REVIEW ARTICLE

Review on Non-alcoholic Fatty Liver Disease

ALAM A

Abstract

Non-alcoholic fatty liver disease (NAFLD) is the common public health problem. NAFLD is characterized by hepatic steatosis detected by either imaging or histology without secondary causes. It spans a spectrum of the disease from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) and ultimately to cirrhosis and its complications. Most people have a simple fatty liver with no or mild nonspecific inflammation, without liver fibrosis. Conversely, NASH, the more severe form of the disease, has varying degrees of liver fibrosis, resulting in cirrhosis and its complications. The prevalence of NAFLD in South Asian countries is high, due to several factors such as socioeconomic growth, urbanisation, westernised diet, increasingly sedentary lifestyle and poor health awareness. Bangladesh is also experiencing an increasing trend of NAFLD due to changing dietary patterns and sedentary lifestyles. Dietary recommendations and lifestyle interventions, weight loss, and the treatment of underlying metabolic syndrome remain the mainstays of therapy once the diagnosis is established. This review gives an overview of NAFLD and its treatment options.

Key words: Non-alcoholic fatty liver disease (NAFLD), Non-alcoholic steatohepatitis (NASH), Oxygen free radicals (OFR), Tumour necrosis factor-alpha (TNF-a)

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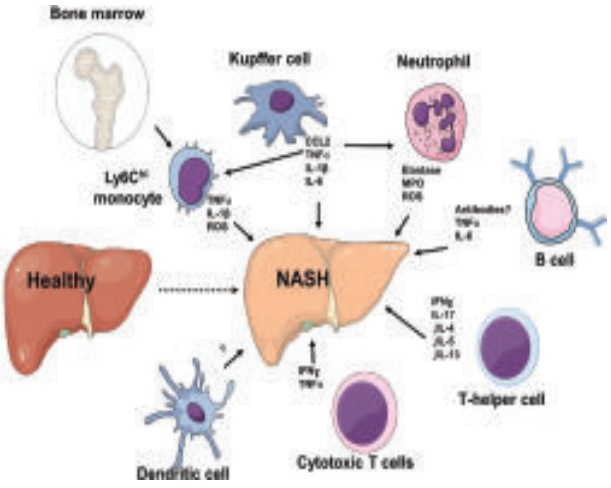
Introduction:

Non-alcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease worldwide. NAFLD is a spectrum of the disease characterized by hepatic steatosis when no other causes for secondary hepatic fat accumulation (e.g. excessive alcohol consumption) can be identified. NAFLD ranges from the more benign condition of non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), which is at the more severe end of the spectrum. NAFLD may progress to fibrosis and cirrhosis.[1-2] In NAFLD, hepatic steatosis is present without evidence of inflammation, whereas in NASH, hepatic steatosis is associated with lobular inflammation and apoptosis that can lead to fibrosis and cirrhosis.[1–4]

Prevalence

The World Health Organization Global Health Observatory data in 2014 indicates that globally obesity occurs in 15% of women and 11% of men aged 18 and over.[5-6] A study evaluating the prevalence of NASH estimated that 5.7–17% of the US population is affected.[5-6] About one-third of the population of Bangladesh is affected by NAFLD.[7]



Healthy VS NASH

Causes of NAFLD

- Overweight or obesity
- Insulin resistance, in which our cells don't take up sugar in response to the hormone insulin
- High blood sugar (hyperglycemia), indicating prediabetes or type 2 diabetes

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- High levels of fats, particularly triglycerides, in the blood

These combined health problems appear to promote the deposit of fat in the liver. For some people, this excess fat acts as a toxin to liver cells, causing liver inflammation and NASH, which may lead to a buildup of scar tissue in the liver.

Risk Factors

A wide range of diseases and conditions can increase risk of NAFLD, including:

- High cholesterol
- High levels of triglycerides in the blood
- Metabolic syndrome
- Obesity, particularly when fat is concentrated in the abdomen
- Polycystic ovary syndrome
- Sleep apnea
- Type 2 diabetes
- Underactive thyroid (hypothyroidism)
- Underactive pituitary gland (hypopituitarism)

NAFLD can be divided into two distinct types. The first type of NAFLD has a narrow relationship with metabolic syndrome and the current beliefs are that insulin resistance is the primary pathophysiological mechanism. The second type of NAFLD has a relationship with infectious pathologies that can lead to the occurrence of liver steatosis. In this case infections like hepatitis C and HIV can be a cause, but it is also associated with medication (total parenteral nutrition, glucocorticoids, tamoxifen, tetracycline, amiodaron, methotrexate, valproic acid, vinyl chloride) and specific toxins or inherited/acquired metabolic diseases (e.g. lipodystrophy or cachexia or intestinal bypass surgery).[8-9]

