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Review Article

Non-Alcoholic Fatty Liver Disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is characterized by the buildup of fat in the liver, and it is not caused by excessive alcohol consumption. NAFLD is highly prevalent, affecting approximately 30% of the population in developed countries and around 10% in developing nations. As a result, NAFLD has become the most prevalent liver condition worldwide.

The development of NAFLD is closely linked to insulin resistance, making it common among individuals who have central obesity or diabetes. Insulin resistance and excess body fat contribute to a higher influx of lipids into the liver and an increased production of new fats within the liver, known as de novo hepatic lipogenesis. These processes ultimately lead to the accumulation of triglycerides in the liver, a characteristic feature of NAFLD.

NAFLD is closely associated with components of the metabolic syndrome, and individuals with type 2 diabetes have an increased risk of developing cirrhosis and its related complications. While cardiovascular disease and extra hepatic malignancy are the leading causes of death in people with NAFLD, the presence of advanced liver fibrosis is a significant indicator of liver-related outcomes and overall mortality. Non-invasive tests that combine various methods can be used to assess the extent of liver fibrosis. Patients diagnosed with cirrhosis should undergo screenings for hepatocellular carcinoma (a type of liver cancer) and esophageal varices. Currently, there are no approved therapies for NAFLD; however, there are several drugs in advanced stages of development that show promise for future treatment options.

Keywords: Non-alcoholic fatty liver disease, Weight management, Bariatric surgery, Metabolic surgery, Conservative therapy.

Introduction:

Non-alcoholic fatty liver disease (NAFLD) is a term that encompasses a range of liver disorders. It is characterized by the presence of steatosis, which is when more than 5% of hepatocytes (liver cells) show excessive fat accumulation, despite minimal alcohol consumption or without any alcohol consumption at all.¹⁻³

Non-alcoholic steatohepatitis (NASH) is a condition that falls on the more severe end of the spectrum within NAFLD. It lies between NAFL, which is a milder form of the disorder, and the broader category of NAFLD. NAFLD itself has the potential to progress to cirrhosis and fibrosis over time.^(4,5) Hepatic steatosis is present in NAFLD but there is no sign of inflammation, whereas in NASH, it is linked to lobular inflammation and apoptosis, which can result in fibrosis and cirrhosis.⁽⁴⁻⁷⁾

Prior to the middle of the previous decade, NASH was largely regarded as a dangerous disorder that virtually exclusively affected obese females who have Type 2 Diabetes Mellitus (T2DM), a prognosis that is generally favorable, and who have cardiovascular disease, stroke, and diabetes risk factors.⁴⁻⁷

According to a recent meta-analysis, the worldwide prevalence of non-alcoholic fatty liver disease (NAFLD) among individuals with type 2 diabetes was found to be over twice as high as in the general population, reaching nearly 60%. Additionally, non-alcoholic steatohepatitis (NASH), a more severe form of NAFLD, was present in approximately one-third of these patients. Moreover, among those who underwent liver biopsy, 17% exhibited advanced fibrosis (AF), which is a significant factor contributing to increased overall mortality and negative outcomes specifically related to liver health across different stages of NAFLD.⁸⁻¹⁰

Due to the rise in obesogenic lifestyles, the aging population, and the increasing prevalence of type 2 diabetes, it is estimated that by 2030, there will be a significant surge in NASH-related hepatocellular carcinoma (HCC) cases, with an anticipated increase of 137%. Additionally, liver-related deaths associated with NASH are projected to rise by 178% during the same period. These projections highlight the urgent need for interventions and strategies to address the growing burden of NASH and its associated complications.¹¹

Pathophysiology:

The progression of non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH) has been explained by the "two-hits hypothesis." However, recent evidence suggests a more intricate mechanism known as the "multiple parallel

hits hypothesis." This theory proposes that various factors act simultaneously rather than in a sequential manner. These factors include insulin resistance (IR), genetic and epigenetic influences, mitochondrial dysfunction, endoplasmic reticulum stress, gut microbiota, chronic low-grade inflammation and

dysfunction of adipose tissue. According to this theory, these factors collectively contribute to the development and progression of both NAFLD and NASH. This multifactorial perspective provides a more comprehensive understanding of the complex processes involved in NAFLD pathogenesis.¹²⁻¹⁵

