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Non-Alcoholic Fatty Liver Disease and Its Cardiovascular Complications: Comprehensive Analysis of its Pathophysiology and Management

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is an increasing international health concern, affecting roughly a quarter of the population and being linked to metabolic syndrome, obesity, and insulin resistance. This study offers a thorough analysis of NAFLD and its complicated pathophysiology, which includes lipotoxicity, insulin resistance, gut dysbiosis, and genetic predispositions such as PNPLA3 variants. NAFLD not only causes liver damage, but it also increases the risk of cardiovascular disease (CVD), making it a major contributor to worldwide morbidity and death. Lifestyle variables, notably dietary choices and physical exercise, have an important role in both the development and management of NAFLD, with interventions showing promise for slowing disease progression. The significance of this review originates from its emphasis on the dual burden of NAFLD and CVD, which highlights the common pathophysiological pathways that contribute to both illnesses. NAFLD is expected to become the major cause of liver transplantation, knowing its cardiovascular consequences is important for improving patient prognosis.

Keywords: Non-alcoholic fatty liver disease, NAFLD, cardiovascular disease, cardiology, hepatology, gut health, dysbiosis

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a prevalent chronic condition characterized by the accumulation of triglycerides in the liver, affecting approximately 25 percent of the global population. It encompasses a spectrum ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), with the potential to progress to cirrhosis and liver cancer. Closely associated with metabolic syndrome, obesity, and insulin resistance, NAFLD is typically diagnosed through a combination of clinical history, laboratory tests, and imaging, with liver biopsy being the gold standard. Management primarily revolves around lifestyle modifications, such as weight loss and dietary changes, as there are currently no FDA-approved treatments for the condition. NAFLD is expected to become a leading cause of chronic liver disease and the primary

indication for liver transplantation as hepatitis C prevalence declines. Furthermore, NAFLD has been increasingly recognized as a significant risk factor for cardiovascular disease (CVD), with severe forms being linked to an increased CVD risk independent of other cardiometabolic factors. Mechanisms contributing to this risk include insulin resistance, oxidative stress, abnormal adipocytokine profiles, endothelial dysfunction, and lipid abnormalities, with NAFLD patients often exhibiting atherogenic dyslipidemia. Additionally, the liver's release of pro-inflammatory and pro-atherogenic factors may further contribute to the development of CVD, making NAFLD an important mediator of cardiovascular risk [1,2,2–5].

Definitions and Pathophysiology

The rise in sedentary lifestyles and shifting dietary habits has led to a global increase in obesity and insulin resistance, making liver fat accumulation a frequent finding in abdominal imaging and liver biopsies. When alcohol intake is low, this condition is termed non-alcoholic fatty liver disease (NAFLD) [6].

NAFLD is a major complication of obesity and is considered a hepatic manifestation of metabolic syndrome. Affecting both adults and children globally, it is characterized by steatosis which is the accumulation of fat in the liver. In addition to inflammation, cell death, and fibrosis, NAFLD can progress to end-stage liver disease or even hepatocellular carcinoma. Recent studies have found hepatic fat to be acting as an independent marker for increased cardiovascular risk. While imaging and lab studies can detect steatosis and fibrosis, the precise diagnosis and staging of NAFLD majorly relies on histologic evaluation. This includes the identification of specific patterns and lesions in the liver tissue, with notable differences between adult and pediatric presentations. Key histological distinctions are made between steatosis and statohepatitis along with the types and location of fibrosis. The pathophysiology of NAFLD is complex, involving various factors. Overconsumption of nutrients can lead to gut dysbiosis and increased intestinal permeability, allowing microbial molecules to enter the liver and trigger inflammation. Additionally, certain dietary components can directly activate disease mechanisms in liver tissue, contributing to NAFLD progression [5,7,8]. This review addresses some of these important pathophysiologic correlations and mechanisms like lipotoxicity, dietary correlation, role of gut dysbiosis, insulin resistance, association of hormone actions, inflammation, and genetic factors as well. Refer to the Table to understand different pathophysiological pathways leading to NALFD and disease progression.

