

Therapies for patients with coexisting heart failure with reduced ejection fraction and non-alcoholic fatty liver disease

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Abstract

Heart failure with reduced ejection fraction (HFrEF) and nonalcoholic fatty liver disease (NAFLD) are two common comorbidities that share similar pathophysiological mechanisms. There is a growing interest in the potential of targeted therapies to improve outcomes in patients with coexisting HFrEF and NAFLD. This manuscript reviews current and potential therapies for patients with coexisting HFrEF and NAFLD. Pharmacological therapies, including angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, mineralocorticoids receptor antagonist, and sodium-glucose cotransporter-2 inhibitors, have been shown to reduce fibrosis and fat deposits in the liver. However, there are currently no data showing the beneficial effects of sacubitril/valsartan, ivabradine, hydralazine, isosorbide nitrates, digoxin, or beta blockers on NAFLD in patients with HFrEF. This study highlights the importance of considering HFrEF and NAFLD when developing treatment plans for patients with these comorbidities.

Further research is needed in patients with coexisting HF_rEF and NAFLD, with an emphasis on novel therapies and the importance of a multidisciplinary approach for managing these complex comorbidities.

Key Words: Non-alcoholic fatty liver disease; Heart Failure; Heart failure reduced ejection fraction; Novel therapies; Cardiovascular disease

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Core Tip: This manuscript provides an overview of potential therapies for patients with coexisting heart failure with reduced ejection fraction and nonalcoholic fatty liver disease (NAFLD). The authors discuss the current research of pathogenesis in heart failure and NAFLD, as well as pharmacological therapies that have been shown benefits. We also discuss the potential role of diet, physical activity and novel therapies in managing these conditions.

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INTRODUCTION

Heart failure (HF) is a major clinical, economic, and public health concern worldwide. The prevalence of HF in the United States and Europe is estimated to be 1.5% to 1.9% of the population, reaching a considerable number among people aged > 65 years[1]. The predominant etiologies of HF include coronary artery disease (CAD), hypertension, tachyarrhythmia, and valvular disease, and as an additional emerging risk factor, non-alcoholic fatty liver disease (NAFLD)[2].

NAFLD represents evidence of hepatic steatosis (*via* imaging or histology) with a lack of secondary causes of hepatic fat accumulation and can be categorized as non-alcoholic fatty liver (Without evidence of hepatocellular injury) or Non-alcoholic Steatohepatitis (NASH: Hepatocellular injury with or without fibrosis)[3]. Most patients with NAFLD have associated conditions, such as obesity, diabetes mellitus, hypertension, and dyslipidemia. Recently, NAFLD has been associated with other conditions such as chronic kidney disease, osteoporosis, obstructive sleep apnea, psoriasis, colorectal cancer, and HF.

Some authors have mentioned that the association between NAFLD and cardiovascular disease (CVD) is inconsistent. They hypothesized that this connection might disappear after controlling for modifiable CVD risk factors[4]. However, there are strong arguments connecting NAFLD to CVD. Chiang *et al*[5] demonstrated that non-obese and relatively healthy subjects with NAFLD have an increased risk of developing cardiovascular events[5]. In addition to Chiang *et al* [5], other studies have shown that NAFLD patients have an increased risk of CVD after adjusting for major demographic, clinical, and metabolic confounders[6].

Furthermore, emerging epidemiological studies support a strong and independent association between NAFLD and HF. These studies estimated that the prevalence of HF in patients diagnosed with NAFLD is 6.4%, with a higher risk for HF preserved ejection fraction (HF_pEF) than HF reduced ejection fraction (HF_rEF)[7].

The association between HF and NAFLD involves similar processes in both HF_pEF and HF_rEF, which are mediated by inflammatory and fibrotic processes. The pathophysiological relationship between NAFLD and HF_pEF is attributable, at least in part, to the secretion of adipokines and proinflammatory cytokines, such as leptin, which, at the level of the liver tissue, has profibrotic activity, and in the heart, it produces cardiac hypertrophy and endothelial dysfunction. Other important factors are tumor necrosis factor- α (TNF- α) and interleukin (IL) -6, which contribute to hepatocyte injury and NAFLD, whereas damaged hepatocytes release IL-33, which promotes a profibrotic effect. In the heart, IL-33 is released in response to myocardial fiber stretching[8].

