocytes into the liver, and then differentiate into proinflammatory macrophages to promote the development of NAFLD. Kupffer cells are closely associated with insulin resistance, FA accumulation, and inflammatory injury to promote the progression of fibrosis[93]. High fructose intake triggers the activation of Kupffer cells, which leads to an inflammatory response. As mentioned above, fructose plays an important role in inducing NAFLD. The main types of macrophages can be divided into proinflammatory and anti-inflammatory subgroups (M1 and M2), and both estrogen and androgen receptors can be found in murine macrophages and promote M2 phenotype differentiation[94]. The effect of sex on the differentiation of hepatic macrophages in patients with NAFLD has not been reported. However, accumulating evidence shows that testosterone reduces the secretion of proinflammatory cytokines by macrophages and exerts anti-inflammatory effects[95].

COMPLICATIONS

HCC

HCC is the fourth leading cause of cancer-related death worldwide, and its morbidity and mortality rates are both increasing[96,97]. With improvements in the prevention, diagnosis and treatment of viral hepatitis, the proportion of end-stage liver disease caused by NAFLD progression is increasing. NAFLD is the most common cause of chronic liver disease in the world. HCC is one of the major complications of NASH-associated cirrhosis[98]. NASH-related liver disease has become the leading indicator of liver transplantation (LT)[99]. The incidence of liver cancer in males is significantly higher than that in females. Premenopausal women are also at a lower risk of NAFLD than men. Some studies have found that estrogen may prevent the occurrence of liver cancer and can play a beneficial biological role once HCC develops[100]. Among patients with nonsurgical liver cancer and patients undergoing surgical resection, the

prognosis of women is better than that of men[101,102], but the benefits from LT in patients exhibit no significant gender differences[101]. Moreover, under the current organ allocation system, the proportion of women who receive a LT is lower than that of men. The explanations of this sex difference in LT may include size mismatch and lower creatinine levels in women, which leads to lower Model for End-Stage Liver Disease scores[103,104].

Cardiovascular disease

An increasing number of studies have shown that NAFLD can increase the incidence and prevalence of cardiovascular disease (CVD). In addition, the incidence of CVD presents a sex difference similar to that of NAFLD: Men younger than 50 years are at a higher risk of developing CVD than women, but the incidence of CVD in postmenopausal women is higher[105]. Women are also at a lower risk of death from CVD than men[106]. As mentioned above, women exhibit better blood lipid values than men, and men with NAFLD have worse TG and high-density lipoprotein levels than women[107]. In addition, the incidence of other cardiovascular risk factors in patients with NASH, such as hypertension, renal failure and smoking, is lower in women than in men. Women are more likely to develop obesity and diabetes. A retrospective observational cohort study of 41005 adult patients with NASH conducted by Gayatri Pemmasani found that males have a higher incidence of most CVDs, such as coronary artery disease, myocardial infarction, and heart failure, than females[108]. However, another previous study showed that women with NAFLD lose the protective effect that women have against cardiovascular disease[109]. These researchers found that women and men with NAFLD have a similar risk of CVD and that women with NAFLD develop CVD earlier than women without NAFLD. This finding may be due to the high metabolic burden of patients with NAFLD because these metabolites neutralize the protective effect of estrogen.

T2DM

NAFLD is associated with an increased risk of T2DM, is involved in the pathogenesis of T2DM and promotes insulin resistance. Obesity is a risk factor for NAFLD and T2DM. However, a recent study obtained a novel finding that NAFLD has a hazard ratio of 2.331 for the incidence of diabetes. Among lean patients with NAFLD, the effect appeared to be more pronounced in women, particularly postmenopausal women, than in men (5.53 *vs* 2.02)[110]. A study conducted in Japan also showed that the female sex is an independent risk factor for T2DM through the follow-up of patients diagnosed with NAFLD[111].

Others

A previous study showed that the serum insulin levels are directly correlated with a higher risk of colorectal adenomas (OR, 1.5; 95%CI, 1.1-2.0; $P = 0.005$) and hyperplastic polyps (OR, 1.3; 95%CI, 1.0-1.7; $P = 0.075$)[112]. Disorders of insulin and adipocytokine metabolism are now thought to influence the development of colon tumors[113]. Patients with NAFLD always show fat metabolism disorders, insulin resistance, and high insulin levels. A large number of studies have shown that NAFLD is a risk factor for adenomatous polyps and hyperplastic polyps[114,115]. However, the correlation exhibits significant sex differences: NAFLD is associated with an increased risk of colorectal adenomatous and hyperplastic polyps in men (OR = 1.53, 95%CI: 1.18-2.00, $P < 0.05$; OR = 1.42, 95%CI: 1.04-1.95, $P < 0.05$) but is not a significant risk factor in women (OR = 0.44, 95%CI: 0.18-1.04, $P > 0.05$; OR = 1.18, 95%CI: 0.50-2.78, $P > 0.05$)[115]. The promoting mechanism of NAFLD on colorectal adenoma and hyperplastic polyps is unclear, but some researches believe that this mechanism may be related to the metabolic disorder of adipocytes and the effect of inflammatory cytokines[113]; thus hypothesis needs further exploration.