Lipotoxicity

Lipid accumulation or lipotoxicity in hepatocytes is a key feature of NAFLD with lipid droplets forming inside the cells as discussed. Genetic variation in the *PNPLA3* Gene encodes for a protein called adiponectin. This is found in adipocytes and hepatocytes. It is an important regulator of lipids in these cells and is responsible for the hydrolysis of retinyl-palmitate in hepatic stellate cells in humans [9,10]. Epidemiologically, it has been studied that PNPLA3 I148M acts as a major genetic modifier for this condition [11]. The I148m mutation in PNPLA3 leads to an altered modelling of fatty acids in the hepatocytes; moreover, this variant leads to an accumulation of PNPLA3 on lipid droplets, since the protein degradation via the ubiquitination pathway is reduced compared to the wild-type protein. [11–13] . This genetic variation heightens susceptibility to NAFLD by disrupting fatty acid metabolism and reducing the degradation of proteins, which leads to lipid buildup in the liver. Experimental studies have shown that knocking down PNPLA3 in mice reduces steatosis, suggesting it is a potential therapeutic target. Additionally, GCKIII kinases, such as MST3 and MST4, are associated with more severe forms of

NAFLD, and lowering their levels in hepatocytes decreases triacylglycerol synthesis and lipid droplet formation. These kinases also inhibit β-oxidation, contributing to oxidative stress and lipotoxicity, both key drivers of NAFLD progression. Free cholesterol is another factor, as increased expression and activity of HMG CoA reductase led to higher cholesterol synthesis and inflammation. Furthermore, excess free cholesterol can crystallize within lipid droplets, further contributing to fibrosing NASH and inflammation through interactions with YAP-TAZ and the depletion of mitochondrial glutathione. Cholesterol metabolism, influenced by bile acids and receptors like FXR, plays a crucial role in controlling hepatic fat accumulation and reducing lipogenesis [7,14–19] .

Lifestyle correlation

Several researches have indicated a strong correlation between dietary patterns and NAFLD [20,21]. Higher levels of carbohydrate intake and consumption of Western dietary patterns with frequent fast food, refined grains, and red meat are linked to increased risk and prevalence of NAFLD. Additionally, higher intake of vitamin A and folate as well as adherence to Mediterranean diet are associated with lower risk of NAFLD. Other metabolic factors such as triglycerides, uric acid, adiponectin levels, and waist-hip ratio differ significantly between NAFLD patients and healthy individuals. These differences highlight the potential importance of dietary interventions in both preventing and managing NAFLD, emphasizing the role of nutrition in addressing the metabolic imbalances associated with the disease [21–23] .

In addition to dietary factors, several lifestyle factors have a substantial impact on NAFLD. Sedentary behavior, obesity, and insufficient physical activity are all major contributors to an increased risk of developing NAFLD. Regular exercise, particularly outside activities that expose you to the sun, can help prevent and manage the condition. Furthermore, lifestyle therapies such as omega-3 supplementation, green tea use, and abstaining from smoking and alcohol provide further benefits. Importantly, adopting multiple healthy lifestyle habits can result in significant reductions in mortality risks, with studies indicating a 36% decrease in all-cause mortality and a 43% reduction in cardiovascular disease-related deaths among NAFLD patients who adopt healthier lifestyles, emphasizing the importance of comprehensive lifestyle management in addressing this condition [24–27].

Association with gut dysbiosis

Gut dysbiosis is a key factor in the initiation and progression of nonalcoholic fatty liver disease. According to research, the severity of NAFLD is associated with changes in gut microbiota composition and metabolic processes. For example, increasing *Bacteroides* abundance is connected with non-alcoholic steatohepatitis (NASH), but higher *Ruminococcus* levels correlate with substantial fibrosis. The gut-liver axis, which comprises portal circulation, bile ducts, and systemic circulation, regulates how gut dysbiosis influences NAFLD progression. Several processes contribute to this association, including changes in microbial metabolites, gut barrier integrity, and immunological responses. Different stages of NAFLD produce distinct gut microbiota compositions, with *Firmicutes* being more abundant in mild to moderate instances and *Proteobacteria* dominating in advanced fibrosis. Understanding these relationships could lead to the discovery of new treatment targets and management methods for NAFLD [28–31].