PATHOPHYSIOLOGY LINKING NAFLD WITH CARDIOVASCULAR DISEASE AND HF_rEF

Several pathophysiological mechanisms have been proposed to explain this relationship. One potential mechanism by which fatty liver may increase the risk of HF is an increased prothrombotic state and systemic inflammation[8]. The hypercoagulable state of NAFLD is multifactorial and complex. Some studies have suggested that oxidative injury to lipids and lipoproteins may underlie thrombophilia[9]. Plasminogen activator inhibitor type 1 (PAI-1), the most thrombophilic factor reported, significantly increases with exposure to non-oxidized low-density lipoprotein (LDL) and is directly related to hepatic steatosis[10]. Another important process in this proinflammatory stress is the apoptotic pathway, which is activated in NASH as a result of fatty acid-mediated changes in the permeability of lysosomes and mitochondria with the release of cathepsins and cytochrome C, respectively. This activates the proapoptotic caspase cascade (fatty acid

lipotoxicity), thereby resulting in a procoagulant state and contributing to atherosclerotic injury[11]. This process may explain why patients with NAFLD have a higher rate of major cardiovascular (CV) events (30% *vs* 8%)[12]. Additionally, NAFLD is associated with increased production of proinflammatory cytokines, such as IL-6 and high-sensitivity C-reactive protein (Hs-CRP), mitochondrial dysfunction eliciting reactive oxygen species (ROS) production, and stress biomarkers, such as fibroblast growth factors (FGFs), which increase the risk of CV and liver-related mortality[13,14] (Figure 1).

NAFLD is associated with high serum levels of total cholesterol, triglyceride, and LDL-cholesterol levels[15]. This dyslipidemia profile plays an important role in the pathogenesis of atherosclerosis. Nevertheless, existing data suggest that NAFLD *per se* might be an independent risk factor for CAD, even after adjusting for age, sex, traditional coronary risk factors, and visceral adipose tissue[16].

Cardiac structural and functional alterations are pivotal processes in HF in NAFLD patients. Most studies showed echocardiographic changes suggestive of left ventricular (LV) diastolic dysfunction, such as LV hypertrophy, increased left atrial volume, impaired LV relaxation, and higher left-sided filling pressures[17,18]. Furthermore, another study showed that hepatic steatosis and fibrosis are associated with diastolic dysfunction and are correlated with altered myocardial glucose uptake[19]. In addition, patients with NAFLD experience epicardial fat thickness, and both are at increased risk of coronary artery calcification[20].

Patients with NAFLD are also at an increased risk for cardiac arrhythmias, which can further increase the risk of LV dysfunction and HF. Cai *et al*[21] showed that NAFLD is associated with an increased risk of atrial fibrillation, and the strength of the association increases partially with the coexistence of cardiometabolic risk factors. In addition, Hung *et al* [22] found that mild, moderate, and severe NAFLD was associated with a high risk of heart rate-corrected QT (QTc) interval prolongation in both diabetic and nondiabetic subgroups. This mechanism is supported by the systemic inflammation and oxidative stress associated with NAFLD, which may trigger cardiac electrical and autonomic remodeling of the heart[23].

WHAT IS THE RELATIONSHIP BETWEEN NAFLD AND CARDIOVASCULAR DISEASE?

NAFLD and clinical CVD share similar risk factors (*i.e.*, sedentary lifestyle, smoking, physiological stress, and sleep deprivation/disorders). Accumulation of visceral and ectopic fat leads to the release of toxic metabolites and the activation of inflammatory pathways, ultimately leading to both entities[24]. With progressive NAFLD, factors such as insulin resistance, activated renin-angiotensin-aldosterone system (RAAS), and oxidative stress markers have the potential to increase the risk of cardiac disease and HF[25]. Specifically, the RAAS system is activated as a compensatory mechanism in early HF owing to hypoperfusion and sympathetic activation, leading to a cascade of angiotensin II and aldosterone, which are responsible for increased preload and afterload at the expense of salt and water retention, cardiac remodeling, and vasoconstriction[26,27].

It has been found that liver disease, renal failure, and diabetes contribute to greater mortality in patients with HFrEF compared to patients with HFpEF[28]. However, a recent cohort study and meta-analysis demonstrated that patients with NAFLD are at an increased risk of incident HFpEF rather than HFrEF[7,29].

Simon *et al*[30] showed that patients with biopsy-proven NAFLD had a significantly higher incidence of HF across all stages of NAFLD. Likewise, in a recent meta-analysis, NAFLD patients had a lower ejection fraction than non-NAFLD patients and increased left ventricular mass and epicardial adipose thickness[31].

These findings support the notion that NAFLD is a “multisystem” disease with multiple potential pathophysiological mechanisms that may increase the risk of HF. Herein, we discuss the possible mechanism of ventricular dysfunction and its impact on the patient's lifestyle. Therefore, our review provides an overview of novel therapies for patients with coexisting HFrEF and NAFLD with the aim of developing future interventions to prevent and treat both diseases.