Pathogenesis

The histological signs of NAFLD are especially characteristic in the obese population and in patients with DM-2.[10] These two conditions have been associated with peripheral insulin resistance and glucose intolerance. Dyslipidaemia, particularly hypertriglyceridaemia, is also associated with steatosis. However, despite the fact that the majority of patients are overweight and obese, NAFLD may also occur in patients with normal weight and may constitute an independent cardiovascular risk factor.[11] The pathogenic mechanism of NAFLD is associated with insulin resistance and can be explained as the 'double impact theory.[12,13] In the "first impact", the reduction in cellular capacity to respond to the action of insulin causes compensatory hyperinsulinaemia. In adipose tissue it acts on the hormone-sensitive lipase (HSL) increasing the risk of lipolysis with the consequent release of free fatty acids (FFA) to the liver. Glucose absorption decreases in the skeletal muscle, while in the hepatocyte hyperinsulinaemia increases gluconeogenesis, decreases glycogen synthesis and increases uptake of FFA, alters the transport of triglycerides such as VLDL and inhibits beta-oxidation. These alterations in the metabolism of fats are the basis of FLD. This "first impact" results from the interaction of various factors, such as hepatic resistance to leptin or the reduction of adiponectin levels, it would therefore be more correct to speak of "multiple impacts", with a predominance of one or the other, depending on the patient. The "second impact" is a consequence of oxidative stress in hepatocytes, which is initially compensated by cellular antioxidant mechanisms. However, liver overload of FFA generates oxygen free radicals (OFR) in the mitochondrial chain that act upon the fatty acids of the cell membranes causing lipid peroxidation. OFR induce proinflammatory cytokine synthesis due to Kupffer cells and hepatocytes, such as: a) tumour necrosis factor-alpha (TNF-a), which activates the caspase pathway and leads to hepatocyte apoptosis; b) transforming growth factor beta-1 (TGF-b1), which activates collagen synthesis due to stellate cells; c) Fas ligand that cause 'fratricide deaths' between adjacent hepatocytes; and d) interleukin-8 (IL-8), powerful neutrophil chemotactic. The end products of lipid peroxidation, 4-hydroxynonenal (HNE) and malondialdehyde (MDA), are also involved in the pathogenesis of liver damage due to direct toxicity, and can intervene in the formation of Mallory body and increase collagen synthesis due to stellate cells; HNE also has neutrophil chemotactic activity .[14-18] This second phase would explain the evolution necroinflammatory phenomenon, fibrosis and liver cirrhosis. [15-24]

Various studies outline other factors involved in the pathogenesis of NAFLD:

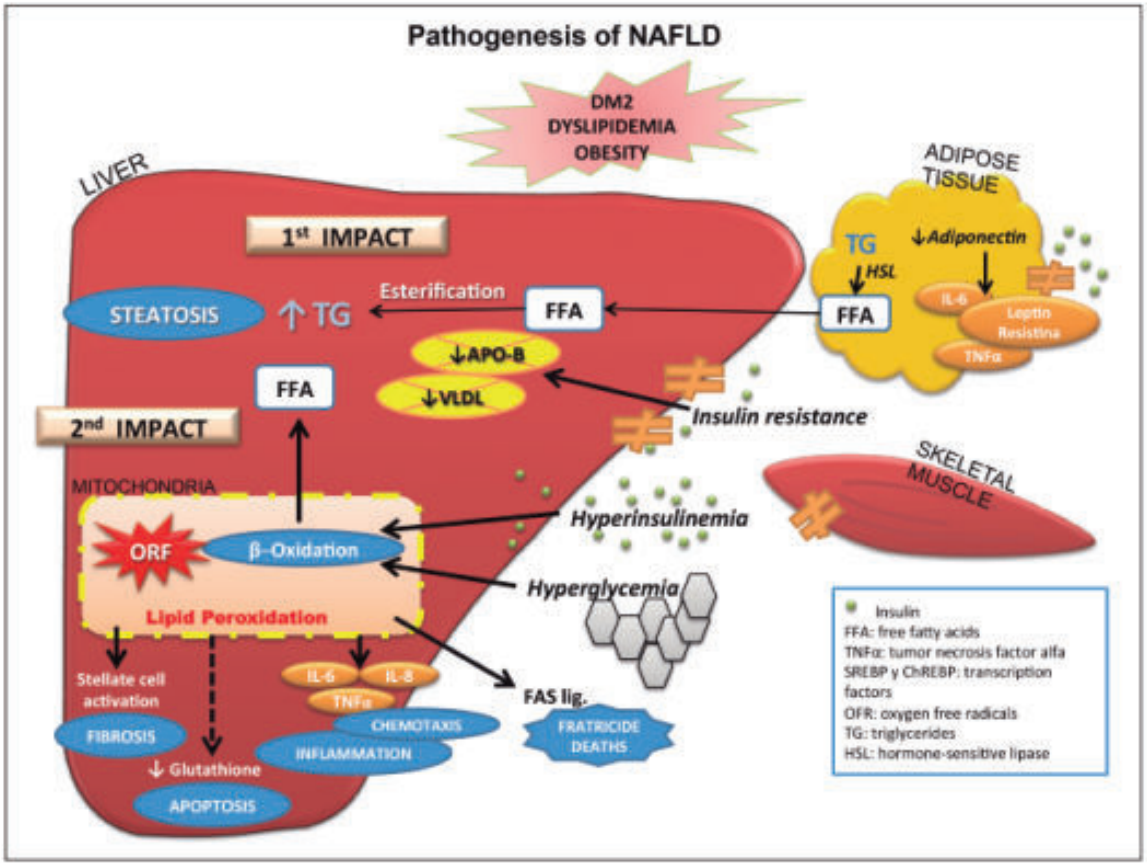
1. Insulin resistance causes elevated serum ferritin levels, increased expression of transferrin receptors and increased hepatic iron, which contributes to the generation of hydroxyl radicals and the accumulation of oxygen free radicals (OFR), however, its role in the pathogenesis of NAFLD is yet to be clarified.
2. It also involves the generation of adipokines due to adipose tissue. Due to its endocrine, paracrine and systemic effects, they behave like hormones and may play a proinflammatory role in NAFLD.
3. The role of adiponectin is widely reported due to its anti-inflammatory, ant atherosclerotic, anti-lipogenic