Insulin Resistance

NAFLD is seen to be closely linked with insulin resistance (IR). IR is understood to be one of the key factors in NAFLD pathophysiology. Elevated free fatty acids (FFAs) can induce hepatic IR in humans. Hepatic IR is associated with intrahepatic diacylglycerol (DAG) content and activation

of PKC-ε. Animal models demonstrate that hepatic steatosis activates PKC-ε and JNK1, leading to interference with insulin receptor substrates 1 and 2 (IRS-1 and IRS-2), which contributes to insulin resistance (IR). Inflammation further drives hepatic IR, with IKK-β activation playing a key role in this process. Additionally, oxidative stress and elevated pro-inflammatory cytokines like TNF activate IKK-β in patients with NAFLD. Given that NAFLD is highly prevalent in individuals with type 2 diabetes mellitus (T2DM), IR emerges as a promising target for therapeutic intervention in this condition [7,32,33] .

Progression to advance liver disease

This nationwide cohort study used the ESPRESSO cohort in Sweden to follow 718 adults with NAFLD, each undergoing at least two liver biopsies six months apart. Of these, 69.2% had simple steatosis, 12.5% had non-fibrotic NASH, and 18.2% had non-cirrhotic fibrosis [34]. Patients with fibrosis had a higher metabolic risk. The progression of NASH and fibrosis increased the risk of end-stage liver disease (ESLD) by 65%, with the highest risk observed in those developing cirrhosis [35–37] .

Table 1. Pathophysiological mechanisms leading to non-alcoholic fatty liver disease

Mechanism	***Key features***	***Associated factors***
Lipotoxicity	Lipid accumulation in hepatocytes due to altered fatty acid metabolism and genetic mutations.	PNPLA3 I448M mutation: Disrupts fatty acid remodeling, leading to build-up of fat in hepatocytes Cholesterol metabolism: Increased cholesterol synthesis contributes to oxidative stress and fibrosis.
Dietary correlation	Dietary habits rich in refined carbohydrates, red meat, and fast food increases the risk of NAFLD High TGL levels, Uric acid levels, and increased waist-hip ratio are common in NAFLD patients	Mediterranean diet and high vitamin A/Folate intake lower the risk
Gut dysbiosis	Alteration in gut microbiota composition influences NAFLD progression Significance of gut-liver axis	*Firmicutes* dominate in the early stages, while *proteobacteria* dominate in the advanced fibrotic stage. Increased permeability: These microbial molecules trigger liver inflammation and fibrosis.
Insulin Resistance	Hepatic insulin resistance results from lipid accumulation, inflammation, and oxidative stress	PKC-E and JNK1 activation disrupt insulin signaling. Inflammatory cytokines (TNF) promote IR in NAFLD patients, especially in those with T2DM.
Disease Progression	NAFLD progresses to fibrosis, NASH, cirrhosis, and ESLD.	Fibrosis and cirrhosis increase the risk of ESLC by up to 65 percent. Patients with higher metabolic risk factors have a more rapid progression rate.

Clinical diagnosis

The investigation of patients with suspected non-alcoholic fatty liver disease (NAFLD) should begin by ruling out excess alcohol consumption and other liver diseases, including viral, autoimmune, and metabolic causes. Once these factors are excluded, the focus shifts to confirming the presence of NAFLD, differentiating simple steatosis from non-alcoholic steatohepatitis (NASH), and assessing the extent of any hepatic fibrosis. While there is no single diagnostic blood test for NAFLD, biochemical tests can provide important clues [6,38]. Elevated serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are typically modest, often less than twice the upper limit of normal. ALT levels

may decrease as fibrosis progresses, leading to the characteristic AST ratio reversal seen in NASH as the disease advances toward cirrhosis. Although routine blood tests cannot accurately determine the degree of liver fibrosis, calculated scores such as the NAFLD Fibrosis Score and FIB-4 Score can rule out advanced fibrosis, allowing clinicians to prioritize care for those most likely to have significant disease [39,40].