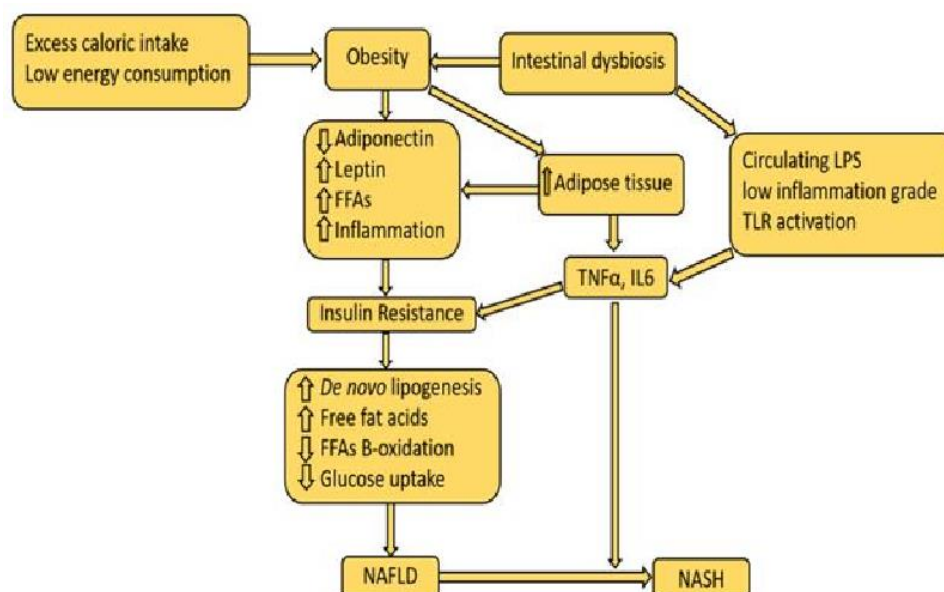


Figure 1: Schematic representation of the pathophysiological mechanisms of Non-Alcoholic Fatty Liver Disease (NAFLD) development. LPS: lipopolysaccharides; TNF- α : tumor necrosis factor-alpha; IL-6: interleukine-6; TLR: toll-like receptor; FFAs: free fatty acids.

It has been proposed that the development of NASH is a two-step process based on this body of evidence. The first stage of this process involves the accumulation of fat in the liver, which will make insulin resistance worse. The second stage of this process involves cellular and molecular alterations brought on by oxidative stress and the oxidation of fatty acids in the liver as a result of numerous factors, including cytokine injury, hyperinsulinemia, hepatic iron and/or lipid peroxidation, variation in the extracellular matrix, altered energy homeostasis, and altered immune system function.^(14,15) The process of insulin resistance development is complex. As is the situation for many people with NASH who have metabolic syndrome (MS), the rise in fat. Insulin resistance is primarily caused by bulk and adipocyte differentiation.

NAFLD, or Non-Alcoholic Fatty Liver Disease, can be classified into two distinct types based on their underlying causes and mechanisms.

The first type of NAFLD is closely associated with metabolic syndrome. Metabolic syndrome refers to a cluster of conditions such as obesity, insulin resistance, high blood pressure, and dyslipidemia. In this type, insulin resistance is considered the primary pathophysiological mechanism. Insulin resistance impairs the body's ability to effectively utilize insulin, leading to elevated blood glucose levels. This, in turn, promotes the accumulation of fat in the liver, resulting in NAFLD.

