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Research Progress on Multidisciplinary Intervention for Metabolic Dysfunction-Associated Steatotic Liver Disease and Related Liver Cancer

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Abstract

In recent years, non-alcoholic fatty liver disease (NAFLD) has developed rapidly worldwide and has become the main cause of chronic liver disease. With the increase in prevalence, the incidence of NAFLD-related hepatocellular carcinoma (HCC) has increased sharply. These patients are often diagnosed late, have a poor prognosis, and there is still a lack of corresponding intervention measures. The close connection between NAFLD and metabolic comorbidities has given rise to a new name, "Metabolic dysfunction-associated steatotic liver disease" (MASLD), which provides us with new intervention ideas to curb the progression of liver disease through the common intrinsic mechanisms related to regulating metabolic conditions through multidisciplinary combined treatment of early metabolic comorbidities. This review analyzes the clinical status of NAFLD/MASLD and the intrinsic relationship with related metabolic syndrome, explores the potentially beneficial interventions for MASLD and related HCC in multidisciplinary treatment, including some commonly used clinical drugs, deepens the understanding of the disease and provides references for prevention and intervention.

Keywords

Non-Alcoholic Fatty Liver Disease, Metabolic Dysfunction-Associated Steatotic Liver Disease, Hepatocellular Carcinoma, Metabolic Syndrome, Multidisciplinary, Intervention

1. Introduction

Liver cancer is the sixth most common cancer worldwide and the third leading

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cause of cancer-related death [1]. Hepatocellular carcinoma (HCC) is the most common primary liver cancer, accounting for approximately 90% of liver cancers. With the prevalence of overnutrition and sedentary lifestyle, non-alcoholic fatty liver disease (NAFLD) has become an important cause of hepatocellular carcinoma. According to the latest epidemiological statistics, the global prevalence of NAFLD has exceeded 30% [2], synchronized with the prevalence of obesity and type 2 diabetes [3] [4]. At the same time, the disease shows a trend of onset in younger people, and the incidence rate in children is also very high. It is expected that by 2030, the incidence of NAFLD-related HCC in China and the United States will increase by 82% and 122%, respectively, compared with 2016 [5]. This will bring huge medical and financial burdens, so the importance of NAFLD prevention and treatment is self-evident.

The occurrence and development of NAFLD are closely related to metabolic syndrome, cardiovascular disease, diabetes, chronic kidney disease and other malignant tumors [6]. Therefore, metabolic (dysfunction)-associated steatotic liver disease (MASLD), which has been renamed in recent years, may better reflect the pathogenesis of NAFLD [7]. This review will analyze the current clinical status of NAFLD/MASLD and its relationship with related metabolic comorbidities. Explore new strategies to effectively intervene in MASLD and related HCC through multidisciplinary treatment of early metabolic comorbidities.

2. Clinical Status of MASLD

The concept of NAFLD/MASLD as a benign disease is deeply rooted, and even medical workers often ignore it in clinical practice. The lack of early symptoms and the misunderstanding that there are no serious consequences are the main reasons for the prevalence of the disease. Widespread acceptance of MASLD as a disease is currently a major issue. Clinicians also need to re-examine this type of disease, correct their concepts and inform people of the necessity for treatment. Pinpointing the development trajectory of the disease allows us to take timely measures to intervene before irreversible liver damage occurs. The severity of MASLD needs to be assessed based on the activity of liver inflammation and the degree of liver fibrosis [8], the lack of highly sensitive, specific and cost-effective detection tools is an important problem in the diagnosis. MASLD-related HCC patients are often diagnosed at an older age due to lack of clinical monitoring, resulting in missing the best clinical treatment opportunities and poor survival prognosis. Therefore, the early identification and monitoring of high-risk patients are of great significance to avoid progression of the disease. However, it is often more challenging in the MASLD population. 25% - 50% of patients with NAFLD-related HCC can develop without cirrhosis [9] [10]. At the same time, more than 10% of NAFLD patients have a thin constitution, especially Asians, which makes them likely to have the same or more serious degree of lesions under a “healthy” appearance [11]. Clinicians are very limited in their assessment and management of MASLD patients. Although progress has been made in related drugs in recent

years, it usually has a single therapeutic effect, which cannot be completely cured and has certain side effects. Therefore, the FDA (U.S. Food and Drug Administration) has not approved any drugs for MAFLD at present. In general, the overall prognosis of patients of MASLD is poor, and there is a long way to go to explore new and effective treatments. Early diagnosis and appropriate clinical intervention are inevitable choices to curb disease progression.

