

## Pathophysiology and Risk Factors of Non-alcoholic Fatty Liver

### Disease: Review Article

Moustafa Abd El Hamid Ali\*, Reem Mahmoud Makbol

Tropical Medicine and Gastroenterology Department, Faculty of Medicine, Sohag University, Egypt

\*Corresponding author: Moustafa Abd El Hamid Ali, Mobile: (+20) 01004348810, E-Mail: m\_metwally88@yahoo.com

#### ABSTRACT

**Background:** About 25% of the global population suffers from non-alcoholic fatty liver disease (NAFLD), making it the most prevalent form of liver disease. One form of NAFLD, nonalcoholic steatohepatitis (NASH), can ultimately lead to cirrhosis, hepatocellular carcinoma (HCC), and mortality. The most common causes of fatty liver disease are being overweight or obese, having insulin resistance, leading an inactive lifestyle, consuming a high-fat diet and having a family history of the condition. The pathogenesis of NAFLD is associated with a weaker intestinal barrier caused by an altered gut microbiota, which exposes the host to bacterial components and triggers immunological defense and inflammation pathways via toll-like receptor signalling, ultimately leading to the development of NASH. The objective of the present review article is to discuss the risk factors and pathophysiological pathways that lead to NAFLD.

**Development:** PubMed, Google scholar and Science direct were searched using the following keywords: Steatohepatitis, Steatosis, Hepatocellular carcinoma, Metabolic syndrome, Dysbiosis and Non-alcoholic fatty liver disease. The authors also screened references from the relevant literature, including all the identified studies and reviews, only the most recent or complete study was included between December 2002 and April 2021. Documents in a language apart from English have been excluded as sources for interpretation was not found. Papers apart from main scientific studies had been excluded: documents unavailable as total written text, conversation, conference abstract papers and dissertations.

**Conclusion:** Globally, NAFLD is the most prevalent form of chronic liver disease. The pathophysiology of NAFLD is complex and requires the interaction of multiple factors. Metabolic syndrome, insulin resistance, unhealthy dietary habits and gut microbiota play major roles for the development of NAFLD.

**Keywords:** Steatohepatitis, Steatosis, Hepatocellular carcinoma, Metabolic syndrome, Dysbiosis, Non-alcoholic fatty liver disease.

#### INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) affects about 25% of the global population <sup>(1)</sup>.

Steatosis, nonalcoholic fatty liver (NAFL), and nonalcoholic steatohepatitis (NASH) are both histological manifestations of NAFLD. NASH is an inflammatory, progressive disease that can lead to fibrosis, cirrhosis, and ultimately hepatocellular cancer (HCC) <sup>(2)</sup>.

NAFLD has a multifaceted and intricate aetiology. Most cases of NAFLD and NASH can be traced back to having the metabolic syndrome (MetS). NAFLD is more common in people with metabolic syndrome, and it has been shown to worsen a number of MetS symptoms and comorbidities <sup>(3)</sup>.

Hepatic de novo lipogenesis (DNL), decreased lipolysis in adipose tissue (AT), and an accumulation of fatty acids in the liver are all factors in the pathophysiology of steatosis/NASH <sup>(4)</sup>.

Both NAFLD and NASH have been linked to dysbiosis, which is characterized by both qualitative and quantitative alterations of the gut microbiota <sup>(5)</sup>. Fatty liver disease is exacerbated by dysbiosis, which both raises the mucosal permeability and exposure of the liver to pro-inflammatory bacterial metabolites <sup>(5)</sup>.

The focus of this review article is on the pathophysiological mechanisms behind NAFLD and the primary risk factors contributing to its development.

#### RISK FACTORS

##### Disorders of metabolism such as metabolic syndrome and Type 2 Diabetes

Three of the following conditions must be met for a diagnosis of metabolic syndrome (Table 1). NAFLD is on the rise, and that trend is linked to the prevalence of Mets. More and more of the Mets criteria must be met before a person is diagnosed with NAFLD, and it has been reported that this is the case <sup>(6,7)</sup>.