The second type of NAFLD is linked to infectious pathologies. Infections such as hepatitis C and HIV can contribute to the development of liver steatosis, which is the accumulation of fat in the liver. Additionally, certain medications can also cause this type of NAFLD. Examples include total parenteral nutrition (intravenous feeding), glucocorticoids (steroids), tamoxifen (used for breast cancer treatment), tetracycline (an antibiotic), amiodarone (used for heart rhythm disorders), methotrexate (used for various medical conditions), valproic acid (used for epilepsy and mood disorders), and exposure to

vinyl chloride (a chemical). Furthermore, specific toxins or inherited/acquired metabolic diseases, such as lipodystrophy (abnormal fat distribution), cachexia (severe weight loss and muscle wasting), or intestinal bypass surgery, can also be associated with this second type of NAFLD.^{16,17}

NAFLD and Type 2 Diabetes:

The prevalence of NAFLD (Non-Alcoholic Fatty Liver Disease) in patients with type 2 diabetes mellitus (T2DM) can indeed vary depending on the screening methods employed in different studies. The wide range you mentioned, from 29.6% to 87.1%, highlights the variability in reported prevalence rates.¹⁸⁻²⁰ hyperglycemia and insulin resistance (IR) play significant roles in the development of NAFLD (Non-Alcoholic Fatty Liver Disease) and the progression to liver fibrosis. The relationship between elevated blood glucose levels and liver damage is well-established.

Hyperglycemia, which refers to persistently high levels of glucose in the blood, can induce toxicity in the liver. When blood glucose levels are chronically elevated, it can lead to increased production of reactive oxygen species (ROS) and oxidative stress.²³ This oxidative stress can damage liver cells and initiate inflammation within the liver, contributing to the development of NAFLD.²¹ Indeed, there is evidence suggesting a correlation between HbA1c (glycated hemoglobin) levels and liver fat content in individuals with NAFLD. HbA1c is a marker of long-term blood glucose control, and higher levels are indicative of poorer glycemic control over time. A study demonstrating a linear correlation between HbA1c and liver fat content suggests that elevated HbA1c levels are associated with a greater accumulation of fat in the liver.

The coexistence of type 2 diabetes mellitus (T2DM) and insulin resistance (IR) has been found to contribute to an increased risk of cardiovascular disease (CVD). Both T2DM and IR are characterized by impaired glucose metabolism and elevated blood glucose levels, which can have detrimental

effects on cardiovascular health.²³⁻²⁷

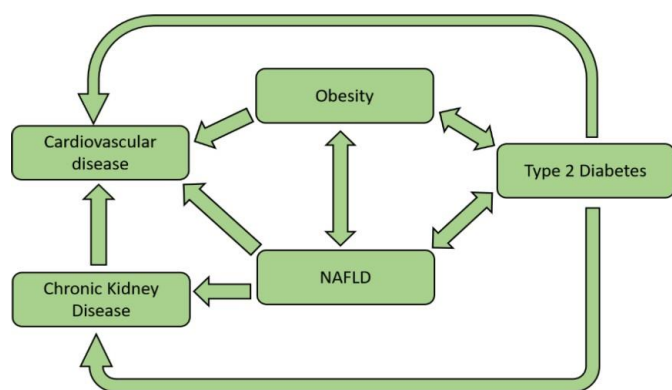


Figure 2: Schematic representation of NAFLD associated cardiorenal disease and type 2 diabetes development

Signs and symptoms:

The majority of patients with NAFLD do not experience any symptoms, but some may report fatigue, discomfort in the right upper quadrant of the abdomen, enlarged liver (hepatomegaly), acanthosis nigricans (dark patches of skin), and lipomatosis (excessive fat deposits). In some cases, individuals with cirrhosis, which can develop from NAFLD, may present with end-stage liver disease symptoms. Approximately 48-100% of cases of NASH can be asymptomatic and are often discovered incidentally during medical evaluations for other reasons. While clinical signs of chronic liver failure are rare in this population, one study found that 25% of patients had splenomegaly (enlarged spleen) at the time of diagnosis. Abnormal liver function tests, such as elevated levels of aminotransferases (ALT and AST), or the identification of hepatic steatosis through radiologic abdominal findings, can often lead to the diagnosis of NASH or NAFLD.²⁸

During physical examination, hepatomegaly (enlarged liver) can be detected in some individuals with NAFLD. This enlargement is typically a result of fatty infiltration in the liver. As fat accumulates in the liver cells, the liver may increase in size and become palpable during a physical examination.

