

Non Alcoholic Fatty liver disease; Disease burden, management, and future perspectives

Abstract:

Non-alcoholic fatty liver disease (NAFLD) is a significant and pertinent human ailment linked to a modified way of life, characterized by a fast increasing occurrence and prevalence in the majority of countries worldwide. Non-alcoholic fatty liver disease (NAFLD) can lead to significant health problems at various stages of chronic liver disease, including cirrhosis and related consequences such as hepatocellular carcinoma (HCC) and decompensation (such as bleeding from esophageal varices, accumulation of fluid in the abdomen, and impaired brain function due to liver dysfunction). In addition to hepatic problems, non-alcoholic fatty liver disease (NAFLD) patients frequently experience the metabolic syndrome, type 2 diabetes (T2D), and cardiovascular disease (CVD). While the current comprehension of the fundamental pathways in relation to NAFLD is growing, the precise pathophysiological impact of NAFLD on T2D and CVD remains incompletely known. One of the main theories suggests that a sub-clinical pro-inflammatory milieu is caused by lipotoxicity, insulin resistance (IR), and the intestinal microbiota. The primary foundation of the treatment involves lifestyle adjustment, which encompasses weight reduction, nutritional intervention, and consistent physical activity. While achieving this aim may be challenging for numerous patients, it is advisable for treating physicians to recommend and provide support for it. A variety of therapy choices, ranging from non-invasive management and medical intervention to surgical techniques (such as bariatric surgery), have been created with different results, particularly for the non-invasive treatment methods. The range of innovative therapeutic techniques is extensive, with several intriguing candidates. Collectively, NAFLD represents a significant healthcare concern that is projected to escalate in the future. Consequently, it is imperative for physicians from many disciplines to enhance their understanding of this condition to effectively address it with their patients.

1) INTRODUCTION:

Non-alcoholic fatty liver disease (NAFLD) is a prevalent etiology of chronic hepatic disorder on a global scale. NAFLD is a range of the illness distinguished by the presence of fatty liver when there are no other identifiable reasons for the buildup of fat in the liver (such as excessive alcohol consumption)[1-3]. NAFLD encompasses a spectrum of liver conditions, ranging from the less harmful non-alcoholic fatty liver (NAFL) to the more severe non-alcoholic steatohepatitis (NASH). Non-alcoholic fatty liver disease has the potential to advance to fibrosis and cirrhosis[4]. In NAFLD, the liver contains excess fat without any signs of inflammation. However, in non-alcoholic steatohepatitis (NASH), the liver still has excess fat but is accompanied with inflammation and cell death in the liver lobes. The inflammation and cell death can eventually result in the development of fibrosis and cirrhosis[5-8].