Abdominal obesity and insulin resistance are risk factors for erosive esophagitis (EO). Metabolic syndrome (MS) and NAFLD are significantly associated with EO. A previous study revealed significant sex differences in the effects of NAFLD and MS on EO: MS (OR 1.26; 95%CI 1.09 to 1.45) shows a greater detrimental effect on EO in males, NAFLD (OR 1.93; 95%CI 1.43 to 2.59) is significantly associated with EO in females, and the relationship between NAFLD and EO is stronger in premenopausal females than in postmenopausal females (51.1% *vs* 48.9%)[116]. In addition, MS is independently associated with EO through increased serum cytokines. Men exhibit increased visceral obesity deposition than women, and visceral obesity increases the esophageal reflux by increasing the serum cytokine levels[117]. The sex difference between NAFLD and EO may be related to estrogen, which reduces oxidative stress

and serum cytokines. Hence, the decrease in estrogen levels found in female patients with NAFLD leads to a decrease in the protective effect on EO.

THERAPY

Very low-carbohydrate ketogenic diets

Obesity is a risk factor for NAFLD. Very low-carbohydrate ketogenic diets (VLCKDs) constitute a new treatment for obesity that functions by reducing the caloric intake and promoting the transformation of energy metabolism from carbohydrates to TGs to reduce weight. Previous studies have suggested that VLCKDs are associated with inducing the activity of lysosomal acid lipase and improving hepatic steatosis, which can benefit patients with NAFLD[118]. Studies have shown that men benefit more from this therapy than women, particularly premenopausal women[119]. This finding may be related to the fact that men have more visceral adipose tissue and exhibit a higher basal energy expenditure.

Inhibition of protein tyrosine phosphatase 1B

Protein tyrosine phosphatase 1B (PTP1B) is an enzyme with multiple functions that can inhibit leptin and insulin signal transduction, which results in abnormal glucose tolerance and hepatic steatosis. PTP1B inhibition may be a potential weight loss therapy that increases energy consumption, weight loss and insulin sensitivity[120]. A study of the role of proopiomelanocortin neuronal-specific PTP1B deficiency in metabolic regulation after consumption of a high-fat diet found that male but not female mice fed this diet exhibit significantly reduced liver lipid accumulation than control mice[121]. This result may indicate that PTP1B is a potential target in the treatment of NAFLD in men.

Others

At present, the treatment of NAFLD remains focused on prevention, as reflected by the control of risk factors, such as weight loss, reduced fat and fructose intake, increased exercise, and vitamin D supplementation. Men lose weight mainly by reducing their visceral adipose tissue and exhibit better histological improvement than women[122,123]. Women are more affected by dietary factors than men. Reducing lipid and fructose intake is more beneficial for female patients. Physical activities are beneficial to the prevention of NAFLD, and exercise can reduce liver enzymes in postmenopausal women[124]. Vitamin D deficiency is an independent risk factor for NAFLD in men, and men should be screened early and administered timely supplementation. Therefore, the optimal prevention of NAFLD may differ by sex, but no consensus has been reached, and further exploration is still needed.

CONCLUSION

As mentioned above, NAFLD exhibits significant sex dimorphism in many aspects, particularly in influencing factors, pathophysiology (Figure 1) and intrahepatic and extrahepatic damage (Figure 2). In general, the higher incidence among males than females is related to adipose distribution, adipose metabolism, differences in estrogen and its receptors, liver metabolism and other factors. The protective effects of estrogen reduce the degree of liver fibrosis in women. Robust evidence shows that NAFLD is closely associated with liver cancer, cardiovascular disease, T2DM and other diseases, and men with NAFLD are at a higher risk of experiencing these complications than women. However, once NAFLD occurs, the inflammation and disease progression is markedly worse among female than male patients, and the treatments for females are more limited than those for men. Although we found a large number of sex differences in NAFLD, the relevant principles are unclear, and further research is needed. Whether sex differences should be considered in future research and whether they can be applied to clinical personalized treatment and prevention are still worth exploring.

