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doi: 10.53388/ghr2022-06-049

SPECIAL ISSUE

Research progress on the correlation between metabolic-associated fatty liver disease and cardiovascular disease

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Abstract:
Metabolisc-associated fatty liver disease (MAFLD) is a multi-system disease in which cardiovascular disease plays an important role and is considered the main cause of death. Notably, cardiovascular disease events in young patients with MAFLD have attracted extensive attention. This article reviews the research progress on the correlation between MAFLD and cardiovascular disease.

Key Words: non-alcoholic fatty liver disease, metabolic-associated fatty liver disease, extrahepatic complications, cardiovascular disease

***Acknowledgments*:** Thanks the editage for polishing the language of the manuscript.

***Abbreviations*:** MAFLD, metabolisc-associated fatty liver disease; CVD, cardiovascular disease; NAFLD, non-alcoholic fatty liver disease; MASH, metabolism-related steatohepatitis; OR, odds ratio; FRS, framingham risk; IR, insulin resistance; EFT, epicardial fat thickness; ALT, alanine aminotransferase; CIMT, carotid intima-media thickness; AAC, abdominal aorta calcification; CAVI, cardio ankle vascular index; baPWV, brachial ankle pulse wave velocity; TLR, the Toll-like receptor; AngII, angiotensin II; oxLDL, oxidized low-density lipoprotein; GPCR, G protein-coupled receptor; olfr78, olfactory receptor 78; NO, nitric oxide; FFA, free fatty acid.

***Authors' Contributions*:** Zhao-Chun Chi proposed the idea of the paper and wrote the manuscript.

***Competing interests*:** The author declares no competing interests.

***Citation*:** Chi ZC. Research progress on the correlation between metabolic-associated fatty liver disease and cardiovascular disease. *Gastroenterol Hepatol Res*. 2022;4(2):7. doi: 10.53388/ghr2022-6-049.

***Executive Editor*:** Ming-Zhong Xiao.

***Submitted*:** 14 March 2022, ***Accepted*:** 20 April 2022, ***Published*:** 30 June 2022

doi: 10.53388/ghr2022-04-049

1.Significance of the new name and definition of non-alcoholic fatty liver disease

Since Ludwig et al. conceptualized the term "non-alcoholic fatty liver disease" (NAFLD) in 1980, it has been used for 40 years [1]. Through clinical practice and research, this term was found to have many shortcomings and deficiencies. Therefore, to solve a series of problems caused by the issues with the naming and typing of NAFLD, in February 2020, an international expert group composed of 30 experts from 22 countries renamed "non-alcoholic fatty liver disease" to "metabolic-associated fatty liver disease" Experts agree that NAFLD does not reflect the current knowledge and that MAFLD is a more appropriate omnibus term [2]. This allows research groups to update the naming and subphenotypic typing of diseases, thereby accelerating the transformation path to new treatments. This new definition is a positive diagnostic criterion that lists metabolic dysfunction as an important cause of liver disease, which can better define the population of patients with MAFLD and contribute to the disease classification of patients. This demonstrates the high heterogeneity of MAFLD and puts forward clinical research countermeasures for new drug research and development of metabolism-related steatohepatitis (MASH) and noninvasive diagnosis of liver fibrosis. The expected benefits of the revised name are comparable to those of previous recommendations. First, the shift to the inclusive diagnostic criteria, i.e., the presence of metabolic dysfunction rather than the absence of other diseases, better reflects our understanding of the potential metabolic dysfunction that primarily drives MAFLD. Second, this term is expected to better define the number of patients with MAFLD to improve the classification of patients and pave the way for personalized medicine and improved clinical trials. Third, this definition does not mention alcohol, avoiding the competition between the diagnosis of alcoholic liver disease and MAFLD and reducing the risk of humiliating patients [3]. The advent of MAFLD will provide improved understanding of the disease and new treatment strategies.