NON-PHARMACOLOGICAL THERAPIES FOR PATIENTS WITH NAFLD AND HFrEF

Lifestyle modifications

Lifestyle modifications, such as dietary changes, physical activity, and weight loss, are first-line treatments for NAFLD. These modifications affect body fat adipose deposits, which also influences the development of CV comorbidities[18]. It has been studied that HF is associated with splanchnic circulation congestion, which leads to bowel wall edema and impaired intestinal barrier function, which concomitantly promotes bacterial translocation and inflammation[32]. For example, trimethylamine N-oxide, an organic compound from gut bacteria, is an independent predictor of poor prognosis in patients with HF and is strongly linked to the pathogenesis of CVD[33].

Dietary change is one of the most important factors for the treatment of NAFLD and HF. Montemayor *et al*[34] concluded that customized hypocaloric dietary and enhanced physical activity interventions may be useful in ameliorate NAFLD[34]. The Mediterranean Diet, rich in vegetables, fruits, legumes, potatoes, non-refined cereals, fish, white meat, and red wine, seems to have a favorable association with NAFLD in Iranian adults, especially in women and patients with or without abdominal obesity[35]. The DASH diet, which is rich in antioxidants, micronutrients, fiber, and nitrates and has low saturated and trans fats, has been shown to decrease proinflammatory cytokines and ROS, restore micronutrient status, and promote endothelial function[36]. Belanger *et al*[37] demonstrated that a DASH diet progressively reduced high-sensitivity cardiac troponin I and Hs-CRP over 12 wk[37].