**Table (1): Metabolic syndrome diagnostic criteria <sup>(6)</sup>.**

Hypertension (In rest)	Systolic to be equal or more than 130 mmHg Diastolic to be equal or more than 90 mmHg
Triglycerides (in fasting state)	Equal or higher to 1.5 gm/L
HDL cholesterol	To be lower than four hundred milligrams per liter in males To be lower than five hundred milligrams per liter in females
Fasting Hyperglycemia	To be equal or more than 1.1 gm/liter
Waist circumference	102 centimeters among male 88 centimeters among female

Liver fat levels in people with type 2 diabetes mellitus (T2DM) are 80% higher than in people who don't have the disease. Moreover, the risk of fatty liver disease consequences is increased two- to fourfold in these patients<sup>(7)</sup>.

### **Ethnic differences**

Hispanic patients have a higher incidence of NAFLD than other demographics. NAFLD is also increasing in prevalence in Asia, and, interestingly, it has been observed in people with normal body mass index (BMI). In a study conducted in the United States, it was discovered that Asians and Hispanics had a higher prevalence of NAFLD whereas African Americans had a lower prevalence of steatosis compared to whites<sup>(8)</sup>.

### **Gender and age**

NAFLD is more common in men, according to a number of studies. 13-15, while contrary evidence was shown by others<sup>(7)</sup>. However, in their review **Lonardo et al.**<sup>(9)</sup> found that NAFLD increases between the ages of 20 and 50, it is more prevalent in men than in women, with a subsequent decline in prevalence between the ages of 60 and 70. However, postmenopausal women (especially those aged 60–69) have a higher NAFLD prevalence than younger women (especially those aged 20–49), and it is hypothesized that NASH is more severe on a histological level in women than in men.

NAFLD prevalence is found to increase consistently with age, going from 20% in those under the age of 20 to over 40% in those over the age of 60. Patients aged 50 and up were shown to have a higher incidence of NASH and cirrhosis compared to younger age groups, indicating that longer age is related with a higher frequency of advanced illness<sup>(10)</sup>. However it stills uncertain whether this increasing incidence and severity of the disease represents the end result of long duration of NAFLD/NASH and other components of the metabolic syndrome in these populations<sup>(8)</sup>.

Childhood obesity is a key risk factor for the development of NAFLD, just as it is in adulthood. About one-third of overweight children have NAFLD, per the Study of Child and Adolescent Liver Epidemiology. Fatty liver is the most frequent form of liver disease in children, and it often manifests between the ages of 2 and 19<sup>(10)</sup>.

### **Life style, smoking and Diet**

A high-fat diet, in particular, has been identified as a separate risk factor for the development of NAFLD. People whose diets are more westernized (consisting of more red meat, refined carbs, pastries, and sugar-sweetened beverages) are more prone to develop metabolic syndrome and NAFLD<sup>(11)</sup>.

**Hamabe et al.**<sup>(12)</sup> noted that tobacco use was a major contributor to the development of NAFLD in their retrospective study. Insulin resistance (IR) is a known risk factor for T2DM, and numerous studies have connected cigarette smoking to this condition<sup>(13)</sup>.

Lifestyle factors that raise the risk of developing NAFLD and NASH include insufficient physical activity and poor fitness, with NASH becoming even more severe in the absence of regular exercise. NAFLD screenings should incorporate an assessment of physical activity levels, as suggested by clinical practice guidelines for NAFLD management from the European Association for the Study of Obesity (EASO), the European Association for the Study of Diabetes (EASD) as well as the European Association for the Study of the Liver (EASL)<sup>(14)</sup>.

### **Polycystic ovarian syndrome (PCOS)**

PCOS women had a greater prevalence of NAFLD than a healthy control group with similar BMI<sup>(14)</sup>.

PCOS is associated with hyperandrogenemia, a disorder characterized by increased levels of the androgen testosterone. Women with PCOS are of great risk to have insulin resistance, which in turn increases ovarian androgen production and decreases liver sex hormone binding protein (SHBG) formation. This causes a rise in free androgens in the body's circulation. NAFLD is more common in patients with PCOS because of the increased risk of insulin resistance produced by hyperandrogenism<sup>(15)</sup>.