Imaging plays a vital role in diagnosing NAFLD. Ultrasound is the most frequently utilized method, offering a qualitative assessment of hepatic fat content. However, its sensitivity is limited when less than 33% of hepatocytes are affected. Advanced imaging techniques like computed tomography (CT), magnetic resonance imaging (MRI), or magnetic resonance spectroscopy (MRS) are more sensitive but are less commonly used due to resource constraints. Liver biopsy remains the gold standard for diagnosing and assessing the degree of inflammation and fibrosis in NAFLD, revealing key histological features such as steatosis, hepatocellular injury, and inflammatory infiltrates. However, its invasive nature makes routine use impractical, leading to a growing reliance on non-invasive tests (NITs) such as serum biomarkers, transient elastography (TE), and magnetic resonance elastography (MRE). These methods, particularly the FIB-4 index and NAFLD fibrosis score, enable effective assessment of liver health while minimizing patient risk. Given the challenges of diagnosing NAFLD, including its potential manifestation in patients with normal liver tests, this review systematically evaluates both invasive and non-invasive diagnostic tests for NAFLD in diverse populations, highlighting the need for reliable assessments to guide clinical management [8,41–44].

Cardiovascular complications of NAFLD

NAFLD is a relatively prevalent illness affecting up to 30 percent of adults globally, and it is closely linked to an elevated risk of cardiovascular disease (CVD). NAFLD patients had a greater death rate from myocardial infarction than the overall population. The condition is associated with a variety of cardiac problems, including left ventricular dysfunction, hypertrophy, heart failure, valvular heart disease, and arrhythmias such as atrial fibrillation. The severity of NAFLD, particularly liver fibrosis, corresponds to the magnitude of CVD risk. This relationship is thought to be caused by an increase in insulin resistance, atherogenic dyslipidemia, hypertension, and the production of pro-inflammatory, pro-coagulant, and pro-fibrogenic mediators. Based on these findings, NAFLD patients may benefit from extensive surveillance and early therapies to reduce CVD risk [7,45–47].

NAFLD is strongly linked to an increased risk of cardiovascular complications, especially in individuals with type 2 diabetes mellitus (T2DM). NAFLD contributes to systemic inflammation, insulin resistance, and endothelial dysfunction, all of which accelerate the development of cardiovascular diseases such as myocardial infarction, ischemic stroke, and heart failure. Studies indicate that the severity of NAFLD correlates with the risk of cardiovascular events, with patients exhibiting advanced NAFLD having significantly higher incidences of these complications. This highlights the need for vigilant cardiovascular risk assessment in patients diagnosed with NAFLD, especially those with T2DM [48].

NAFLD and cardiovascular diseases are closely associated due to the common risk factors and their association with metabolic syndrome. This makes it difficult to separate their contributions to cardiovascular diseases. Accumulation of visceral fat in the liver and other vital organs is linked with cardio-metabolic events contributing to both the progression of NAFLD and CVD. Dyslipidemia in NAFLD is marked by high levels of triglycerides (TGL), low-density lipoprotein (LDL) as well as other atherogenic factors. Hepatic fat accumulation in NAFLD results from an imbalance in lipid metabolism, including de

novo lipogenesis (DNL) and increased production of very low-density lipoprotein (VLDL). As discussed above, insulin resistance is commonly seen in NAFLD. This contributes to CVD development through persistent hyperinsulinemia. These conditions serve as factors of vascular inflammation and atherogenic environment. Toll-like receptor (TLR) activation in NAFLD patients causes inflammation via the NLRP3 inflammasome, which promotes vascular damage and atherosclerosis. Elevated levels of homocysteine, asymmetric dimethyl arginine (ADMA), and coagulation disorders all increase the risk of atherosclerosis. Furthermore, the accumulation of epicardial fat around the heart causes inflammation and fibrosis, raising the risk of coronary artery disease, heart failure, and atrial fibrillation. Genetic variables, including polymorphisms in PNPLA3 and TM6SF2, contribute to NAFLD progression, however,` other genetic variants may protect against severe liver disease development [12,49,50].