and hypoglycaemic effects, and also due to its protective mechanism of fatty liver development and its ability to act on stellate cells inhibiting fibro genesis. Two adiponectin receptors have been identified: type I - in the skeletal muscle and type II - in the liver, whose decrease has been associated with a greater degree of steatosis in patients with similar adiponectin levels, although there was increased expression of its receptors with NAFLD progression. Obesity (especially visceral) and being overweight have been associated with low adiponectin levels due to TNF-a inhibition - this imbalance may be one of the pathophysiological mechanisms of NAFLD and the regulation of pathways that control production and signalling may represent a promising therapeutic target. The decrease in adiponectin may be the "expression in the organ of metabolic syndrome".

4. Leptin is another cytokine whose primary resistance was described at hypothalamic level in the nuclei of satiety control, although, at present, insulin resistance is associated with peripheral leptin resistance in the skeletal muscle. In patients with NAFLD, serum leptin concentration levels are elevated and are related to the degree of steatosis. However, they are not correlated with the degree of fibrosis and do not appear to improve or reverse the problem - the "leptin resistance theory" has thus been proposed, which is associated with obesity, insulin resistance and elevated glucose levels in patients with NAFLD.

5. Bacterial overgrowth and increased bacterial translocation to portal and systemic circulation, as well as increased serum levels of lipopolysaccharide (LPS), bacteria and endotoxin and the activation of proinflammatory signalling (TNF-a and IL-6) have been observed in various chronic liver diseases including NAFLD .

6. The cannabinoid system plays a fundamental role in the pathophysiology of chronic liver disease. The positive regulation of the endocannabinoid system during chronic liver disease participates in the pathogenesis of hepatocyte necrosis, inflammation and fibrogenesis.[24]



Symptom /Sign

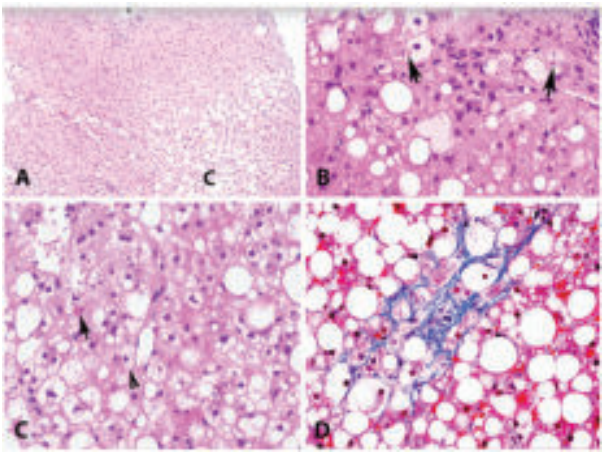
The majority of the patients with NAFLD do not experience any symptoms, however some of them may complain of fatigue, right upper quadrant discomfort, hepatomegaly, acanthosis nigricans, and lipomatosis.[25] A significant number of patients with cirrhosis can be present themselves with end-stage liver disease. In approximately 48-100% NASH canbe asymptomatic and very often it is discovered during medical evaluations for other reasons. Although clinical stigmata of chronic liver failure are rarely seen in this population, one study showed that at the time of diagnosis splenomegaly was present in 25% of the patients.[25]