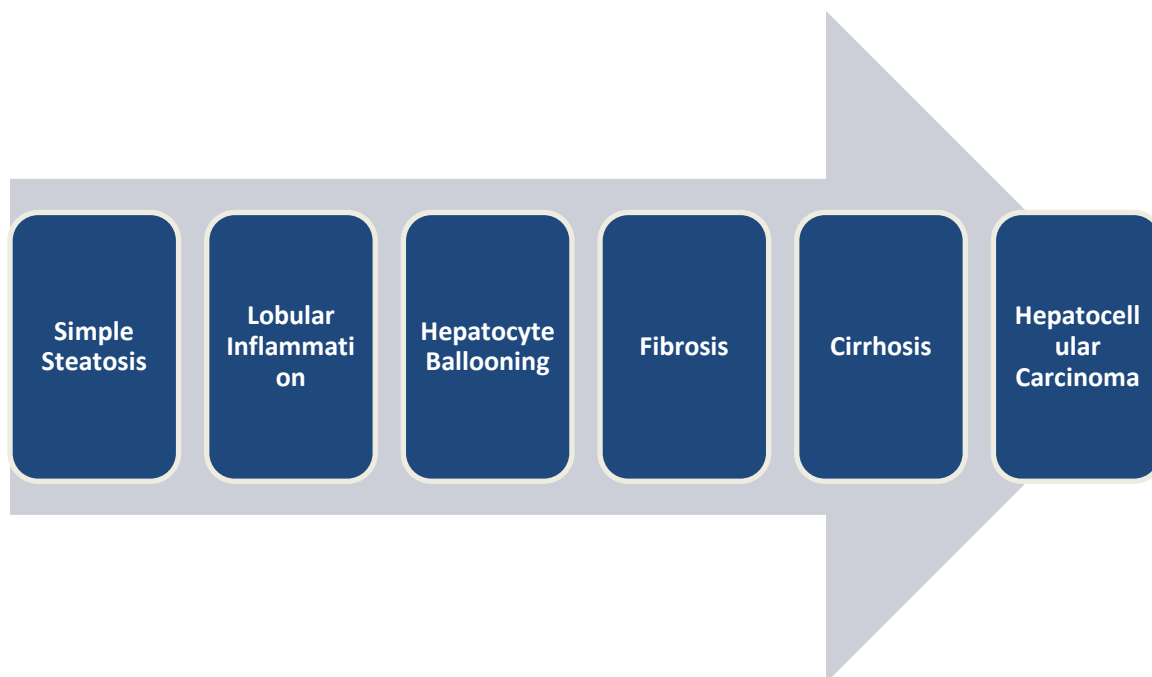


Figure 1 From NAFLD TO HCC

Prior to the mid-2000s, NASH was commonly regarded as a significant condition that primarily affected obese females[9]. It was frequently linked to Type 2 Diabetes Mellitus (T2DM) and had a relatively mild prognosis. These factors were indicative of an increased risk for cardiovascular disease, stroke, and diabetes. NAFLD has experienced a significant increase in occurrence in Western countries, with a global prevalence rate of 25% [9.10]. NAFLD is increasingly prevalent

as a chronic liver condition in Western industrialized nations, especially among those with central obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and metabolic syndrome[10, 11].

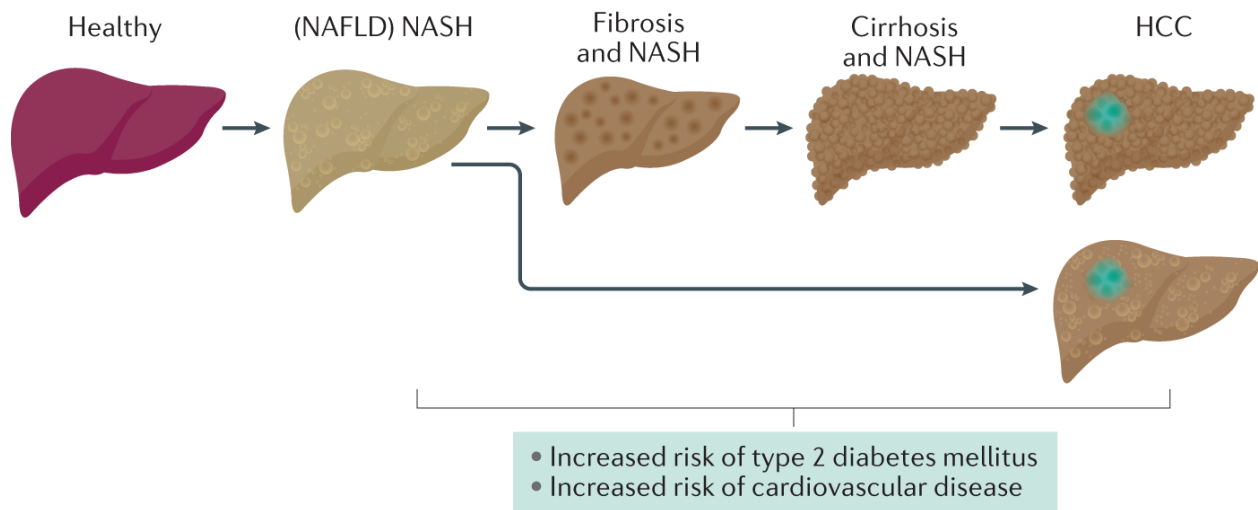


Figure 2 Progression of NAFLD [12]

When it comes to diagnostic examinations, the most reliable method to examine any type of liver inflammation or damage is a liver biopsy. Liver biopsies are highly valuable in diagnosing NAFLD and related conditions. The findings from these biopsies might vary, ranging from the presence of triglyceride deposits as droplets in the liver cells to more severe types of non-alcoholic steatohepatitis (NASH). NASH is often defined by the aforementioned lipid droplets present in liver cells, accompanied by inflammation and varying levels of liver fibrosis. Most people with hepatic steatosis have a non-progressive form of the illness. However, a small subset of these patients may develop NASH, as described earlier. NASH can advance to liver failure and even hepatocellular cancer[13].