3. Metabolic Comorbidities and Early Intervention of MASLD

The widespread prevalence and poor prognosis of MASLD emphasize the importance of early intervention. With the simultaneous increase in the prevalence of NAFLD and the prevalence of metabolic comorbidities such as obesity worldwide [12], The study finds NAFLD shares risk factors with other manifestations of metabolic syndrome (diabetes, hyperlipidemia, obesity, hypertension). Patients with no or only one metabolic profile of NAFLD have the lowest risk of progression to cirrhosis or HCC, and the risk increases with the addition of metabolic profiles, while the prevalence of metabolic comorbidities also increases with the duration of liver disease [13]. This suggests that metabolic comorbidities may progress simultaneously with MASLD and jointly drive the occurrence of intrahepatic and extrahepatic diseases. These metabolic features are relatively easy to identify and diagnose in clinical practice, they can not only be used as MASLD risk stratification indicators, but also may reduce the risk of disease progression by controlling these metabolic features. Therefore, when MASLD is diagnosed for the first time, measures should be taken to control comorbidities, especially the use of drugs for the treatment of comorbidities that have potential benefits for MASLD and related HCC. It can not only reduce metabolic risk factors, but also potentially improve or even reverse the disease process of MASLD. Some drugs have been found to regulate the risk factors and carcinogenic pathways in MASLD/NAFLD, and have potential in developing and implementing intervention strategies, there may be benefits from starting early with the treatment of comorbidities and prioritizing the use of such agents in appropriate clinical settings.

4. Multidisciplinary Intervention for Comorbidities

4.1. Obesity

Obesity mediates the occurrence of inflammation and liver cancer through multiple pathways and is associated with progression of NAFLD [3], it is an independent risk factor for primary liver cancer and death. Weight loss through lifestyle modification is a basic intervention in NAFLD, which is associated with the regression of steatosis, steatohepatitis and even fibrosis, and may prevent HCC by changing the natural course of the disease. The study confirmed that the degree of weight loss was independently associated with the improvement of all NASH-related histological parameters (OR 1.1 - 2.0; $P < 0.01$). Among patients with weight loss ≥10%, histological improvement and fibrosis regression were most obvious [14]. Therefore, all patients should consider individualized lifestyle

changes and weight control regardless of risk status of MASLD.

A high-quality diet can reduce metabolic burden and better protect liver health. The Mediterranean dietary pattern is currently highly regarded and recommended by the guidelines of EASL (European Association for the Study of the Liver) and AASLD (American Association for the Study of Liver Diseases) [15] [16], this diet has been shown to reduce liver steatosis even in the absence of weight loss [17]. Furthermore, adherence to a Mediterranean diet was significantly associated with lower HCC risk [18]. It is worth noting that regardless of calorie intake, high fructose intake increases the risk of NAFLD, NASH and advanced fibrosis [19], which is also closely related to NAFLD in children.

Physical exercise can reduce weight, reduce liver fat, prevent cardiovascular and other metabolic disorders. It may also intervene in the pathogenic pathways of NAFLD at multiple levels through potential mechanisms [20], and modulate oncogenic signaling pathways to reduce the risk of HCC [21]. AGA clinical practice also recommends that in addition to adjusting diet, 150 - 300 minutes of moderate-intensity exercise or 75 - 150 minutes of high-intensity aerobic exercise should be performed every week to achieve weight loss goals and improve cardiometabolic conditions [22].

For patients who have difficulty achieving weight loss goals, bariatric surgery has been shown to promote regression of NASH and fibrosis [23]. AASLD practice guidance recommends that patients with NAFLD who meet criteria for metabolic bariatric surgery must consider bariatric surgery as a treatment option [16]. However, surgical complications and a small of patients with new or worsened NAFLD after surgery require attention [24].