2. MAFLD is a multi-system disease

The global prevalence of MAFLD is approximately 25.2% and is concentrated in Western countries. Africa has the lowest prevalence of MAFLD, whereas China has a prevalence of 29.2%. Recent in-depth study and understanding of MAFLD has been found that the extrahepatic complication of MAFLD is a multi-system disease that affects various extrahepatic organ systems [4,5]. Moreover, accumulating evidence suggests that MAFLD is related to extrahepatic diseases in young people such as CVD, type 2 diabetes, decreased bone mineral density, renal insufficiency, obstructive sleep apnea, and polycystic ovary syndrome [6-8].

Although MAFLD affects a large proportion of the population, only few cases of advanced liver disease or liver-related diseases can lead to death. In fact, the main cause of death in patients with MAFLD is CVD, followed by extrahepatic malignant tumors and liver-related death [9].

Recent studies have focused on the pathological correlation unrelated to metabolic diseases, including various systemic diseases, such as hypothyroidism, psoriasis, male sexual dysfunction, periodontitis, and urolithiasis. Therefore, clinicians should learn to screen and treat these extrahepatic manifestations to provide appropriate multidisciplinary assessment and strict monitoring [10].

3. MAFLD and CVD risk

CVD is the main cause of death in patients with MAFLD. It usually presents with classic risk factors for CVD including insulin resistance, hypertension, atherosclerotic dyslipidemia, and obesity [11]. In addition to these common CVD risk factors and metabolic-related fatty liver disease, data on patients with metabolic-related fatty liver disease also identified many non-traditional and emerging CVD risk factors, including pro-inflammatory cytokines (L1-6, PCR, and TNF-α), procoagulant factors (fibrinogen, plasminogen, and vascular adhesion molecules), and hyperuricemia [12,13].

Serum L-γ-glutamyltransferase (L-γ-glutamyl transferase glutamyl [γ-GGT]) is one of the main markers of MAFLD. It is also associated with CVD and stroke, even in patients with a low-to-moderate cardiovascular risk. γ-GGT has been isolated from atherosclerotic plaque and seemingly directly promotes the progression of atherosclerotic lesions by inducing oxidative stress [14].

In a recent meta-analysis of 16 studies, 34,043 adult individuals showed a higher cardiovascular risk following the use of MAFLD definition compared with NAFLD definition. During a mean follow-up period of 6.9 years, the total odds ratio (OR) was higher in patients with MAFLD than in control patients (1.64 vs. 2.58) [15].

In addition, regarding CVD mortality, a study of 229 patients with biopsy-confirmed MAFLD with an average follow-up of 26.4 years showed that the risk of death from CVD and liver-related diseases was higher than that in the reference population [16]. Finally, a recent multinational study of 458 patients reported that the CVD-related mortality of patients with MAFLD with bridging fibrosis was higher than that of cirrhotic patients, with the main cause of death in cirrhotic patients being liver-related events [17].

Regarding CVD events, epidemiological studies

have indicated that there is an association between MAFLD and risk of cardiovascular events. In a study on 17,350 participants without known liver disease or heavy alcohol consumption, ultrasonography showed the association of MAFLD with an increased 10-year risk of CVD, as estimated using the Framingham risk (FRS) score, independent of classic risk factors, and other components of metabolic syndrome. After controlling for age, sex, BMI, waist circumference, and individual composition of metabolic syndrome, the OR of MAFLD was 1.35 [95% confidence interval (CI), 1.10–1.65]. In the multivariable model, FRS was >20%, and 10-year CVD risk increased by 1.35 (95% CI, 1.10–1.65). A recent meta-analysis including 34,043 adults showed that MAFLD significantly increased the risk of fatal and/or non-fatal CVD events during a median follow-up of 6.9 years, with a random effect of 1.64 (95% CI, 1.26–3.75). Patients with MAFLD were more likely to develop fatal and non-fatal CVD events than controls (OR, 2.58; 95% CI, 1.78–3.75).

In conclusion, patients with MAFLD have a high risk of CVD, including carotid and coronary atherosclerosis, which is beyond the interpretation of classic cardiovascular risk factors, visceral obesity, and metabolic syndrome. Therefore, patients with MAFLD require careful cardiovascular monitoring. Moreover, those with severer forms of MAFLD need special attention to improve their risk of CVD death.