Figure 3 Healthy Vs Fatty Liver [14]

The US guidelines for managing NAFLD define NAFLD as the presence of steatosis with at least 5% fat infiltration in imaging or histology, and the absence of alcohol, drug, or viral-induced steatosis. Patients with non-alcoholic fatty liver disease (NAFLD) may exhibit high levels of liver enzymes[15, 16].

Patients diagnosed with NAFLD may exhibit one or more elements of the metabolic syndrome (MS), such as systemic hypertension, dyslipidemia, insulin resistance, or overt diabetes. Mounting data suggests that visceral obesity is a risk factor for non-alcoholic fatty liver disease NAFLD[17]. Additionally, it is important to consider that metabolic syndrome (MS) is a recognized risk factor for the development of cardiovascular disease. According to existing literature, cardiac and vascular disorders appear to be the primary cause of death in these patients. However, the precise pathophysiological pathways that link cardiovascular disease and NAFLD are not yet fully comprehended. Insulin resistance is believed to be a shared element in the development of both conditions[18, 19].

Assessing atypical liver enzyme levels in an otherwise healthy patient can provide a difficulty even for a seasoned practitioner. NAFLD is a prevalent cause for atypical liver function test findings in individuals who donate blood. The liver function test identifies the presence of

elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in up to 90% of cases, after ruling out other causes of liver illness[20, 21]. According to the 2014 data from the World Health Organization Global Health Observatory, the prevalence of obesity among those aged 18 and above is 15% among women and 11% among men worldwide. An assessment examining the frequency of NASH determined that around 5.7–17% of the population in the United States is impacted by this condition[22-25].

2) Pathophysiology of NAFLD:

The progression of NASH is an intricate phenomenon that remains incompletely comprehended. Recently, there has been a significant amount of animal research focused on studying the pathophysiology of NAFLD and NASH. The research mostly examines the effects of several dietary models, such as high fructose, high fat, or methionine/choline deficient diet (MCD). According to this collection of information, it has been proposed that the progression of NASH occurs in two distinct stages. The initial stage of this process involves the accumulation of fat in the liver, leading to an elevation in insulin resistance. The second phase of this process entails cellular and molecular alterations characterized by oxidative stress and the oxidation of fatty acids in the liver. These changes are caused by various factors, including cytokine injury, hyperinsulinemia, hepatic iron and/or lipid peroxidation, variations in the extracellular matrix, disturbances in energy homeostasis, and alterations in immune system function. The emergence of insulin resistance is a complex process. In the context of metabolic syndrome (MS), similar to many individuals with NASH, the escalation of fat mass and the process of adipocyte differentiation are crucial factors in the development of insulin resistance[26-30].