4.2. Diabetes

Type 2 diabetes is an important risk factor for the development of NAFLD and the progression of fibrosis [25]. Insulin resistance (IR) can cause inflammation, oxidative stress and stimulate cellular pathways, as well as promote anabolism and increase the accumulation of liver fat [26], which is the core in the pathogenesis of T2DM and NAFLD. Several epidemiological studies have established an association between T2DM and the incidence of HCC and demonstrated that diabetes is an independent risk factor for the development of HCC [27] [28]. Patients with long-term poor glycemic control appear to be at higher risk of HCC, whereas the risk of patients of HCC with good glycemic control is reduced by 31% (HR 0.69; 95% CI 0.62 - 0.78) [28]. With the progress of liver disease, insulin resistance and pancreatic beta cell failure will be further aggravated, making the treatment of diabetes more challenging. In general, diabetes promotes the occurrence and development of MASLD, which in turn worsens the IR state, thus forming a vicious circle, and the use of some antidiabetic drugs may be beneficial.

1) Thiazolidinedione: It is widely used in type 2 diabetes by activating peroxisome proliferators to improve insulin sensitivity and thus regulate blood sugar. Pioglitazone is associated with improvement in liver histology based on steatosis,

activity and fibrosis scores [29]. Due to the excellent characteristics of histological improvement, AASLD and EASL recommend pioglitazone as first-line treatment for patients with biopsy-proven NASH [15] [16]. However, the side effects of weight gain, osteoporosis, increased risk of myocardial infarction and bladder cancer cannot be ignored, so individualized evaluation is required before use.

2) Glucagon-like peptide-1 receptor agonist (GLP-1 RA): GLP-1 is secreted by intestinal L cells, mediates insulin synthesis and secretion, inhibits glucagon secretion, and plays an important role in blood sugar control and weight regulation. The studies have found that treatment with Simaglutide and Liraglutide is associated with the remission of NASH [30] [31], they can reduce liver fat content, improve histological resolution and reduce liver enzyme levels without exacerbating fibrosis [32]. Treatment with Liraglutide reduced the risk of progression from prediabetes to T2DM by more than 50% in a randomized, double-blind trial [33]. The effects of GLP-1 receptor agonists on improving body weight, glycolipid metabolism and cardiovascular outcomes make them attractive agents for intervention in MASLD, especially in obese patients. Since DPP-4 can inactivate GLP-1, DPP-4 inhibitors can achieve pharmacological effects similar to GLP-1 receptor agonists theoretically [34].

3) Sodium glucose co-transporter 2 inhibitor (SGLT-2i): It lowers blood sugar primarily by reducing renal glucose reabsorption. In addition to reducing hepatic lipid content, it also improves endothelial function and reduces high glucose-induced oxidative stress [35] [36]. In the mouse model experiment of NASH, 8 weeks of treatment with Canagliflozin improved hepatic steatosis, 20 weeks of treatment inhibited the development of liver fibrosis, and the number of liver tumors was significantly reduced after 1 year of treatment [37]. In a prospective cohort study, Canagliflozin significantly reduced serum blood glucose (BS), glycated hemoglobin (HbA1c), triglyceride (TG), uric acid (UA), and ferritin levels and the FBI-4 index was improve [38]. SGLT2 inhibitors are recommended for the prevention of heart failure in patients with type 2 diabetes and high cardiovascular risk [39]. The significant advantages of SGLT2 inhibitors in controlling comorbidities such as diabetes and heart failure make them have broad application prospects in MASLD.

4) Biguanides: It improves insulin resistance by reducing gluconeogenesis and glycogen degradation, thus reducing the overall blood glucose level. As a first-line drug for the treatment of type 2 diabetes, it has the advantages of low cost, safety, strong efficacy and intolerability. Metformin has not yet been found to have a clear histological benefit in NAFLD [40]. However, there is a correlation between the use of metformin and the reduction of all-cause mortality and the risk of hepatocellular carcinoma in the histologically confirmed cohort study of patients with histologically confirmed NASH and fibrotic T2DM [41]. Multiple studies support the potential benefit of metformin in preventing the development and progression of liver tumors [28] [42] [43], it is suggested that early use of metformin may be beneficial to the long-term prognosis of MASLD.

4.3. Cardiovascular Disease

Patients of NAFLD usually have high cardiovascular risks, have already experienced cardiovascular events, or have high risk factors such as diabetes and metabolic syndrome [26]. NAFLD is closely related to hypertension, coronary heart disease, cardiomyopathy and arrhythmias, resulting in an increase in cardiovascular morbidity and mortality [44], making it the most common cause of death in NAFLD [45]. A meta-analysis found that patients with NAFLD have a 64% higher risk of fatal or nonfatal cardiovascular events than patients without NAFLD (OR 1.64; 95% CI 1.26 - 2.13) [46]. The mechanism by which NAFLD drives cardiovascular disease is not yet fully understood, but glucose metabolism disorders and insulin resistance are considered the key factors in the pathogenesis and are closely related to the occurrence and progression of NAFLD [47]. The strong association between cardiovascular disease and MASLD emphasizes the need for early identification and intervention of cardiometabolic risk factors in this population. In addition to statins, antiplatelet aggregation drugs and aldosterone receptor inhibitors may be beneficial in MASLD while reducing cardiovascular risk.