Several studies link NAFLD to severe cardiovascular events and even increased cardiovascular mortality. NAFLD is seen to significantly impact mortality in both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). The majority of them have studied that the association of NAFLD with CVD is independent of traditional risk factors like age, hypertension, and other lifestyle factors like smoking, alcohol intake, and BMI.

According to a study done by Targher et al., there is a 64 percent higher risk of severe cardiovascular events in NAFLD. These are both fatal and non-fatal events. It has been studied that patients with severe NAFLD experience a two-fold increase in the risk of cardiovascular events and over three-fold risk of cardiovascular mortality compared to individuals without NAFLD. Another such study confirmed that NAFLD patients have an increased risk of coronary artery disease (CAD) and hypertension. The presence of NASH elevates the CVD specifically in the patients with advanced fibrotic conditions [7,48,49].

Arterial hypertension is a key modifiable risk factor for cardiovascular disease (CVD), which has been related to strokes and ischemic heart disease. It also increases the risk of heart failure, peripheral arterial disease, and arrhythmias, particularly atrial fibrillation. The prevalence of hypertension among patients with nonalcoholic fatty liver disease (NAFLD) ranges from 40% to 70%, with evidence associating NAFLD with an increased risk of prehypertension and hypertension. Studies have shown a 2-3-fold rise in hypertension incidence among NAFLD patients, while the OPERA study found higher systolic and diastolic blood pressure readings. Furthermore, NAFLD is linked to coronary artery disease and unfavorable cardiovascular events, including increased mortality following acute coronary events. NAFLD patients are also more likely to develop cardiac arrhythmias as a result of systemic inflammation and impaired myocardial function, which contributes to the increased cardiovascular morbidity and mortality found in this population [35,46,50]. The Association of NAFLD and risk of cardiovascular events can be illustrated in Figure 1.