### **Obstructive sleep apnea (OSA)**

OSA is estimated to be between 4 and 6 percent in prevalence, but it is significantly higher among the obese population, at between 35 and 45%<sup>(14)</sup>. In their study, **Tanné and colleagues**<sup>(15)</sup> comparing people with severe OSA to those without OSA but with a similar BMI, those with OSA showed more insulin resistance, a higher proportion of steatosis, and higher fibrosis as well necrosis scores detected by liver biopsies.

### **Genetics**

Multiple researches, including those on familial clustering, twins, and racial/ethnic susceptibility, have pointed to a genetic basis for NAFLD<sup>(16)</sup>.

In the first genome-wide association analysis, **Romeo et al.** discovered a link between the PNPLA3 gene and hepatic triacylglycerol (HTAG) buildup in NAFLD patients<sup>(17)</sup>. The following investigations confirm the presence of this variant (PNPLA3 rs738409) in NAFLD patients from Japan, India, and China.

PNPLA3 polymorphism rs738409 is strongly linked to the presence of NAFLD<sup>(17)</sup>, severity of necroinflammatory changes, higher risk for advanced fibrosis, and is considered as an independent risk factor for HCC in those with cirrhosis<sup>(16)</sup>.

NAFLD is associated with seven groups of genes. After conducting an exome-wide association study, researchers identified three polymorphisms that were significantly linked to increased liver fat content. Two in the aforementioned PNPLA3 gene are essential for appropriate VLDL secretion, and one in the TM6SF2 gene<sup>(16)</sup>.

### Pathophysiology of NAFLD

Genetic, metabolic, environmental, and dietary factors all interact in complicated ways to contribute to the development of NAFLD and NASH<sup>(18)</sup>.

#### Two-hit hypothesis:

Excess intrahepatic buildup of fat is the primary culprit, as proposed by this theory; this phenomenon may be traced back to various risk factors such as an unhealthy diet, inactivity, obesity, and insulin resistance (IR). Multiple metabolic shocks can produce inflammation and fibrogenesis in the liver, but this first blow leaves the liver more susceptible to subsequent blows<sup>(19)</sup>, that so, it's generally agreed that this idea has passed its expiration date. There are many molecular

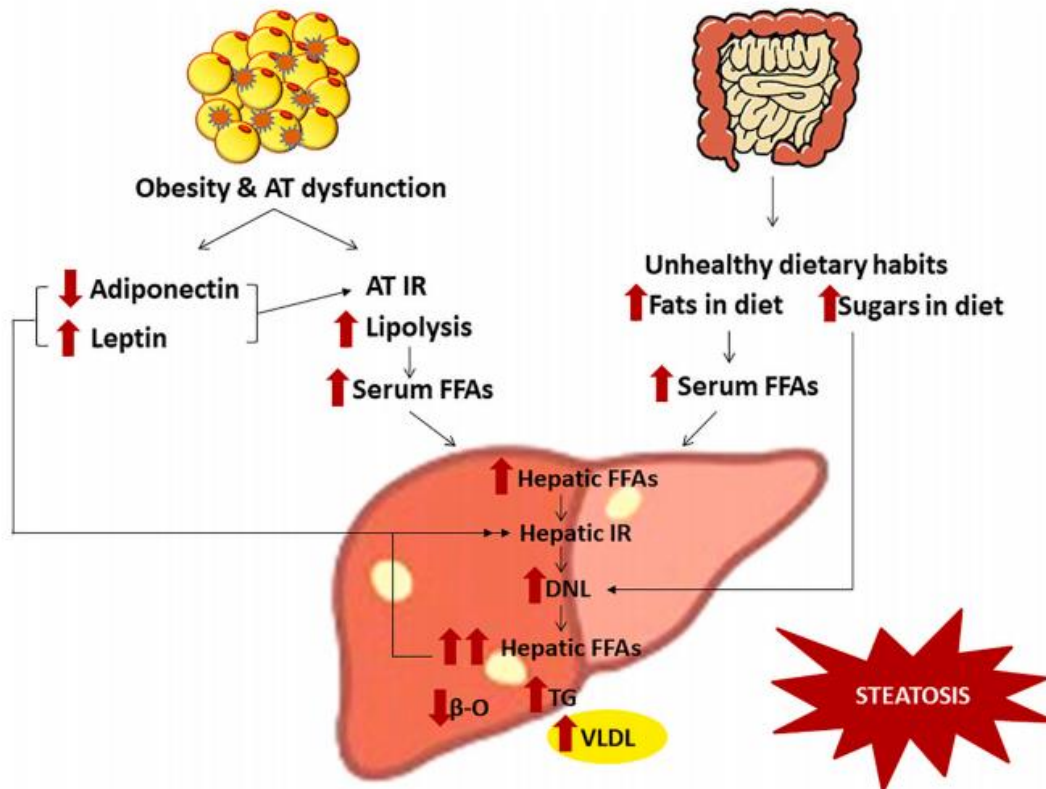
routes that can lead to NASH, and it is not known if NAFLD is required for NASH to develop<sup>(3)</sup>.