1) Statins: It inhibits the synthesis of cholesterol by inhibiting HMGCoA reductase. It also has properties of anti-inflammatory, antioxidant and anti-angiogenesis. The study finds the use of statin associated with a lower prevalence of NASH and fibrosis [48], and reduced incidence of severe liver disease [49]. Statins are safe for patients with NAFLD [50], and simultaneously reduce cardiovascular morbidity and mortality. Clinical trial reports that statins can effectively reduce the risk of HCC [51], especially among Asian population [52]. A meta-analysis including 9 retrospective cohort studies also reported that statins reduced the risk of HCC-related death (RR 0.78; $P = 0.001$) and HCC recurrence (RR 0.55; $P < 0.001$) [53]. Although more studies are needed to confirm, the use of statins has long-term benefits in MASLD patients with dyslipidemia and high-risk CVD.

2) Antiplatelet drugs: Increasing evidence suggests that platelets are involved in inflammatory processes in liver disease, promoting the progression of fibrosis and tumors. As a classic anti-platelet aggregation drug, aspirin inhibits platelet aggregation by inhibiting cyclooxygenase, and provides protection against MASLD and high-risk cardiovascular complications at the same time. Daily aspirin significantly reduces NASH and fibrosis in biopsy-confirmed NAFLD study [54]. The study shows taking at least 650 mg of aspirin regularly per week reduces HCC risk by 50% (HR 0.51; 95% CI 0.34 - 0.77) [55]. Some studies have also shown that long-term use of aspirin can significantly reduce the incidence of liver cancer and overall mortality in patients with cirrhosis without increasing the risk of gastrointestinal bleeding [56]. The specific effect of antiplatelet aggregation therapy on the liver in the context of MASLD is still unclear, but blocking platelet aggregation may be a beneficial treatment strategy in MASLD patients with high-risk cardiovascular and cerebrovascular diseases after individual evaluation.

3) Aldosterone receptor inhibitor: As the first-line drugs for hypertension management and cardiovascular protection in vulnerable populations, Angiotensin-

converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) can inhibit vasoconstriction and water and sodium retention, improve insulin resistance, endothelial function and vascular remodeling, etc. by acting on the renin-angiotensin-aldosterone (RAAS) system. RAAS inhibitors also reduce the tumor load of HCC and progression to higher grade fibrosis, leading to the regression of HCC and restoration of liver histology [57]. In a retrospective cohort study, the treatment of ACEI was associated with a lower risk of liver-related events, particularly in patients with chronic kidney disease (CKD) [58]. A study of biopsy-confirmed NAFLD found that hypertensive patients taking RAS blockers had less progression of liver fibrosis and was inversely related to advanced fibrosis (OR 0.37; 95% CI 0.21 - 0.65; P = 0.001) [59]. ACEI/ARBs may have significant advantages for patients with MASLD who have combined cardiovascular disease and certain chronic kidney diseases. However, the long-term effectiveness, cost-effectiveness, and potential drug interactions of these drug combination regimens require further evaluation.

5. Conclusion and Outlook

We have gradually realized that MASLD is not a single disease, but a kind of metabolic-related systemic disease. Its complex intrinsic connections also determine that it is often accompanied by other comorbidities, and the existence of metabolic comorbidities is also a risk factor for the occurrence and progression of MASLD and related HCC. Therefore, we propose to start with early intervention in the treatment of MASLD-related comorbidities, examine it from the perspective of multidisciplinary treatment, improve lifestyle, and choose appropriate intervention drugs to control related metabolic symptoms. By treating the common pathogenic factors of the comorbid organs to improve or even reverse the disease process and prognosis of MASLD, multidisciplinary combined treatment not only expands the therapeutic scope of drugs, but also greatly improves treatment compliance of patients. However, the actual role of related drugs on MASLD and related HCC and the specific benefits of patients in early combined intervention of comorbidities need more research and verification in the future.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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