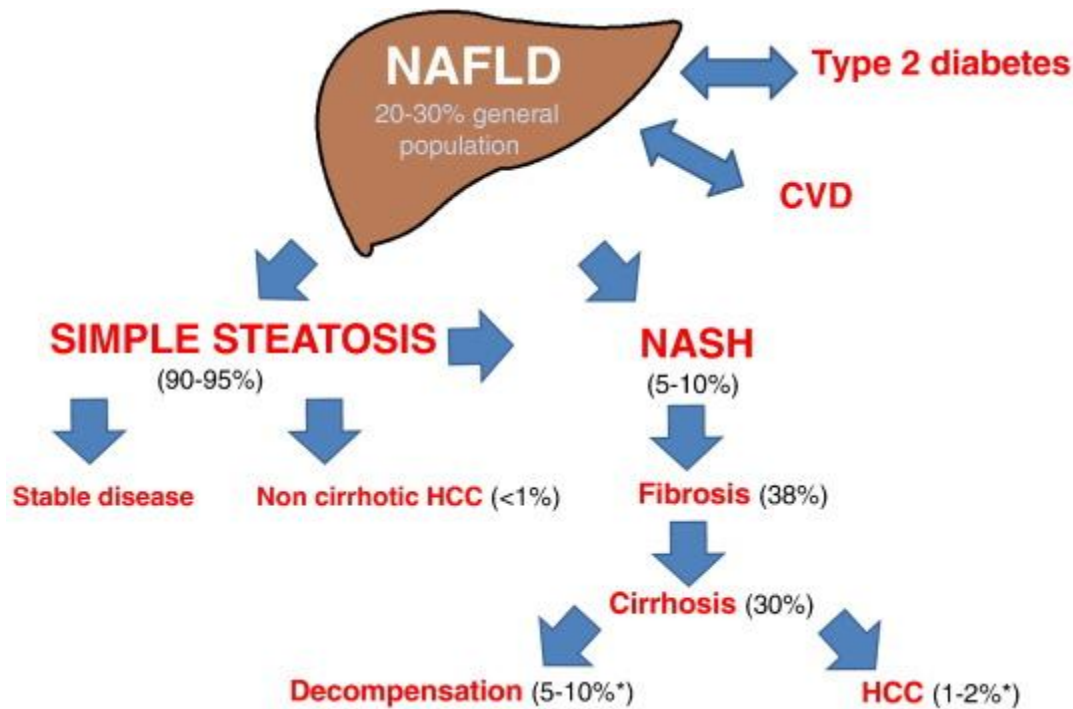


Figure 4 Pathophysiology of NAFLD [31]

NAFLD can be categorized into two different subtypes. The first form of NAFLD is closely associated with metabolic syndrome, and it is widely believed that insulin resistance is the main underlying mechanism responsible for its development. The second variant of NAFLD is associated with infectious diseases that might result in the development of hepatic steatosis. In this scenario, infections such as hepatitis C and HIV can be a contributing factor. However, it is also linked to the use of certain medications (such as total parenteral nutrition, glucocorticoids, tamoxifen, tetracycline, amiodarone, methotrexate, valproic acid, and vinyl chloride), as well as exposure to specific toxins or the presence of inherited or acquired metabolic disorders (such as lipodystrophy, cachexia, or intestinal bypass surgery)[32-34].

2.1. Risk Factors:

Individuals with NAFLD typically exhibit features commonly seen in metabolic syndrome (MS), along with the accompanying risk factors for cardiovascular disease[35]. As previously mentioned, NAFLD is strongly associated with metabolic syndrome and obesity[36]. Type 2 diabetes mellitus (T2DM) and dyslipidemia are recognized as significant risk factors for NAFLD[37]. Research has demonstrated a higher occurrence of cardiovascular disease (CVD) in

individuals with NAFLD, regardless of whether they had diabetes or not. Hence, NAFLD is commonly linked to an unhealthy way of living, and there is evidence indicating that modifying unhealthy lifestyles can lower transaminase levels and enhance NAFLD[38]. A study on patients with T2DM discovered a higher occurrence of peripheral vascular, coronary, and cerebrovascular diseases in individuals with NAFLD compared to those without NAFLD[39]. The prevalence of coronary, cerebrovascular, and peripheral vascular disease was significantly higher in subjects with NAFLD, even after accounting for normal cardiovascular disease risk factors, medication usage, and diabetes-related variables. More than 20 investigations, including both prospective and retrospective ones, have examined the connection between NAFLD and cardiovascular disease, and it has been determined that cardiovascular disease poses a significant and immediate risk [29]. This finding is consistently being supported by ongoing studies.[40, 41]