#### Multiple-hit hypothesis:

Both genetic predisposition and environmental variables, such as poor diets and excessive intake of high-calorie meals, promote to the expansion of insulin resistance, obesity, adipose tissue malfunction, and alterations in the intestinal flora<sup>(19)</sup>.

More specifically, hepatocytes, Kupffer cells, and hepatic stellate cells (HSCs) all play a role in the pathogenesis of NASH through a variety of intracellular processes and intercellular interaction<sup>(18)</sup>.

Figure 1 summarizes hepatic steatosis development.



**Figure (1):** Fat buildup in the liver is a classic symptom of non-alcoholic fatty liver disease (NAFLD). adipose tissue as well as obesity cause decreased levels of adiponectin and elevated levels of leptin, which in turn promote insulin resistance in both the liver as well as adipose tissue. Increased lipolysis in adipose tissue and an excessive fat intake contribute to hepatic steatosis and insulin resistance. There is an increase in free fatty acids and triglycerides in the liver because of the increased de novo lipogenesis that occurs when insulin resistance exists in the liver. Acronyms: adipose tissue (AT), de novo lipogenesis (DNL), free fatty acids (FFAs), insulin resistance (IR), triglycerides (TG), and very low density lipoprotein (VLDL). Adapted from Gerges et al<sup>(25)</sup>.

### **Adipose tissue and liver IR:**

IR occurs when the body has trouble responding to insulin, especially in terms of insulin-mediated glucose absorption, while having normal or increased insulin levels. Normal insulin action on liver cells promotes glycogenesis, suppresses gluconeogenesis, and encourages de novo lipogenesis (DNL). However, insulin inhibits lipolysis and stimulates lipogenesis in adipocytes via esterification of fatty acids. Therefore, IR causes an increase in adipocyte lipolysis, leading to a rise in blood FFAs that are absorbed by the liver<sup>(20,21)</sup>.

Lipid metabolites and free fatty acids (FFAs) accumulated in the liver cause the insulin receptor (IRS) to get phosphorylated on serine and threonine residues, which in turn activates inhibitor of nuclear factor kappa B kinase subunit beta (I $\kappa$ B $\beta$ ), c-Jun NH<sub>2</sub>-terminal kinase (c-JNK) as well as protein kinase C, as a result, hepatic IR progresses. Hyperglycemia and hyperinsulinemia are caused by hepatic IR, which prevents glycogenesis and increases gluconeogenesis. Despite the fact that insulin promotes DNL in hepatocytes, hepatic IR actually increases DNL rather than inhibiting it<sup>(21)</sup>.