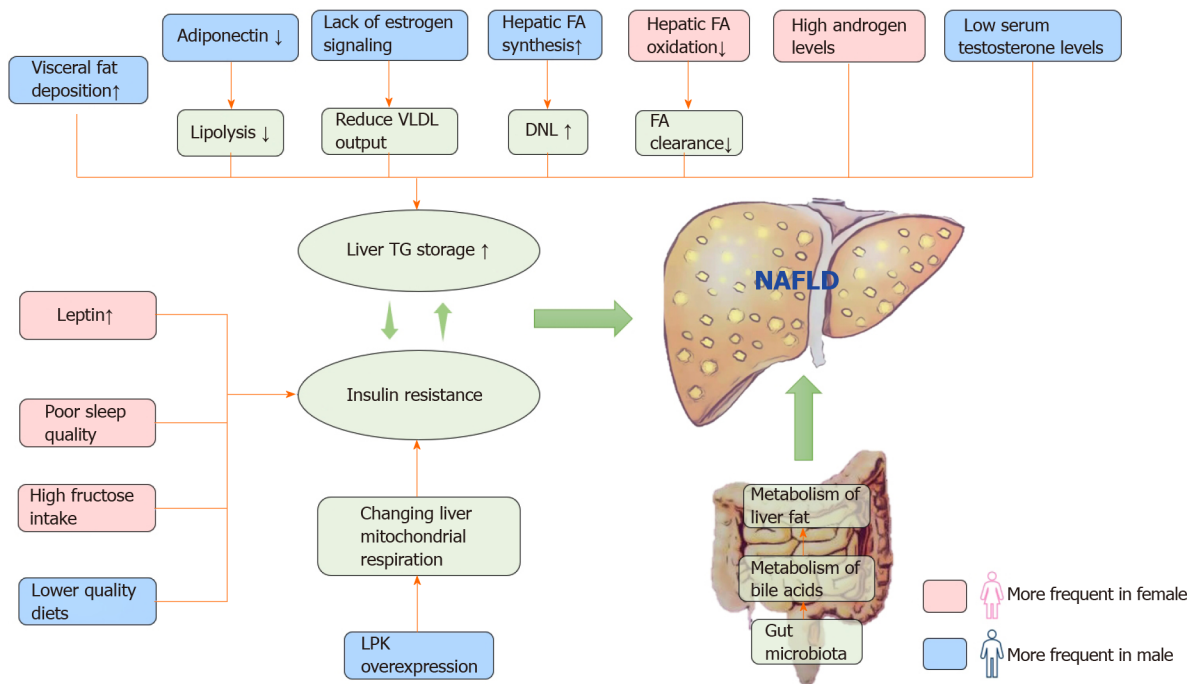


Figure 1 Overview of sex differences in etiology and pathogenesis of nonalcoholic fatty liver disease. Men store more visceral adipose tissue than women. Adipokines mediate fat metabolism, and adiponectin can increase lipolysis; however, excessive leptin can lead to insulin resistance and steatosis. The estrogen receptor plays an important role in the regulation of fat metabolism. Increased androgen levels in women and low testosterone in men are prone to visceral fat accumulation. In the process of fatty acid metabolism, men tend to synthesize, and women tend to oxidize. We found that the overexpression of liver pyruvate kinase can lead to changes in liver mitochondrial function, which leads to the deformation of liver fat. The difference in intestinal microflora between men and women also plays a role in the sex difference in nonalcoholic fatty liver disease (NAFLD). In addition, sleep quality, high sugar intake and diet quality can also affect the formation of NAFLD. VLDL: Very low-density lipoprotein; DNL: De novo lipogenesis; TG: Triglyceride; LPK: Liver pyruvate kinase; FA: Fatty acid; NAFLD: Nonalcoholic fatty liver disease.

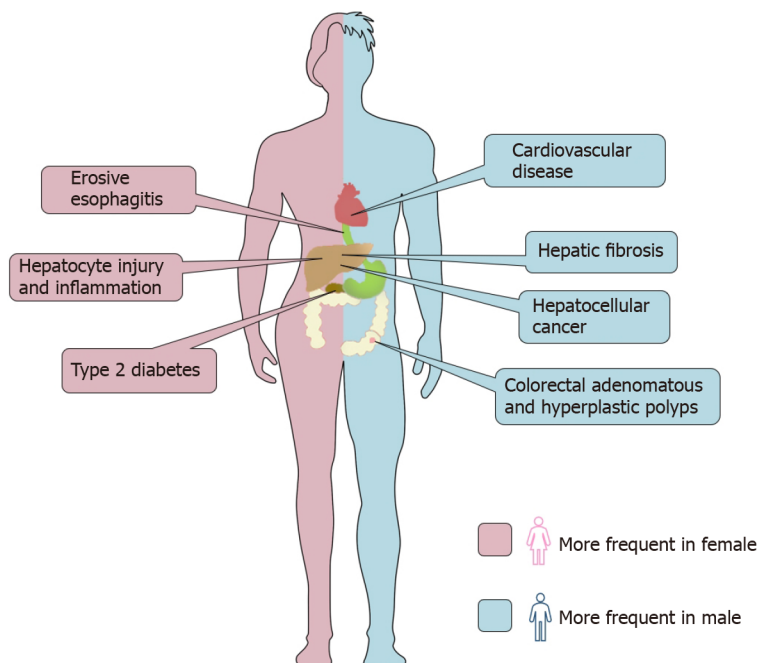


Figure 2 Sex differences in intrahepatic and extrahepatic outcomes in nonalcoholic fatty liver disease. As a metabolic disorder, nonalcoholic fatty liver disease (NAFLD) is related not only to liver injury but also to a variety of extrahepatic diseases. The picture summarizes the differences between men and women in this respect. Without the protection of estrogen, men have more serious liver fibrosis than women and are more likely to develop liver cancer. The incidence of cardiovascular events and colorectal adenoma in men with NAFLD is higher than that in women. However, female patients have more severe hepatocyte injury and inflammation than male patients and have a higher risk of erosive esophagitis and type 2 diabetes.

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