Figure 5 Risk Factors of NAFLD

The association between NAFLD and smoking is a subject of debate. Smoking is a significant contributor to the occurrence of chronic, non-communicable diseases (NCD) worldwide, including cancer, T2DM, respiratory problems, and cardiovascular conditions [42]. Research conducted on rats with obesity revealed that exposure to cigarette smoke intensified the histopathological severity of non-alcoholic fatty liver disease (NAFLD) [43]. A cross-sectional study conducted on individuals with NAFLD observed that the prevalence of liver substantial fibrosis and advanced hepatic fibrosis was significantly greater among smokers compared to non-smokers. A comprehensive analysis of 20 published studies conducted a systematic review and meta-analysis, revealing a strong correlation between smoking and NAFLD[44]. The study also emphasized the need for additional research to elucidate the underlying processes of this association. Although smoking was previously believed to be a significant risk factor for the development of NAFLD, a study involving 933 patients (368 smokers and 565 non-smokers as controls) found no difference in the occurrence of NAFLD between the two groups (22.2% versus 29%), including heavy smokers who consumed more than 20 packs of cigarettes per year[45].

3) Etiology Of NAFLD:

- **Insulin Resistance and Metabolic Syndrome:** The primary cause of NAFLD is often linked to metabolic risk factors, including insulin resistance, obesity, high levels of fats in the blood (hyperlipidemia), and conditions like type 2 diabetes. These factors contribute to the accumulation of fat in the liver[46].
- **Genetic Predisposition:** Genetic factors can influence an individual's susceptibility to NAFLD. Certain genetic mutations or variations may increase the risk of developing the condition[47].
- **Dietary Factors:** Consuming a diet high in calories, especially from sugars and unhealthy fats, can contribute to the development of NAFLD[48].
- **Lifestyle Factors:** Sedentary lifestyles and lack of physical activity are associated with an increased risk of NAFLD[49].
- **Other Medical Conditions:** Certain medical conditions like polycystic ovary syndrome (PCOS), sleep apnea, and hypothyroidism are linked to a higher risk of NAFLD[50].

4) Epidemiology:

The prevalence of NAFLD has been rising globally, in parallel with the increasing rates of obesity and metabolic syndrome. Key epidemiological points include:

- **Global Prevalence:** NAFLD is one of the most common liver diseases worldwide. Its prevalence varies by region, but it is estimated that around 25% of the global population has NAFLD[51].
- **Association with Obesity:** Obesity is a significant risk factor for NAFLD. A substantial portion of obese individuals have NAFLD, and the prevalence increases with higher body mass index (BMI)[52].
- **Age and Gender:** NAFLD can affect individuals of all ages, including children. However, it is more prevalent in middle-aged and older adults. Men tend to have a higher prevalence of NAFLD compared to premenopausal women, but after menopause, the risk in women increases[53].
- **Ethnic and Geographic Variations:** There are variations in NAFLD prevalence among different ethnic groups and geographical regions. Certain populations, such as Hispanics and Asians, may have a higher predisposition to NAFLD[54].
- **Association with Other Conditions:** NAFLD is often associated with other health conditions like cardiovascular disease, type 2 diabetes, and chronic kidney disease, making it a significant health concern due to its potential complications[55].