### **Unhealthy dietary habits:**

Hepatic fat accumulates in response to high-fat diets, and hepatic DNL rises in response to excessive sugar intake. Fructose is a dietary component that causes oxidative stress and elevation of TNF- $\alpha$ . It is lipogenic and pro-inflammatory. Fructose-1-phosphate is produced during its metabolism in the liver, which occurs independently of insulin action. Substrates for DNL are created when it is transformed to triose phosphate and sent through the glycolytic pathway.<sup>(22)</sup> Fructose causes intestinal permeability and bacterial overgrowth in mouse models. Mouse studies have shown that fructose consumption can lead to copper shortage and NAFLD. Increased fibrosis is linked to daily fructose consumption in people with nonalcoholic fatty liver disease. Possible explanations for this phenomenon include hepatic ATP depletion<sup>(23)</sup>.

### **Obesity:**

AT expands, and adipocytes store more lipids when people are overweight. A decrease in AT insulin sensitivity results from the initiation of the inflammatory I $\kappa$ B $\beta$  as well as c-JNK pathways. Therefore, obesity may contribute to IR and NAFLD<sup>(24)</sup>.

### **Adipokines:**

As an anti-inflammatory, antioxidant, and obesity-fighting hormone, adiponectin is produced by fat cells. As a result, it's possible that mitochondrial malfunction, IR, and obesity develop in its absence. If adipocyte cell size and IR both grow, adiponectin expression will go

down. Obesity and diabetes are two examples of chronic metabolic illnesses in which it is reduced<sup>(26)</sup>.

The adipose tissue hormone leptin helps control appetite and boosts energy expenditure. The accumulation of lipids in organs other than the AT, such as the liver, is thereby avoided. In obese and NASH individuals, leptin resistance develops, leading to elevated leptin levels. Increased gluconeogenesis and impaired glucose absorption due to elevated leptin levels cause hyperglycemia IR<sup>(27)</sup>.

### **Hepatokines:**

Patients with NAFLD have elevated levels of hepatokines such as angiopoietin-related growth factor, selenoprotein P, fetuin-A, sex hormone-binding globulin (SHBG), leukocyte derived chemotaxin 2 (LECT2), fibroblast growth factor-21 (FGF-21), and, all of which stimulate gluconeogenesis while decreasing glycogen synthesis and heightening insulin resistance.<sup>(28)</sup>

### **Development of NASH:**

#### **Lipotoxicity**

Toxic effects of FFAs on cells as reactive oxygen species are defined using this term (ROS)<sup>(27)</sup>. There are several guises in which it can manifest. Accumulating free fatty acids (FFAs) that aren't esterified can cause inflammation and cell death since they aren't sequestered in lipid droplets. High levels of DNL are also linked to an elevated danger of lipotoxicity and cellular damage<sup>(29)</sup>. Hepatocellular injury as well as even morbidity also results from the accumulation of cholesterol both inside and outside of cells, which stimulates the formation of cholesterol particles and inflammatory cytokines release such interleukin 6 (IL-6) and as tumor necrosis factor alpha (TNF- $\alpha$ )<sup>(30)</sup>.

#### **Inflammation**

Hepatic IR is caused in part by the activation of the serine/threonine kinases c-JNK and I $\kappa$ B in response to the high levels of circulating and intrahepatic FFAs. An overabundance of inflammatory cytokines such tumor necrosis factor alpha (TNF-alpha) and interleukin-6 (IL-6) are triggered by both c-JNK and I $\kappa$ B. Overproduction of inflammatory cytokines in the liver is a hallmark of nonalcoholic steatohepatitis (NASH), resulting in histological changes such as formation of Mallory bodies, neutrophil infiltration, and hepatocellular necrosis<sup>(31)</sup>.

Chronic inflammation also contributes to the worsening of hepatic IR. Researchers discovered that TNF- stimulates adipocyte lipolysis and increases hepatic insulin receptor phosphorylation through activating c-JNK<sup>(30)</sup>. Downregulation of IRs and glucose transporter-4 by IL-6 was also observed to promote IR<sup>(32)</sup>.