4. MAFLD and cardiac dysfunction (cardiomyopathy and arrhythmia)

In addition to the increasing evidence that MAFLD has adverse effects on coronary atherosclerosis, this multi-system disease seemingly affects all other anatomical structures of the heart, thereby increasing the risk of cardiomyopathy, cardiac valve calcification, and arrhythmias [18].

Several small studies have shown a significant correlation between MAFLD and impaired diastolic function.

In a recent cross-sectional study of 2,713 middle-aged asymptomatic adults, MAFLD was found to be closely related to subclinical myocardial remodeling and dysfunction [19]. In a recent case–control study of 308 patients with MAFLD, hepatic fibrosis (assessed by transient elastography) and steatosis (assessed by controlled attenuation parameter) were found to be related to large left atrial volume, and left ventricular diastolic dysfunction was independently associated with lower myocardial glucose intake, as assessed by fluorodeoxyglucose positron emission tomography [20]. Similarly, other studies on patients with MAFLD confirmed by biopsy have reported a hierarchical relationship between myocardial dysfunction and histological severity of MAFLD, indicating that, since the changes in myocardial tissue occur long before the occurrence of liver cirrhosis, these changes may not be the direct consequence of portal hypertension [21,22]. Subsequently, in a study of 1,058 patients with heart failure with an average follow-up of 3 years, MAFLD severity, as assessed by the fiber biopsy-4 score, was independently associated with left ventricular diastolic dysfunction, larger atrial volume, and higher all-cause mortality [23]. Some studies have emphasized that the relationship between metabolic fatty liver disease and aortic valve sclerosis and mitral annulus calcification is independent of various cardiac metabolic risk factors that are associated with adverse cardiovascular outcomes and arrhythmias [24].

Atrial fibrillation (AF) is the most common persistent arrhythmia, consistent with some large-scale studies.

It has been demonstrated that MAFLD is independently associated with an increased risk of AF [25]. The risk of the 702 patients with type 2 diabetes in the reported cohort of patients with MAFLD was 3.04 times higher than that in patients with MAFLD without diabetes. In a subsequent prospective study, investigators followed a group of patients with type 2 diabetes mellitus for 10 years, and the risk and incidence of MAFLD and AF increased four-fold [26]. On the same topic, a recent meta-analysis of five cohort studies (238,129 participants) showed that the prevalence and incidence of AF almost doubled [27].

Chang et al.[28] recently conducted a cross-sectional study to evaluate the effects of alcohol consumption and metabolic status in 105,328 participants.

Correlation between coronary artery calcification (CAC) score and fatty liver disease (FLED)

Studies have shown that alcoholic liver disease and MAFLD are associated with elevated CAC scores. They also found that the insulin resistance (IR) index is a robust and independent predictor of the CAC score, even after controlling for traditional CV risk factors, MetS, and C-reactive protein. Wolff et al.[29] evaluated the data of 2,351 participants from the population-based Rotterdam study and proved that the liver

Increased proportions of fat have been associated with increased epicardial fat thickness (EFT) and CAC, independent of traditional CV risk factors. In contrast, Kim et al.[30] performed a cross-sectional analysis of 2,238 patients.

Jung et al.[31] aimed to study liver fat and serum alanine aminotransferase (ALT) levels in 1,218 participants.

Cross-sectional study on the relationship between ALT and CAC scores

Results have suggested that participants with hepatic steatosis and elevated ALT levels had higher CAC scores. In patients with MAFLD, higher CAC scores are independently associated with liver hardness values assessed using transient elastography. The incidence of

doi: 10.53388/ghr2022-04-049

increased CAC, hypertension, aortic valve sclerosis, diastolic dysfunction, atherosclerotic plaque, and carotid intima-media thickness (CIMT) in patients with MAFLD was higher than that in patients without MAFLD [32]. Perera et al.[33] noted that 46.7% of patients with acute coronary syndrome had MAFLD.

MAFLD and carotid artery disease

CIMT, MAFLD, subclinical atherosclerosis, and myocardial infarction

MAFLD is independently associated with stroke. Kim et al.[34] studied the relationship between atherosclerotic diseases and sex differences in patients with FLD and concluded that its prevalence and that of carotid plaque in men was higher than that in women. IR possibly mediates metabolic abnormalities and subclinical atherosclerosis in women. Li et al.[35] recently conducted a study on 1,007 postmenopausal women and demonstrated that MAFLD is associated with an increased risk of arterial stiffness in postmenopausal women without MetS. Improvements in MAFLD severity, as assessed using magnetic resonance spectroscopy and serum cytokeratin-18, a marker of liver necrosis inflammation, were associated with decreased CIMT progression.