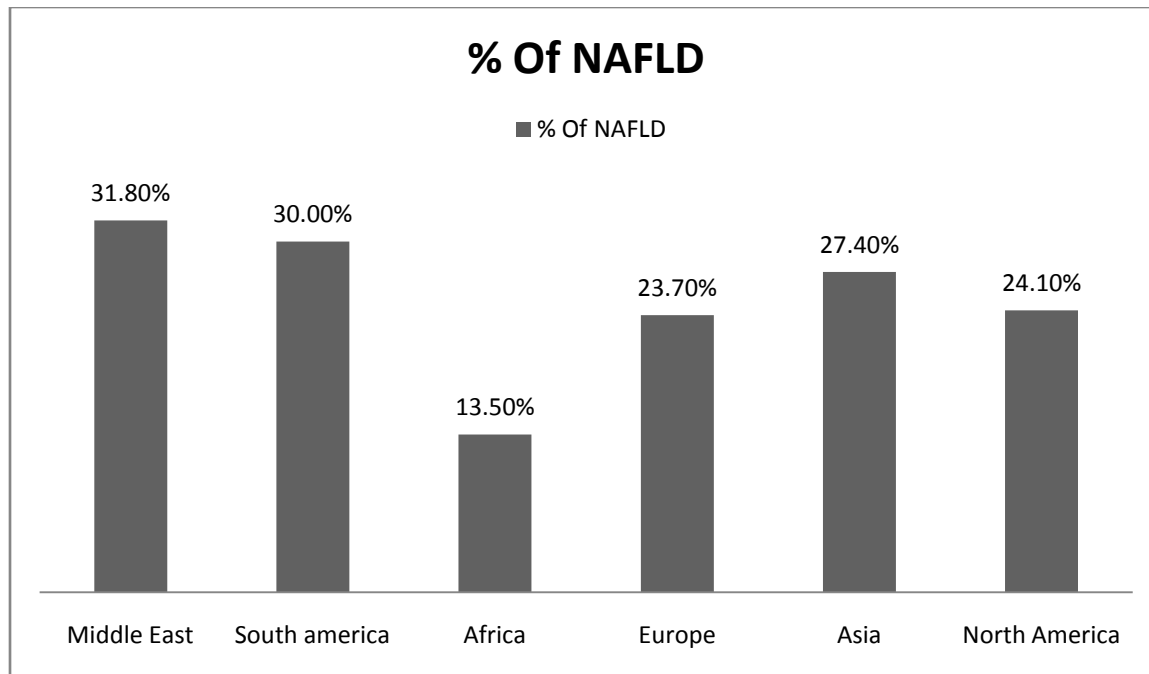


Figure 6 Epidemiology of NAFLD

Understanding the causes and epidemiology of NAFLD is crucial for developing effective prevention strategies and treatments, especially given its increasing prevalence worldwide. Regular exercise, maintaining a healthy weight, and adopting a balanced diet are essential preventive measures against NAFLD.

5) Diagnosis:

NAFLD is a condition characterized by the accumulation of fat in the liver cells, not due to alcohol consumption. Diagnosis typically involves a combination of medical history, physical examination, blood tests, imaging studies, and sometimes a liver biopsy[56, 57].

- **Medical History and Physical Examination:** The doctors take detailed medical histories to understand the patient's risk factors, such as obesity, diabetes, high cholesterol, or metabolic syndrome. A physical examination may reveal an enlarged or tender liver[58].
- **Laboratory Tests:** Blood tests are commonly used to assess liver function and rule out other liver diseases. These tests may include liver enzymes (AST, ALT), markers of liver function (bilirubin, albumin), and other markers such as gamma-glutamyl transferase

(GGT) and alkaline phosphatase. Elevated liver enzymes can indicate liver inflammation or damage[59].

- **Imaging Studies:** Various imaging techniques help in diagnosing and assessing the extent of NAFLD. Ultrasound is often the first imaging test used, showing fat accumulation in the liver. Other imaging methods like computed tomography (CT) scans or magnetic resonance imaging (MRI) can provide more detailed information[60].
- **Fibrosis Assessment:** As NAFLD can progress to more severe conditions like non-alcoholic steatohepatitis (NASH) and fibrosis, assessing the degree of fibrosis is crucial for prognosis. Non-invasive methods like transient elastography (FibroScan) or magnetic resonance elastography (MRE) are used to assess liver stiffness, indicating the degree of fibrosis without the need for a liver biopsy[61, 62].
- **Liver Biopsy:** In some cases, a liver biopsy may be recommended, especially if the diagnosis is uncertain or if there is a need to determine the severity of liver damage and rule out other liver conditions that typically involves taking a small sample of liver tissue for microscopic examination[63, 64].
- **Serum Biomarkers and Scoring Systems:** Some emerging serum biomarkers and scoring systems (like NAFLD Fibrosis Score, FIB-4 index, etc.) are used to assess the risk of advanced fibrosis in NAFLD without the need for a liver biopsy[65, 66].

The diagnosis and management of NAFLD should be done by healthcare professionals. The approach to diagnosis may vary based on individual patient characteristics and available resources [67].