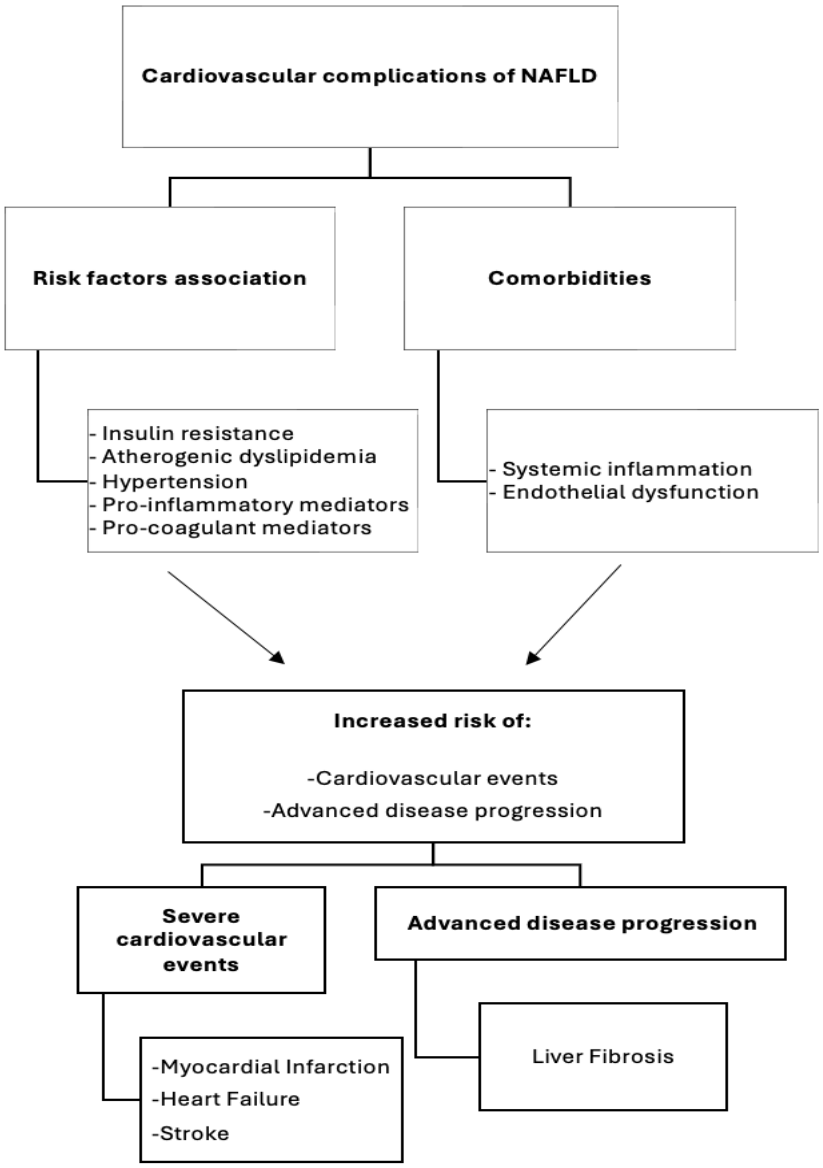

Figure 1. Cardiovascular complications of non-alcoholic fatty liver disease.

Management of NAFLD

Managing NAFLD involves a multidisciplinary approach and mostly a personalized intervention regime tailored to each case as illustrated in Figure 2. The management primarily emphasizes lifestyle modifications, specifically weight loss through dietary changes and physical activity [38]. Weight loss, even by 5% to 10%, can improve liver enzyme levels and histology, making it a cornerstone of treatment. Dietary adjustments, such as switching to a low-fat or Mediterranean diet rich in fruits, vegetables, olive oil, and seafood, have proven effective in reducing liver fat, insulin resistance, and cardiovascular risk. Regular physical activity, including both aerobic and resistance training, enhances glucose metabolism and can lower liver fat accumulation, with high-intensity interval training (HIIT) being particularly beneficial [44]. Exercise also improves liver function without significant weight reduction, but it

should be approached cautiously in people with cardiovascular risk [51].

When lifestyle changes are insufficient, pharmacological treatments may be considered, often in combination with lifestyle modifications. Vitamin E and pioglitazone have shown promise in reducing liver inflammation and fat content, particularly in patients with biopsy-confirmed nonalcoholic steatohepatitis (NASH) [42] . Pioglitazone, a PPAR-γ agonist, improves liver histology and reduces insulin resistance, while Saroglitazar, a dual PPAR-α/γ agonist, has demonstrated improvements in liver fat content and metabolic parameters. Other medications, such as sodium-glucose cotransporter 2 inhibitors (SGLT2i) like empagliflozin, and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), have shown potential in improving liver health, particularly in type 2 diabetes patients [51,52]. Different strategies for the management of NAFLD are illustrated in Figure 2.