Investigations

In terms of diagnostic tests, the gold standard to investigate any form of liver inflammation e.g. damage, is a liver biopsy. In the diagnosis of NAFLD and related disorders, liver biopsies can be extremely helpful and its findings can range from triglyceride deposition as droplets in the hepatocyte to more extensive forms of nonalcoholic steatohepatitis (NASH). NASH is normally characterised by lipid droplets in hepatocytes, with concomitant inflammation and a variable degree of hepatic fibrosis. In the majority of the liver steatosis patients, the disease is 'non-progressive', however a small portion of these patients develop NASH, which can lead to liver failure and even hepatocellular carcinoma.[26-27]

Evaluation of abnormal liver enzyme levels in an otherwise healthy patient can pose a challenge to even an experienced clinician. It determines asymptomatic elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in up to 90% of cases, once other liver disease are excluded.[5-6]. When performing laboratory tests, serum markers like aminotransferases (AST, ALT), are mild to moderately elevated.[28] However, the AST and ALT levels can be specific in patients with NAFLD or related conditions. In other words, AST and ALT levels can either be elevated or normal in NAFLD.[28-30] In patients with NAFLD, ALT elevations are more common than elevations of AST. The ALT levels tend to be higher in NASH than in simple steatosis. Serum ferritin level commonly increased in patients with NAFLD, and increased transferrin saturation is found in 6–11% of patients.[28-30]

In liver diseases such as NAFLD and NASH, various imaging modalities can be used to substantiate the diagnosis, however none of them are routinely used for differentiating between (histological) subtypes of NAFLD or NASH.[31] Computed tomography (CT) scans, abdominal ultrasound (US), or Magnetic Resonance Imaging (MRI) can detect these liver diseases. Imaging findings in patients with NAFLD include increased echogenicity on ultrasound, decreased hepatic attenuation on CT, and an increased fat signal on MRI.[31]



Steatosis and steatohepatitis. A, Simple steatosis at zone 3 (P, portal tract; C, central zone). B, Steatohepatitis showing steatosis, mild lobular inflammation, and many classic ballooned hepatocytes, some with Mallory-Denk bodies (arrows). C, Acidophilic body (arrow) and nonclassic ballooned hepatocyte (arrowhead). D, Perisinusoidal/pericellular fibrosis (hemoxylin-eosin stain, original magnifications ×100 [A] and ×400 [B and C]; trichrome stain, original magnification ×400 [D]).

Complications of NAFLD

The main complication of NAFLD and NASH is cirrhosis, which is late-stage scarring in the liver. Cirrhosis occurs in response to liver injury, such as the inflammation in NASH. As the liver tries to halt inflammation, it produces areas of scarring (fibrosis). With continued inflammation, fibrosis spreads to take up more and more liver tissue.

If the process isn't interrupted, cirrhosis can lead to:

- Fluid buildup in the abdomen (ascites)
- Swelling of veins in esophagus (esophageal varices), which can rupture and bleed
- Confusion, drowsiness and slurred speech (hepatic encephalopathy)
- Liver cancer
- End-stage liver failure, which means the liver has stopped functioning

Between 5% and 12% of people with NASH will progress to cirrhosis.

Treatment of NAFLD

To date, there is no specific drug treatment for NAFLD, however it is believed that a combination of treatment goals (lifestyle adjustments, increasing physical activity and smoking/ alcohol cessation) can be beneficial.[32-33] A high protein diet is suggested to be beneficial for NAFLD management. [34]

Other dietary components can also be beneficial in the treatment of NAFLD, like changes in Vitamin E, caffeine and polyphenol intake. Vitamin E is a fat-soluble vitamin that works as an antioxidant.[35] Current data support the use of Vitamin E in non-diabetic patients with nonalcoholic fatty liver disease. However, it should not be considered as the first option for treatment.[35]

Conclusion:

With the growing obesity pandemic and the rising prevalence of comorbid conditions like T2DM and NAFLD, the management of these patients has become even more complex. There are some treatment methods, however there is lack of high-quality studies that compared different treatment methods with each other. Considering that bariatric surgery is increasingly utilized, prospective studies answering the remaining questions on the connection of insulin resistance, fatty liver, and fibrosis progression should become available in the near future. To reduce risk of NAFLD, we have to take- a healthy plant-based diet that's rich in fruits, vegetables, whole grains and healthy fats. We have to maintain a healthy weight. If you are overweight or obese, reduce the number of calories you eat each day and get more exercise. Because prevention is better than cure.

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