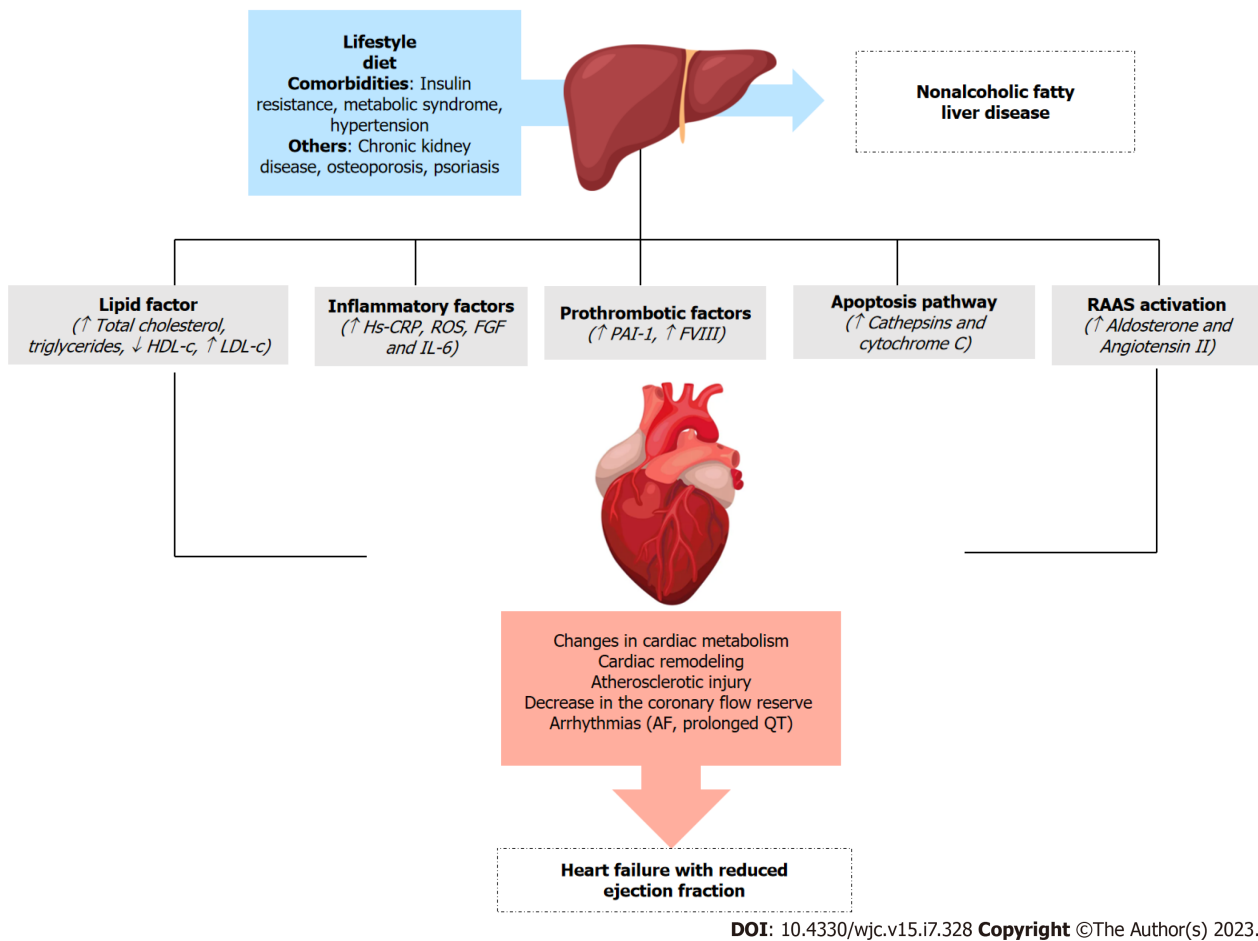


Figure 1 Pathophysiology of non-alcoholic fatty liver disease and heart failure with reduced ejection fraction. LDL-c: Low-density lipoprotein-cholesterol; HDL-c: High-density lipoprotein-cholesterol; Hs-CRP: High-sensitivity C-reactive protein; ROS: Reactive oxygen species; FGF: Fibroblast growth factor; IL: Interleukin; PAI-1: Plasminogen activator inhibitor type 1; AF: Atrial fibrillation; RAAS: Renin angiotensin aldosterone system.

Bariatric Surgery

Bariatric surgery (BS) is one of the most effective treatments for obesity and its comorbidities[38]. The literature suggests that BS has also been associated with long-term improvements or even resolution of NAFLD in both clinical and histological features and has been shown to reduce CVD risk in patients with obesity by improving glucose tolerance and lipid panels[39-41]. Additionally, a recent meta-analysis showed that BS was associated with lower incidences of HF and myocardial infarction (MI)[42]. Another study showed that 96 months after BS, the cumulative incidence of HF was 4.2% and 11.5% in the surgical and non-surgical groups, respectively[43]. All these effects of BS seem to be related to changes triggered by gastrointestinal hormones such as Glucagon-like peptide 1 (GLP-1), gastric inhibitory polypeptide, leptin, gut hormone peptide YY, and ghrelin after anatomical intervention.

Additionally, changes in the gut microbiota are crucial for NAFLD[38]. Studies have shown a relationship between the gut microbiome and HF development[44]. This interplay involves gut microbial metabolites (which serve as mediators in HF pathophysiology), immune responses, and a vicious cycle caused by gut hypoperfusion in HF and subsequent additional microbiome alterations[33,44].

PHARMACOLOGICAL THERAPIES IN HFREF WITH EFFECT ON NAFLD

Currently, several therapies with strong evidence of benefit for HFREF have also been reported to have an effect on NAFLD. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been shown to reduce fibrosis and fat deposition in the liver. Mineralocorticoids receptor antagonist (MRA), such as spironolactone, have been reported to have a clear effect on the combination of this diuretic with vitamin E. Sodium-glucose cotransporter 2 inhibitors (SGLT-2i) have been reported to reduce liver stiffness and improve steatosis. Unfortunately, there are currently no data showing the beneficial effects of sacubitril/valsartan, ivabradine, hydralazine, isosorbide nitrates, digoxin, or beta-blockers (BB) on NAFLD (Table 1).

ACEIs and ARBs

ACEIs and ARBs block the effects of angiotensin II. These drugs are commonly prescribed to treat high blood pressure

Table 1 Effects on non-alcoholic fatty liver disease of drugs that have strong evidence of benefit on heart failure