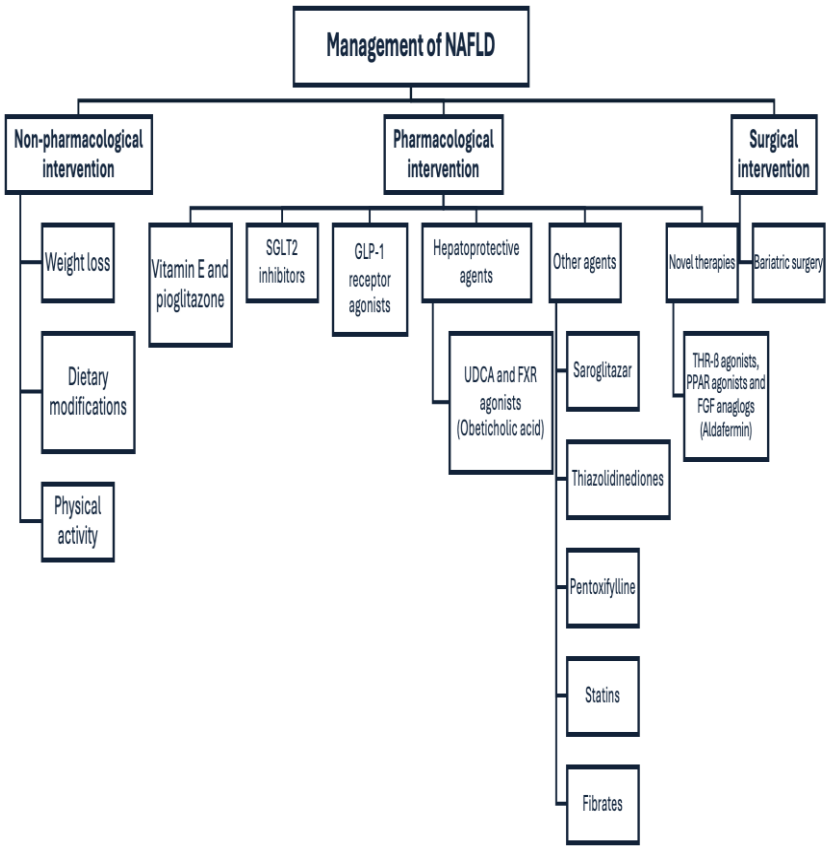

Figure 2. Management of non-alcoholic fatty liver disease.

Additional pharmacologic agents under investigation include thiazolidinediones, statins, and various lipid-lowering medications. Statins once thought to be hepatotoxic, are now being reconsidered for NAFLD management due to their benefits in reducing cancer-related mortality and cardiovascular risk. Other drugs, such as fibrates, omega-3 fatty acids, and pentoxifylline, have shown variable degrees of benefit, though they have limited advantages over lifestyle interventions. Novel therapies, including PPAR agonists, THR-β agonists like MGL-3196, and FGF analogs like Aldafermin, are under investigation, showing promising outcomes in lowering liver fat and improving metabolic parameters [53,54] .

Bariatric surgery is considered in cases of severe obesity, as it has been shown to improve liver histology and reduce fibrosis, though it carries risks, especially in advanced liver disease. Hepatoprotective agents, such as UDCA and FXR agonists

like obeticholic acid, show potential in protecting liver function, although adverse effects have been reported [10,44,55–57].

Patients with NAFLD should be monitored for disease progression, particularly signs of fibrosis, cirrhosis, portal hypertension, and hepatocellular carcinoma. One must adhere to lifestyle modifications for the long-term prevention of relapse.

CONCLUSION

Non-alcoholic fatty liver disease or NAFLD is a multi-system disorder with significant cardiovascular complications. The pathophysiological interconnections between NAFLD and cardiovascular diseases involve processes like insulin resistance, systemic inflammation, lipid dysregulation, oxidative stress, and endothelial dysfunction, which contribute to both the progression of liver disease and increased cardiovascular risk. Early diagnosis and personalized management regimes are essential to lower these risks emphasizing lifestyle modifications. Given the common risk factors for NAFLD and cardiovascular problems, a multidisciplinary strategy combining various aspects should be considered. Ongoing research into innovative therapeutic techniques, such as GLP-1 receptor agonists and SGLT2 inhibitors, provides promise for more successful treatments. However, more research is needed to determine long-term efficacy and safety in this patient population. By addressing both the hepatic and cardiovascular elements of NAFLD, physicians can considerably improve patient outcomes, stressing the importance of early intervention and tailored treatment approaches in lowering total morbidity and mortality. Future studies should focus more on personalized interventions based on precise pathophysiologic dysfunction in the patient to provide sustainable management and reduce the risk of recurrence.

Declaration by Authors

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