6) MANAGEMENT:

NAFLD is a prevalent liver condition characterized by an accumulation of fat in the liver cells in individuals who consume little to no alcohol. It encompasses a spectrum of liver disorders, ranging from simple fatty liver (steatosis) to non-alcoholic steatohepatitis (NASH), which involves liver inflammation and can progress to fibrosis, cirrhosis, and even liver failure in

severe cases. As the incidence of NAFLD continues to rise globally, the development of effective treatment options becomes increasingly crucial[68, 69].

6.1. Lifestyle Modifications:

- **Dietary Changes:** A fundamental aspect of managing NAFLD involves adopting a balanced, healthy diet. This typically includes reducing the intake of sugars, saturated fats, and processed foods while increasing consumption of fruits, vegetables, whole grains, and healthy fats like those found in nuts, avocados, and fish[70].
- **Weight Management:** Weight loss, particularly for individuals who are overweight or obese, is a cornerstone of NAFLD treatment. Gradual weight reduction, typically around 5-10% of body weight, has shown substantial improvements in liver health and can lead to a reduction in liver fat[71].
- **Regular Exercise:** Physical activity plays a pivotal role in NAFLD management. Exercise, along with dietary changes, aids in weight loss and helps improve insulin sensitivity, reducing liver fat and inflammation[72].

6.2. Medications:

- **Insulin Sensitizers:** Certain medications, like pioglitazone and metformin, are used off-label to improve insulin sensitivity, manage blood sugar levels, and potentially reduce liver inflammation in NAFLD patients with insulin resistance or diabetes[73, 74].
- **Antioxidants and Cytoprotective Agents:** Vitamin E, due to its antioxidant properties, has been studied in NASH patients and has shown some promise in reducing liver inflammation and fibrosis[75].
- **Lipid-Lowering Medications:** Statins or other lipid-lowering drugs may be prescribed to manage cholesterol levels, which can help in reducing liver fat accumulation[76].

6.3. Clinical Interventions:

- **Bariatric Surgery:** For severely obese individuals with NAFLD or NASH, bariatric surgery might be considered in cases where lifestyle changes have not been successful in achieving weight loss. Studies have shown improvements in liver histology following significant weight reduction post-surgery[77, 78].
- **Clinical Trials:** Ongoing research investigates various pharmaceutical agents targeting different pathways involved in NAFLD/NASH pathogenesis. These trials explore new drug classes focusing on liver fat metabolism, inflammation, and fibrosis[79].

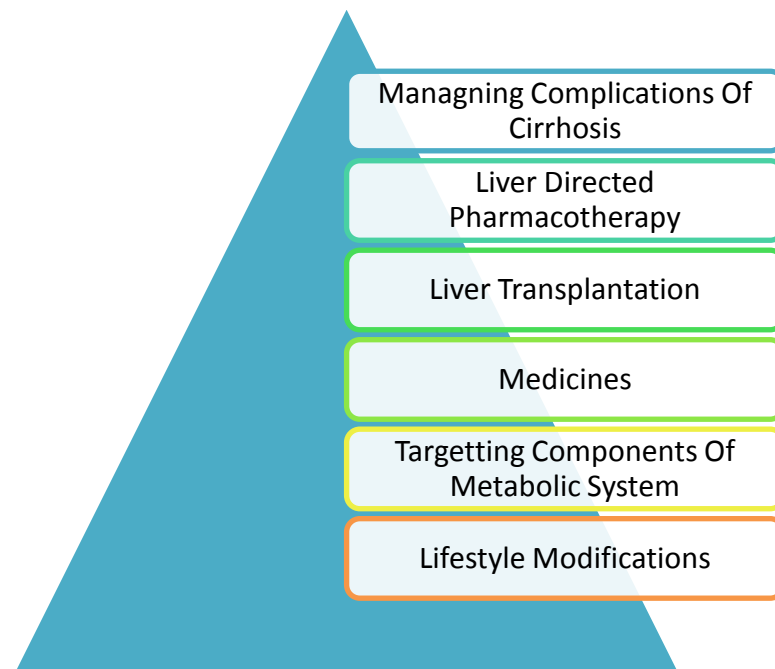


Figure 7 Management options for NAFLD

6.4. Liver Transplantation:

In advanced stages of NAFLD-associated liver disease, such as cirrhosis or liver failure, liver transplantation remains the definitive treatment option. However, due to the rise in NAFLD cases, transplantation resources might face challenges in meeting the demand[80]. The management of NAFLD involves a multidisciplinary approach, integrating lifestyle modifications, medications, and sometimes surgical interventions. Patients should consult with healthcare professionals for personalized treatment plans and ongoing monitoring to mitigate disease progression and reduce the risk of complications. Moreover, early detection and intervention play a vital role in preventing NAFLD from advancing to more severe stages[81].