Hepatomegaly can be an indication of liver disease, including NAFLD, but it is important to note that not all individuals with NAFLD will have an enlarged liver, and hepatomegaly can also be caused by other liver conditions or factors. A thorough evaluation and diagnostic tests are necessary to confirm the underlying cause of hepatomegaly in each individual case.²⁸

Risk factors:

Non-alcoholic fatty liver disease (NAFLD) is often associated with metabolic syndrome (MS), which is a cluster of conditions that increase the risk of cardiovascular disease and type 2 diabetes.^{29,30} NAFLD is often associated with an unhealthy lifestyle, including poor dietary habits, sedentary behavior, and lack of physical activity. These lifestyle factors contribute to the development and progression of NAFLD. However, research has also shown that making positive changes in lifestyle can lead to improvements in NAFLD.

Studies have demonstrated that adopting a healthier lifestyle, including regular exercise, a balanced diet, weight loss (especially in cases of obesity), and appropriate management of metabolic risk factors such as diabetes and dyslipidemia, can result in improvements in liver function and reduction in transaminase levels (e.g., ALT and AST).³¹⁻³⁴

Diagnosis:

Because NAFLD causes no symptoms in most cases, it frequently comes to medical attention when tests done for other reasons point to a liver problem. This can happen if your liver looks unusual on ultrasound or if you have an abnormal liver enzyme test.

Tests done to pinpoint the diagnosis and determine disease severity include:

➤ Blood tests

1. Complete blood count
2. Liver enzyme and liver function tests
3. Tests for chronic viral hepatitis (hepatitis A, hepatitis C and others)
4. Celiac disease screening test
5. Fasting blood sugar
6. Hemoglobin A1C, which shows how stable your blood sugar is
7. Lipid profile, which measures blood fats, such as cholesterol and triglycerides

➤ Imaging procedures: Imaging procedures used to diagnose NAFLD include:

- Abdominal ultrasound: which is often the initial test when liver disease is suspected.
- Computerized tomography: (CT) scanning or magnetic resonance imaging (MRI) of the abdomen. These techniques lack the ability to distinguish NASH from NAFLD, but still may be used.
- Transient elastography: an enhanced form of ultrasound that measures the stiffness of your liver. Liver stiffness indicates fibrosis or scarring.
- Magnetic resonance elastography: works by combining MRI imaging with sound waves to create a visual map (elastogram) showing the stiffness of body tissues²⁸

Liver tissue examination:

In situations where other tests fail to provide conclusive results, your physician may suggest a liver biopsy, which involves the removal of a small tissue sample from your liver. This sample is then carefully examined in a laboratory to identify any signs of inflammation or scarring.

It's important to note that a liver biopsy can cause some discomfort, and there are certain inherent risks associated with the procedure. Your doctor will provide you with a thorough explanation of these risks and discuss them with you in detail. During the biopsy, a needle is inserted through your abdominal wall and into the liver to extract the tissue sample.

Treatment:

The treatment for non-alcoholic fatty liver disease (NAFLD) typically involves lifestyle changes and management of underlying conditions. Here are some common approaches:

- Weight loss: Losing excess weight is often recommended for people with NAFLD, especially if they are overweight or obese. Gradual weight loss through a combination of a balanced diet and regular exercise can help reduce liver fat and improve liver function.
- Diet modifications: Adopting a healthy eating plan can be beneficial for NAFLD. A diet that is low in saturated fats, trans fats, and refined carbohydrates while being rich in

fruits, vegetables, whole grains, and lean proteins is often recommended. Avoiding sugary beverages and processed foods is also important.

- **Regular exercise:** Engaging in regular physical activity can help improve insulin sensitivity and reduce liver fat. Aim for at least 150 minutes of moderate-intensity aerobic activity per week, along with strength training exercises.
- **Blood sugar control:** If you have type 2 diabetes or prediabetes, managing your blood sugar levels is crucial for NAFLD. Follow your healthcare provider's advice regarding medication, diet, and lifestyle changes to maintain optimal blood glucose levels. Management of underlying conditions: NAFLD is commonly associated with conditions like obesity, high cholesterol, hypertension, and metabolic syndrome. Treating and controlling these conditions through appropriate medications, lifestyle changes, and regular check-ups can help improve liver health.
- **Avoidance of alcohol and certain medications:** It's important to avoid alcohol completely, as it can worsen liver damage. Additionally, some medications may contribute to liver injury, so it's crucial to discuss all medications, including over-the-counter and herbal supplements, with your healthcare provider.
- **Regular monitoring and follow-up:** Regular check-ups and monitoring of liver function, blood sugar levels, and lipid profiles are important to track your progress and adjust treatment as needed.³⁵

Pharmacological treatment:

Numerous studies have explored pharmacological interventions to manage the development and progression of non-alcoholic fatty liver disease (NAFLD), although no drugs are currently approved specifically for its treatment. However, certain medications have shown promise in clinical trials.