Drug	HF phenotype with evidence of benefit	Effect on NAFLD Population	Comparator	Study
ACEI	HF _r EF	Reduced liver-related events, liver cancer, and cirrhosis complications[47]	Placebo	Cohort
ARB	HF _r EF	Trial failed to evidence that losartan 50 mg has antifibrotic effects on NASH due to widespread use[102]	Placebo	Trial
		Patients with CKD-NAFLD taking ACEI or ARB had significantly lower liver stiffness degrees in comparison to those without those drugs[103]	Placebo	Cohort
		Losartan 100 mg in children reduced alkaline phosphatase, but not ALT at 24 wk[104]	Placebo	Trial
		Losartan 50 mg in children reduced ALT more frequently than those patients with placebo[105]	Placebo	Trial
		Telmisartan 40 mg reduced free fatty acid level and increased liver-to-spleen ratio in diabetic patients with NAFLD[106]	Losartan	Trial
		Telmisartan had similar effects to vitamin E in NAFLD histology[107]	Vitamin E	Trial
		Telmisartan 40/80 mg improved NAFLD activity score and fibrosis in NASH[108]	Lifestyle modification	Trial
		Telmisartan and olmesartan improved HOMA-IR and ALT levels[48]	Before-after comparison	Quasiexperimental
		Losartan significantly decreased steatosis degree and visceral adipose tissue, addition of simvastatin further decreased those parameters[109]	Amlodipine and simvastatin	Trial
		Amlodipine, lisinopril and rosuvastatin decreased ALT and alkaline phosphatase[110]	Therapy without rosuvastatin	Trial
Diuretics	HF _r EF and congested HF _p EF	In patients with NAFLD and diabetes lisinopril and hydrochlorothiazide were associated with less likelihood of advanced fibrosis, while furosemide and spironolactone had higher likelihood of it[111]	Other therapies	Cohort
		Spironolactone and vitamin E reduced NAFLD liver fat score, insulin, and HOMA-IR[55,112]	Vitamin E alone	Trial
		Five subjects received eplerenone. The study stopped early due to an unexpected increase in hepatic fat at 24 wk[113]		Open-label proof-of-concept study
SGLT2 inhibitors	HF _r EF and HF _p EF	Empagliflozin reduced liver stiffness measurement and steatosis (in patients with significant steatosis at baseline), liver fat level, AST, ALT and insulin in patients with NAFLD without diabetes[114]	Placebo	Trial
		Tofogliflozin significantly improved the fibrosis scores, steatosis, hepatocellular ballooning, and lobular inflammation[115]	Glimepiride	Trial
		Empagliflozin plus diabetes therapy better-improved liver fat in NAFLD patients with diabetes[116]	Diabetes therapy without empagliflozin	Trial
		Dapagliflozin and omega-3 carboxylic acids reduced liver fat[117]	Placebo	Trial
		Ipragliflozin as add-on diabetes therapy reduced liver steatosis in NAFLD patients with diabetes[118]	Metformin and pioglitazone	Trial
		Empagliflozin was associated with reduction of ALT, liver stiffness and controlled attenuation parameter in patients with NAFLD and diabetes[119]	Before-after comparison	Cohort
		Luseogliflozin improved liver-to-spleen ratio and liver fat in NAFLD patients with diabetes[120]	Metformin	Trial
		Dapagliflozin and pioglitazone significantly increased liver-to-spleen ratio. Only dapagliflozin decreased visceral fat area in patients with NAFLD and diabetes [121]	Pioglitazone and glimepiride	Trial

Ipragliflozin reduced visceral fat area, but not AST or ALT, in patients with NAFLD and diabetes[122]	Pioglitazone	Trial
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ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; HFrEF: Heart failure with reduced ejection fraction; HFpEF: Heart failure preserved ejection fraction; NASH: Non-alcoholic Steatohepatitis; CKD: Chronic kidney disease; NAFLD: Nonalcoholic fatty liver disease; ALT: Alanine aminotransferases; AST: Aspartate aminotransferases; SGLT2: Sodium-glucose cotransporter 2; HOMA-IR: Homeostatic model assessment for insulin resistance.

and HF. However, recent studies have suggested that ACEIs and ARBs may have beneficial effects on NAFLD[45]. Angiotensin II is a key contributor to abnormal lipid metabolism in NAFLD. Angiotensin II can worsen insulin sensitivity, generate ROS, and trigger the production of inflammatory cytokines such as TNF- α , IL-6, and PAI-1, all of which contribute to NAFLD progression[46]. For this reason, Zhang *et al*[47], in their retrospective cohort study of over 12000 patients with NAFLD, found that treatment with ACEIs for at least six months was associated with a lower risk of liver cancer and cirrhosis. Nevertheless, this effect was not seen with ARBs[42]. These data are surprising for Enjoji *et al* [48], who showed that ARBs can restore intracellular insulin signaling and facilitate the movement of excess fat from non-adipose tissues to adipocytes, which may improve markers of liver function such as transaminases, hepatic steatosis, and inflammation[48,49]. Furthermore, several clinical trials and meta-analyses have suggested that ACEIs and ARBs are effective in reducing mortality and hospitalization in patients with HFrEF and Advanced Kidney Disease[50]. Gilstrap *et al*[51] conducted a study to investigate the impact of BB and renin-angiotensin system inhibitors (RASi) on the outcomes of patients aged over 65 years with HFrEF. The study found that the use of BB and/or RASi at hospital discharge was associated with lower 30-d and 1-year mortality rates, even among patients aged > 85 years[51]. Similarly, the CHARM-Alternative trial investigated the use of candesartan *vs* placebo in patients with HF who were intolerant of ACE inhibitors. The study found that during a median follow-up of 3 years, hospitalization or cardiovascular-related death was reported in 33% of candesartan patients *vs* 40% of placebo patients[52].