Changes in cardiac structure and function in patients with MAFLD

Currently, most studies have reported that MAFLD is associated with changes in left ventricular function and structure, even after correction.

There was still a significant correlation between CV and metabolic risk factors. In non-morbidly obese, hypertensive, diabetes patients with MAFLD, there are still early characteristics of mild left ventricular geometric changes and left ventricular diastolic dysfunction. Subclinical cardiac insufficiency has also been observed in asymptomatic patients with MAFLD. There is reportedly a strong positive correlation between the amount of liver fat, diastolic dysfunction, and IR, which is the only independent parameter related to MAFLD found in this study. Petta et al.[36] studied the data of 147 patients with biopsy-confirmed MAFLD to assess the severity of liver fibrosis and cardiac complications. Several cardiac structural changes related to severe liver fibrosis, including diastolic wall thickness, left ventricular mass, relative wall thickness, left atrial volume, left ventricular diastolic dysfunction, ejection fraction, lower tissue Doppler imaging peak velocity (E 'value) and peak gravity flow ratio of mitral annulus in early diastole, and peak velocity (e/a ratio) from early diastole (E wave) to late diastole (a wave) caused by atrial contraction, were reported. After evaluating the integrity of coronary microvascular circulation, it was concluded that the coronary flow reserve of patients with MAFLD was still lower than that of healthy controls, even after adjusting for obesity, traditional CV risk factors, and MetS. O ğ et al.[37] conducted a cross-sectional study and concluded that EFT and osteoprotegerin levels increased in patients with MAFLD compared with values in controls, resulting in decreased aortic blood flow propagation velocity. Another study comprising 868 subjects from the plic study conducted by Baragetti et al.[38] revealed that liver steatosis and EFT are related to increased incidence of extracardiac plaque.

MAFLD and subclinical atherosclerosis

MAFLD accelerates the development of atherosclerosis as demonstrated by the CAC score. The hardening load is an alternative and independent indicator of CHD risk. One study analyzed data from 10,153 professionals who underwent abdominal ultrasonography to assess fatty liver and cardiac computed tomography (CT) CAC scores. Fatty liver was associated with a CAC score of >0, but not with all MetS characteristics (OR = 1.21; 95% CI: 1.01–1.45) [39]. A positive correlation was observed between the ultrasonic diagnosis of hepatic steatosis and CAC, as quantified by electron beam tomography. The prevalence of CAC was higher in patients with hepatic steatosis (52% vs. 37%, P = 0.001). Another coronary artery risk development study comprising 2,424 young participants used CT to quantify liver fat. Moreover, the prevalence of CAC (37.9% vs. 26.0%, P < 0.001) and abdominal aorta calcification (AAC) (65.1% vs. 49.9%, P < 0.001) was higher in patients with MAFLD than in controls. The relationship between MAFLD, CAC, and AAC persisted after adjusting for demographic and health behaviors. However, after adjusting for visceral adipose tissue, this association was not statistically significant. Ultrasound-measured CIMT is a marker of subclinical atherosclerosis. CIMT is a powerful indicator of future vascular events. Compared with myocardial infarction, it can better predict the risk of stroke. Logistic regression analysis showed that MAFLD increased the probability of CIMT elevation by 35%, independent of conventional risk factors and the presence of MetS [40]. A larger meta-analysis included 4 studies [68] comprising 1,947 patients; of these patients, 35.1% of patients with MAFLD had pathological CIMT compared with 21.8% patients without MAFLD (P < 0.0001) [41].

The cardio ankle vascular index (CAVI) represents whole arterial segment stiffness CAVI reflects the progression of atherosclerosis and is positively correlated with its severity of coronary atherosclerosis. It also predicts carotid atherosclerosis and stroke. In a cross-sectional analysis of 2,954 participants, MAFLD has been associated with a 42% increased risk of atherosclerosis. The risk of arterial stiffness increases with disease severity. After adjusting for other risk factors, including body mass index, waist

circumference, smoking status, diabetes, and hypertension, a significant correlation was observed [42].