### Endoplasmic reticulum (ER) stress

An increase in ER stress has been linked to the high amounts of saturated fatty acids generated by the livers of people with NAFLD and NASH. Activation of c-JNK by ER stress further exacerbates hepatic IR and inflammation<sup>(33)</sup>.

### Mitochondrial dysfunction

Excessive intrahepatic accumulation of FFAs leads to the advancement of mitochondrial dysfunction through enhancing inner mitochondrial membrane permeability and so inducing the formation of reactive oxygen species (ROS). Oxidative stress is exacerbated because mitochondrial -oxidation for FFA overload causes electron leakage, which results in excessive ROS production<sup>(34)</sup>. Mitochondrial damage is made worse by hepatic inflammation, which is caused by reactive oxygen species<sup>(22)</sup>.

### Progression to fibrosis:

HSCs secrete collagen and are activated directly by macrophages called Kupffer cells, which are located in close proximity to HSCs. After being stimulated by damage-associated molecular patterns and reactive oxygen species (ROS) generated from dead liver cells, Kupffer cells secrete profibrogenic cytokines including transforming growth factor beta (TGF-) and inflammatory cytokines like interleukin-6 (IL-6)<sup>(35)</sup>.

Activation and proliferation of HSCs lead to fibrosis development through proliferation and production of collagen and other extracellular matrix proteins, thus leading to remodeling of the parenchyma, driving hepatic dysfunction, and elevation of portal blood pressure via reduction of the hepatic elasticity<sup>(33)</sup>. Activated HSCs also produce cytokines and chemokines that induce tissue damage, inflammation, and fibrosis, as well as upregulate expression of alpha smooth muscle actin<sup>(30)</sup>.

### Gut microbiota role:

Dysbiosis refers to both the qualitative and quantitative changes in the gut microbiota that contribute to the onset and progression of chronic illnesses such as NAFLD and NASH<sup>(5)</sup>. Multiple lipid disorders can be aided by dysbiosis. Initially, it was discovered that changes in gut microbiota can affect host metabolism by stimulating the production of short-chain fatty acids (SCFAs). The fermentation of polysaccharides by colonic bacteria results in the production of SCFAs like acetate, propionate, and butyrate. NAFLD models in animals and obese people both demonstrate elevated fecal SCFAs levels<sup>(6)</sup>.

SCFAs bind specific G-protein-coupled receptors (GPRs), including GPR41 and GPR43, which are expressed in the atherosclerotic triglyceride (AT), liver, and gut and have a role in the development of

NAFLD. When any of the three types of SCFAs bind to their respective receptors, they can stimulate a variety of processes, including DNA damage repair, cholesterol production, and modifications to glucose balance<sup>(30)</sup>.

Second, the gut microbiota can influence lipid metabolism directly by inhibiting the production of fasting-induced adipocyte factor (also called angiopoietin-related protein 4), a particular inhibitor of the lipoprotein lipase (LPL). More free fatty acids (FFAs) are released from very low-density lipoprotein particles into the liver when LPL is not inhibited, which encourages the development of steatosis<sup>(21)</sup>.

Finally, the transition from NAFLD to NASH is facilitated by dysbiosis-induced changes to the intestinal barrier that allow bacteria or bacterial products like lipopolysaccharide (LPS) to enter the portal circulation<sup>(18)</sup>.

Fatty liver disease may be caused, in part, by translocated microbial metabolites. Toll-like receptors (TLRs) are involved in this process because they are able to identify bacterial compounds in the gut, particularly lipopolysaccharide (LPS). Increased amounts of gut-derived TLR ligands are detected in the portal circulation after intestinal barrier alterations generated by dysbiosis. These ligands subsequently signal to TLR4 on hepatic Kupffer cells and stellate cells, which in turn unleash a cascade of inflammatory and profibrotic cytokines<sup>(32)</sup>.

### CONCLUSION

Globally, NAFLD is the most prevalent form of chronic liver disease. The pathophysiology of NAFLD is complex and requires the interaction of multiple factors. Metabolic syndrome, insulin resistance, unhealthy dietary habits and gut microbiota play major roles for the development of NAFLD.

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