Spirolactone

Patients with NAFLD and HFrEF may experience beneficial outcomes with the use of aldosterone antagonists such as spironolactone and eplerenone. Wada *et al*[53] investigated the effects of eplerenone on nonalcoholic steatohepatitis and metabolic syndrome in a mouse model. The results showed that Eplerenone effectively ameliorated insulin resistance, blood pressure, and hepatic steatosis with fibrotic changes by inhibiting the inflammatory response in Kupffer cells and macrophages[53]. Similarly, spironolactone effectively improves the accumulation of triglycerides in the liver, reduces inflammation, and downregulates gluconeogenic and lipogenic gene expression[54]. Furthermore, combination therapy with spironolactone and vitamin E appears to have a positive effect on serum insulin levels in individuals with NAFLD [55].

Patients with HF and reduced ejection fraction may benefit from the use of MRA such as spironolactone, as they have been shown to reduce mortality when administered at low doses of 25 mg to prevent hyperkalemia[56]. However, the ATHENA-HF Trial found that a high dose of spironolactone or eplerenone may be a safe and effective treatment option for patients with HFrEF because it is associated with a reduction in NT-pro brain natriuretic peptide (BNP) levels, reduction in body weight, and improved symptoms of HF, such as dyspnea and fatigue, by reducing myocardial fibrosis and improving ventricular function[57,58]. Thus, evidence suggests that RAAS inhibitors, regardless of dose, may be particularly beneficial in patients with HFrEF.

SLGT-2i

SGLT-2i suppress glucose reabsorption in the proximal tubule of the kidney, resulting in excretion of glucose in the urine and improvement of insulin resistance. Initially developed as a diabetes mellitus therapy strategy independent of insulin [59]. The improvement in hyperglycemia and insulin resistance may be related to the control of lipogenesis through transcriptional regulation of lipogenic genes, including acetyl-CoA carboxylase and fatty acid synthase, and the development of hepatic steatosis[60].

Several studies have reported that SGLT-2i can inhibit the development of NAFLD and improve histological hepatic steatosis or steatohepatitis in experimental animal models[61]. Another possible mechanism of action of SGLT-2i in NAFLD is the weight-and visceral fat-dependent effects and inhibition of *de novo* lipogenesis in the liver[62].

SGLT-2i have been shown to reduce the risk of cardiovascular death or hospitalization in patients with HFrEF with or without type 2 diabetes mellitus (T2DM). There are several randomized controlled trials such as DAPA-HF, EMPEROR-Reduced, EMPULSE[63], EMPIRE-HF, SOLOIST-WHF[64], and CANVAS trials[65]. In addition to the most updated American College of Cardiology (ACC) guidelines for the management of HF, SGLT-2i has become a mainstay in the treatment of HFrEF and HFpEF.

A recent meta-analysis, including 1950 patients, evaluated liver structure and function in patients taking SGLT-2i with placebo or other oral antidiabetic drugs. It revealed a decrease in liver function tests (LFT), such as serum alanine and aspartate aminotransferases and gamma-glutamyl transferase, and a decrease in liver steatosis[66]. Another meta-analysis showed that SGLT-2i also reduced liver fat content and improved LFT in patients with NAFLD, as estimated by cardiac magnetic resonance proton density fat fraction[67].

These findings imply that SGLT-2i may be an effective treatment for patients with both NAFLD and HFrEF.

POTENTIAL PHARMACOLOGICAL THERAPIES

GLP-1 receptor agonists

GLP-1 is an incretin hormone secreted in the gut in response to meal ingestion, which increases insulin secretion and inhibits glucagon production, targeting pancreatic β -cells. Consequently, GLP-1 receptor agonists improve hyperglycemia and delay gastric emptying, thereby promoting weight loss[68]. They can be an attractive therapeutic option for treating patients with NAFLD, particularly those with associated diabetes mellitus and obesity.

A multicenter, randomized, double-blind, placebo-controlled trial showed that liraglutide was associated with the resolution of NASH with no worsening of fibrosis score, improvement in steatosis, and hepatocyte ballooning score[69]. Liraglutide and exenatide have been attributed to decreases in trunk fat content, especially in the android region, which is associated with NAFLD and is closely associated with CVD risk[70,71].

In preclinical studies, some of the well-described effects of GLP-1 may reflect indirect mechanisms in the heart, such as augmentation of ventricular function in animals with HF or ischemia-induced ventricular dysfunction, attenuation of the development or progression of atherosclerosis or plaque formation, augmented myocardial or coronary artery blood flow rate control, reduced blood pressure, increased secretion of atrial natriuretic factor, and inhibition of platelet aggregation [72].

According to current guidelines, GLP-1 receptor agonists have no effect on the risk of HF hospitalization, which suggests that they are safe to use but are not beneficial in preventing HF in at-risk patients. Therefore, it should be used cautiously during acute decompensation[73].