Another measure of arterial stiffness is brachial ankle pulse wave velocity (baPWV). A prospective study included 728 men and 497 women without hypertension or diabetes. During the 5-year follow-up, the change in baPWV in the MAFLD group was significantly greater than that in the MAFLD group [43]. Multiple linear logistic regression analysis showed that MAFLD was positively and independently correlated with baPWV [44].

MAFLD and hypertension

Intestinal flora and hypertension

It has been recognized that the excessive growth of intestinal flora, increased permeability of intestinal mucosa, enterogenous endotoxemia, and production of inflammatory factors caused by intestinal microecological imbalance play crucial roles in the occurrence and development of MAFLD. Studies have shown that correcting intestinal flora imbalance can improve IR, reduce weight, improve diabetes, and improve inflammation in patients with MAFLD. Studies have shown that changes in intestinal microbial composition play important roles in the occurrence and development of NAFLD. Intestinal microbes can not only affect the energy balance of the host by regulating the genes related to fat absorption and storage but also lead to an increase in endotoxin levels in the host circulatory system, induce chronic and low-level inflammation, and lead to obesity and IR. Intestinal microorganisms can cause NAFLD through various mechanisms. Recently, it has been proposed that the gut–liver axis is the key mechanism of obesity and NAFLD. Moreover, NAFLD caused by intestinal microorganisms is a result of a complex action of multiple factors, including metabolic endotoxemia, low-grade inflammation, imbalance of energy regulation, regulation of endogenous cannabinoid-like systems, regulation of choline metabolism, regulation of bile acid balance, increases in endogenous ethanol production, and overgrowth of intestinal bacteria. Intestinal microbes cause liver fibrosis by stimulating the Toll-like receptor (TLR)-9-dependent pre-fibrosis pathway in hepatocytes. Intestinal microbes cause intestinal inflammation and intestinal mucosal barrier dysfunction in patients with liver disease. Intestinal bacteria are also key factors in IR, type 2 diabetes, and cardiovascular development [45,46].

Hypertension is another important risk factor for CVD induced by genetic and environmental factors. In view of the increasing recognition of the role of intestinal flora in patients with metabolic diseases [47], the relationship between intestinal flora and hypertension has also been evaluated in recent years. In spontaneously hypertensive rats, Yang et al.[48] found that microbial abundance and diversity were significantly reduced and that the proportion of firmicum/Bacteroides increased. In another study, GF mice injected with angiotensin II (AngII) showed a decreased response to elevated blood pressure of AngII compared with that in conventionally fed mice, indicating that the intestinal microbiota promoted AngII-induced vascular dysfunction and hypertension. Therefore, intestinal microbiota may be related to hypertension. Although the relationship and mechanism between intestinal flora and hypertension have not been fully elucidated, existing evidence highlights the key roles of critical fatty acids and oxidized low-density lipoprotein (oxLDL) in patients with hypertension.

Short-chain fatty acids (SCFAs) and hypertension

SCFAs (such as acetic acid, propionic acid, and butyric acid) from dietary fiber (mainly polysaccharides) play key roles in maintaining the homeostasis of the intestinal microbiota and host immunity [49]. Bacteria that metabolize polysaccharides into different types of SCFAs are unique. For example, the main acetic acid producing bacteria are Streptococcus, Prevotella, Bifidobacterium, Clostridium, Myxobacterium, etc [50]. Propionate is produced through carbohydrate fermentation by Bacteroides, Salmonella, *Streptococcus dienes*, Vickers, chicory bryomyces, *Coptis carlesii*, appendiceae, etc,[51] whereas butyrate is produced by Spirulinaceae, Ruminococcaceae, and Aminococcaceae. A recent study found that fiber and acetate supplementation improved the imbalance of intestinal flora, which is related to the increase in acidophiles and may play a protective role against hypertension and heart failure in hypertensive mice [52].