Non-Alcoholic Fatty Liver Disease (NAFLD) has emerged as a pressing global health concern in recent decades. Characterized by the accumulation of fat in the liver, NAFLD encompasses a spectrum of conditions ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and eventually liver failure. As the prevalence of NAFLD continues to rise worldwide, there is an urgent need for innovative approaches and future perspectives in its treatment.

Future perspectives:

The current management of NAFLD primarily involves lifestyle modifications such as dietary changes, increased physical activity, and weight loss. However, these measures can be challenging to implement and sustain, and they might not be sufficient for many patients, particularly those with advanced stages of the disease[82]. Research in the field of NAFLD treatment has been dynamic, aiming to address the complexity of the condition. Pharmaceutical companies and researchers are actively investigating various drug targets and compounds that could effectively treat NAFLD and NASH. Some of these drugs focus on reducing liver fat accumulation, inflammation, and fibrosis. Several medications targeting metabolic pathways, such as insulin sensitizers, antioxidants, lipid-lowering agents, and anti-fibrotic drugs, are in different stages of clinical trials. These drugs hold potential for altering the natural course of NAFLD progression[83, 84]. Advancements in genomics and precision medicine offer hope for tailored treatments based on an individual's genetic makeup and disease characteristics. Identifying specific genetic variants associated with NAFLD susceptibility and progression could lead to personalized therapeutic strategies, optimizing treatment efficacy and minimizing adverse effects[85].

Growing evidence suggests a strong association between gut microbiota and NAFLD. Manipulating the gut microbiome through probiotics, prebiotics, or fecal microbiota transplantation shows promise in improving liver health by modulating inflammation, metabolic function, and gut barrier integrity[86, 87]. Innovative approaches involving cellular and gene therapies are being explored to target liver regeneration, repair damaged tissues, and modulate metabolic pathways. Techniques like gene editing and stem cell transplantation hold potential for addressing the underlying molecular mechanisms of NAFLD[88]. Integration of technology and

digital health tools, such as mobile applications, wearable devices, and artificial intelligence, can aid in monitoring patients, providing personalized interventions, and promoting adherence to lifestyle modifications and medication regimens[89].

Despite these promising future perspectives, challenges remain in translating these advancements into clinical practice. Rigorous research, ensuring safety and efficacy, regulatory approvals, and accessibility of novel treatments to diverse populations are crucial considerations.

Conclusions:

There is a rising occurrence of NAFLD and NASH, which is directly linked to the growing prevalence of obesity and diabetes. NAFLD and NASH are the principal causes responsible for the escalating incidence of hepatocellular carcinoma (HCC), which is the predominant form of liver cancer. Currently, there is no authorized therapy for NAFLD and NASH. Evaluations have been conducted on novel non-invasive diagnostic markers, such as miRNAs, for the prospective diagnosis of NAFLD. Timely detection of the advancement of NAFLD to liver fibrosis, cirrhosis, or HCC is of utmost significance due to the irreversible or challenging reversibility of severe liver disease. PPARs, GLP-1, miRNAs, and KLFs are important molecules that can be targeted for treating metabolic illnesses including NAFLD and NASH. Preclinical investigations and clinical trials have been conducted to assess prospective therapeutic interventions for NAFLD and NASH, such as synbiotics, pan-caspase inhibitors, CCR2/5 antagonists, FXR agonists, and other similar approaches. Utilizing a comprehensive approach, such as integrating medical treatment with physical activity, may have the potential to decrease the duration of treatment and enhance the overall outcome.

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