Three small randomized controlled trials of GLP-1 receptor agonists were conducted in patients with HF_rEF. The LIVE and FIGHT trials studied liraglutide *vs* placebo and showed no changes in left ventricular ejection fraction (LVEF), quality of life, or functional class at 24 wk. Albiglutide has also been studied and showed no significant differences in LVEF, BNP, 6-min walk test, myocardial glucose, or oxygen use[74]. GLP-1 RAs have a positive chronotropic effect, causing an increase in heart rate and induced increases in cAMP levels, which may worsen HF and increase the risk of death[75].

Although observations from treatment with GLP-1RAs and NAFLD suggest beneficial data, observations from randomized trials suggest no clear benefit in HF-related outcomes and even uncertainty regarding safety in patients with HF_rEF. Larger studies of patients with HF_rEF are recommended.

Tirzepatide

A novel medication for the treatment of T2DM, tirzepatide, a dual glucose-dependent insulinotropic polypeptide and a GLP-1 receptor agonist, has shown promising results in ongoing clinical trials, not only for T2DM but also for improving body weight and steatosis[76]. They compared its effects with those of dulaglutide on NAFLD biomarkers and fibrosis in patients with diabetes mellitus and found that a higher tirzepatide dose significantly decreased NAFLD biomarkers and increased adiponectin levels[77]. Additionally, SURPASS-3, using magnetic resonance imaging, demonstrated that tirzepatide significantly reduced liver fat content, visceral adipose tissue volume, and abdominal subcutaneous adipose tissue[78].

Currently, the efficacy and safety of tirzepatide in patients with HF_pEF and obesity are being assessed[79]. No current data supports the use of tirzepatide in patients with HF_rEF. Studies on patients with HF_rEF are recommended.

Metformin

Metformin is a biguanide that can improve insulin sensitivity and regulate glucose utilization by the liver[80]. Metformin treatment has been shown to be effective in alleviating hepatic lipogenesis in animal models of NAFLD through various mechanisms. However, in clinical studies, metformin modestly reduced body mass index, liver fat content, and liver enzyme levels in patients with NAFLD and diabetes. Despite these reports on the benefits of metformin, some contradictory results still exist. Despite these reports on the benefits of metformin, conflicting results remain. Combination treatments with other antidiabetic drugs, especially thiazolidinedione, GLP-1 receptor agonists, and SGLT2 inhibitors, demonstrated greater efficacy. Further research with a larger sample size is required to confirm these findings[81].

Left ventricular hypertrophy is a common finding in patients with ischemic heart disease and is associated with mortality in those with CVD. Metformin has been shown to reduce oxidative stress and left ventricular mass index. These results suggest a favorable effect of metformin on the left ventricular mass index and LVEF in patients with or without preexisting CVD[82]. In a recent report of diabetic patients with advanced HF_rEF, patients treated with metformin demonstrated better quality of life and improved outcomes than patients not receiving metformin. Metformin remains one of the frontline drugs for the treatment of patients with HF_rEF and Diabetes Mellitus[83].

The long-term clinical impact of metformin on HF_rEF requires additional research despite its potential therapeutic effects on NAFLD.

Thiazolidinediones

Thiazolidinediones act as peroxisome proliferator-activated receptor- γ activators in adipose, muscle, and liver tissues, resulting in a decrease in glucose production and subsequent increase in glucose utilization[84].

A recent meta-analysis compared placebo and pioglitazone, a thiazolidinedione, and found that it significantly improved steatosis grade, inflammation grade, and ballooning grade, whereas in the fibrosis stage, there was no significant improvement in pioglitazone compared with placebo. In addition, pioglitazone significantly reduced fasting blood glucose, glycosylated hemoglobin, serum alanine, and aspartate aminotransferase levels. Owing to the lack of relevant randomized controlled trials and short intervention times, long-term studies are needed to verify its efficacy and

safety[85]. Another systematic review showed that pioglitazone consistently improved histological parameters and normalized liver transaminases, although the evidence supporting the benefits of other drugs in this class is minimal. Thiazolidinediones, particularly pioglitazone, have proven efficacious in patients with NAFLD/NASH[86].

Rosiglitazone has been shown to increase the risk of MI and HF, whereas pioglitazone decreased the risk of major adverse cardiovascular events, such as MI and stroke, but increased the risk of HF[87]. Pioglitazone was associated with higher rates of HF hospitalization in a smaller randomized controlled trial of participants with more severe symptomatic HFrEF than placebo[88]. Patients with T2DM with New York Heart Association functional class I-II CHF and reduced LVEF were randomized to 52 wk of treatment with rosiglitazone, and there were significantly more confirmed events of new or worsening edema and increased HF medication in the rosiglitazone group[89]. According to current guidelines for the treatment of HF from the ACC, given the existing evidence, thiazolidinediones should be avoided in patients with reduced LVEF[90].