Currently, at least three host G protein-coupled receptors have been regulated by SCFA, including G protein-coupled receptor (GPCR) 41, gpr43, and GPR109A. SCFAs can stimulate the regulatory pathway of host GPCRs, leading to renin secretion and thus affecting blood pressure. SCFAs can reduce blood pressure by regulating endothelial cell gpr41 [53]. Olfactory receptor 78 (olfr78) is another GPCR expressed in the kidney that can also be regulated by SCFAs, including acetate and propionate. Moreover, both olfr78 and gpr41 were expressed in the smooth muscle cells of small resistance vessels. Propionate can induce vasodilation and acute hypotension in mice by regulating the activity of olfr78 and gpr41 [54]. In contrast, gpr41 stimulation can reduce the response to hypotension, whereas stimulation with olfr78 can antagonize this effect [55]. In conclusion, although these findings reveal that intestinal microbiota may play an important role in regulating host blood pressure through the production of microbial SCFAs, the potential of SCFAs as a therapeutic target for CVD needs to be confirmed in future studies.

doi: 10.53388/ghr2022-04-049

oxLDL and hypertension

Generally, in addition to the regulation of various receptors, intestinal diseases also contribute to the occurrence of hypertension through oxidative LDL-mediated vasoconstriction. An intestinal microbial imbalance can promote the expression of pro-inflammatory cytokines and induce oxidative stress, which can stimulate oxLDL. Higher levels of oxLDL contribute to hypertension by inhibiting the production of nitric oxide (NO) and endothelin. NO is a good vasodilator produced by the oxidation of L-arginine by NO synthase. oxLDL decreases the production of NO and degree of vasodilation. In addition, endothelin-1 plays a key role in maintaining basic vascular tone and cardiovascular system homeostasis. Endothelin-1 can produce vasodilation at low concentrations by activating endothelial receptor B and promoting the production of NO, but it can increase the production of oxLDL in plaque and activate endothelial receptor A at high concentrations [56].

Although the causal relationship between intestinal flora disorders and hypertension has been confirmed [57,58], the exact role of intestinal flora in mediating hypertension requires further extensive research.

MAFLD and atherosclerotic CVD

Many epidemiological studies have shown that MAFLD is associated with an increased risk of CVD.

MAFLD and arterial porridge

The incidence of sclerosing CVD (CHD, ischemic stroke, and cerebral hemorrhage) was reportedly higher in the MAFLD group than in the non-MAFLD group. Multivariate analysis revealed that MAFLD was an independent predictor of CVD.

In multiple regression analysis, MAFLD was the only independent factor influencing the coronary artery disease (CAD) severity score [59].

Univariate analysis showed that the presence of MAFLD had an independent effect on CAD (OR, 2.58; $P < 0.01$) and Gensini score (OR, 2.02; $P < 0.05$). Sun et al.[60] included 542 patients who planned to undergo coronary angiography, and MAFLD was examined using abdominal CT before coronary angiography. Logistic regression analysis showed that the presence of MAFLD independently increased the risk of CHD on coronary angiography (OR, 7.585; 95% CI, 4.617–12.461). Increased CHD severity is more common in patients with MAFLD than in those without MAFLD. MAFLD is associated with a higher mean CIMT, maximum CIMT, and pathological CIMT. CIMT can predict the risk of future atherosclerotic CVD including stroke. Additionally, Chung et al.[61] reported a relationship between MAFLD and subclinical atherosclerosis, with the severity of the latter depending on the former. Multivariable analysis showed a significant dependency between patients with MAFLD and arterial stiffness (moderate and severe MAFLD, OR, 1.97; 95% CI, 1.28–3.01; P for trend = 0.002) in the group aged <55 years. CAD has been demonstrated to be related to MAFLD, inducing higher incidence, higher severity of CHD, higher risk of future CV events, and increased risk of atherosclerotic CVD in patients with MAFLD [62].

In conclusion, the current understanding is that IR causes insulin resistance to anti-lipolysis and combines visceral and pathological ectopic fat accumulation in patients with MAFLD, resulting in the increased availability of free fatty acid (FFA). Persistent chronic subclinical inflammation, increased oxidative stress, and endothelial dysfunction increase the availability of FFA, thereby promoting atherosclerosis and CV dysfunction.

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