One example is pioglitazone, which is an approved drug for the treatment of type 2 diabetes. Pioglitazone targets adipose tissue metabolism and inflammation by activating peroxisome proliferator-activated receptor gamma (PPAR γ), a transcription factor. By increasing the uptake of fatty acids by adipocytes, pioglitazone reduces hepatic steatosis and the flow of fatty acids to the liver. It also upregulates adiponectin, an adipokine with anti-steatogenic properties.

Diagnosing NAFLD and its more severe form, non-alcoholic steatohepatitis (NASH), typically requires a liver biopsy, but this procedure has limitations. Therefore, noninvasive tests based on biomarkers and transient elastography have gained importance in clinical practice. Diagnostic panels such as the NAFLD fibrosis score, FIB-4, and Fibro Meter have been validated and are used to assess NAFLD/NASH. Transient elastography is particularly useful in evaluating advanced fibrosis and cirrhosis.

Complications:

The complications of non-alcoholic fatty liver disease (NAFLD) can vary in severity and are often associated with the histological stage and grade of liver disease. The most significant complications, listed in descending order, include:

1. **Cardiovascular disease:** NAFLD is strongly associated with an increased risk of cardiovascular diseases, such as heart attack, stroke, and atherosclerosis. The presence of NAFLD is considered an independent risk factor for cardiovascular events, and individuals with advanced stages of NAFLD are at a higher risk.

2. **Hepatocellular carcinoma (HCC):** NAFLD, particularly non-alcoholic steatohepatitis (NASH), can progress to liver cirrhosis, which further increases the risk of developing hepatocellular carcinoma, the most common type of liver cancer. The risk of HCC is higher in individuals with advanced fibrosis or cirrhosis due to NAFLD.
3. **End-stage liver disease:** In severe cases of NAFLD, progressive liver damage can lead to end-stage liver disease, which is characterized by advanced fibrosis, cirrhosis, and liver failure. End-stage liver disease may require liver transplantation as the ultimate treatment option.

Conclusion:

In conclusion, non-alcoholic fatty liver disease (NAFLD) is a prevalent condition characterized by the accumulation of fat in the liver. It ranges from simple steatosis to non-alcoholic steatohepatitis (NASH) and can progress to advanced fibrosis, cirrhosis, hepatocellular carcinoma (HCC), and cardiovascular disease.

The primary approach to managing NAFLD involves lifestyle modifications, including weight loss, a healthy diet, regular exercise, and controlling underlying conditions such as diabetes and obesity. These measures can help reduce liver fat, improve liver function, and mitigate the risk of complications.

While there are currently no approved pharmacological treatments specifically for NAFLD, certain medications, such as pioglitazone, have shown promise in clinical trials. However, further research is needed to identify more effective pharmacological interventions.

Diagnosis of NAFLD and monitoring disease progression can be challenging. Liver biopsies, although considered the gold standard, are invasive and have limitations. Noninvasive methods, such as biomarkers and transient elastography, are being used in clinical practice to assess liver fibrosis and the risk of disease progression.

The complications associated with NAFLD, including cardiovascular disease, hepatocellular carcinoma, and end-stage liver disease, highlight the importance of early detection, monitoring, and appropriate management. Regular check-ups, lifestyle modifications, and adherence to treatment plans are essential in preventing or slowing down disease progression and reducing the risk of complications.

It is crucial for individuals with NAFLD to work closely with healthcare professionals to develop a personalized treatment and monitoring plan that addresses their specific needs and reduces the impact of NAFLD on their overall health and well-being.

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