In conclusion, although thiazolidinediones have demonstrated efficacy in patients with NAFLD, they are not recommended for diabetic patients at a high risk of HF, as they have been proven to increase the risk of HF in this group of patients.

Statins

Statins are safe for patients with NAFLD across the disease spectrum, including those with advanced liver disease, and lead to a demonstrable reduction in cardiovascular morbidity and mortality. The management of dyslipidemia in NAFLD should include the use of moderate- to high-intensity statins as first-line therapy, based on lipid risk levels and atherosclerotic ASCVD risk scores[91].

These medications can impair insulin sensitivity and secretion by pancreatic β -cells and increase insulin resistance in the peripheral tissues. Statins may also contribute to statin-induced T2DM[92]. Moreover, statin use is associated with a significant reduction in cardiovascular mortality and morbidity in both primary and secondary prevention strategies. A reduction in the risk of new-onset HF in patients with a high cardiovascular risk and hospitalization for HF has also been reported[25]. Rosuvastatin did not reduce the primary outcome or the number of deaths from any cause in older patients with systolic HF, although it did reduce the number of cardiovascular hospitalizations[93].

Statins may have a beneficial effect on CV outcomes irrespective of HF etiology and LVEF. Lipophilic statins (*e.g.*, atorvastatin) and non-hydrophilic statins (*e.g.*, rosuvastatin or pravastatin) showed significant reductions in clinical outcomes; however, lipophilic statins seem to be much more favorable for patients with HF[94].

Statins appear to have beneficial effects in NAFLD. Although there is the possibility of triggering T2DM, statins have more benefits than inconveniences in the treatment of NAFLD and reduce the risk of HFrEF.

NOVEL THERAPIES OR *IN VITRO* STUDIES INVESTIGATING NEW DRUGS

Similarly, potential beneficial molecules for NAFLD are currently being investigated. Niacin, a vitamin derived from tryptophan metabolism, is known for its effect on dyslipidemia; however, recent studies have indicated that niacin reduces hepatic fat accumulation and steatosis, inflammation, and fibrosis by inhibiting diacylglycerol acyltransferase 2, an enzyme responsible for the synthesis of triglycerides, blocking the activation of hepatic stellate cells, and decreasing the activity of matrix metalloproteinases 2 and 9[95].

Sesquiterpene glycoside, an extract of the dried root *Codonopsis pilosula*, is a common drug used in traditional Chinese medicine because of its affordable cost and anti-inflammatory effects[96]. Therefore, a recent study provided evidence that the use of sesquiterpene glycosides in mice could protect against NAFLD in patients with T2DM. These findings were related to the repair of insulin signaling and inhibition of cytochrome P450 2E1 (CYP2E1) and NOD-like receptor family 3 *in vivo* and *in vitro*; thus, reducing oxidative stress, inflammation, and inflammatory cytokines and preventing insulin resistance[97].

Flavonoids (*i.e.* Baicalein, silymarin, rutin, and quercetin) has also shown hepatic protection by modulating the function of CYP2E1. These molecules are usually found in fruits, vegetables, and plant-derived beverages, and are used as nutritional supplements. They can improve insulin resistance, endoplasmic reticulum stress, lipid peroxidation, and fibrosis[98].

FGF21 is a hormone that plays an important role in regulating metabolic pathways[99]. This hormone is mainly produced by the liver and its signaling is associated with NAFLD pathogenesis[100]. In addition, FGF21 regulates lipid and glucose metabolism, which is correlated with CVD and HF. In summary, FGF21 may be a potential biomarker for prognosis prediction and as a treatment target in the future. However, further studies are required to determine their precise roles[101].

CONCLUSION

HFrEF is a major public health problem worldwide. Additionally, due to the rising incidence of obesity and associated comorbid conditions, such as diabetes mellitus and metabolic syndrome, NAFLD has also become a common condition. Multiple recent studies have shown a strong association between HF, especially the HFrEF subtype, and NAFLD. Although there are multiple proposed pathophysiological mechanisms, most are common factors in the development of systemic inflammation. To date, several non-pharmacological, pharmacological, and surgical interventions have been

studied in patients with concomitant HFrEF and NAFLD. Evidence shows the potential benefits of dietary changes; certain medications, such as ACEI, ARB, MRA, and SGLT-2i; and BS. However, there is still a lack of robust data and well-designed clinical trials investigating several other drugs or novel therapies that could benefit from these conditions and improve outcomes.

FOOTNOTES

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