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Non-alcoholic fatty liver diseases: A silent killer

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ABSTRACT
NAFLD is a major cause of morbidity and mortality worldwide, owing to cardiovascular, hepatic, and oncologic complications, as well as the fact that it is rapidly becoming the leading cause of end-stage liver disease and liver transplantation. It has epidemic proportions in the United States, with a prevalence of 30%. While the metabolic syndrome is a common risk factor, there are differences between racial and ethnic groups, indicating a complex interaction of hormonal, nutritional, and genetic factors at work in disease pathogenesis. NAFLD symptoms range from mild steatosis to steatohepatitis, which can progress to fibrosis and cirrhosis. The pathogenesis is investigated, including the roles of hormones, nutritional and intestinal dysbiosis, insulin resistance, lip toxicity, hepatic inflammation, and genes.
Keywords: NAFLD, Epidermic, steatohepatitis, Insulin resistance.

I. INTRODUCTION

NAFLD is the liver component of a group of conditions linked to metabolic dysfunction [1]. Although fatty liver hepatitis resulting in cirrhosis had been described nearly 20 years prior, Ludwig and colleagues coined the term non-alcoholic steatohepatitis (NASH) in 1980. NAFLD is defined as the presence of steatosis in more than 5% of hepatocytes in the absence of excessive alcohol consumption (30 g per day for men and 20 g per day for women), as well as other chronic liver diseases [2].

Prevelance

According to current estimates, NAFLD affects 30% of the US population, 32% of the Middle East population, 30% of the South American population, 27% of Asian populations (with the highest prevalence in East Asians), 24% of the European population, and 13% of the African population [3]. 2–4.Men are disproportionately affected in the United States Hispanic Americans have a higher prevalence of NAFLD than Caucasians, while African-Americans have the lowest prevalence of any racial or ethnic group in the United States6 Among Hispanics, those of Mexican ancestry have the highest prevalence, while Dominican Republicans have the lowest [4]. The aetiology of this racial and ethnic disparity is likely multifactorial, with genetic, behavioural, and socioeconomic factors all playing a role.

Causes

Experts are baffled as to why some people accumulate fat in their livers while others do not. Similarly, it is unclear why some fatty livers develop inflammation that progresses to cirrhosis.
Both NAFLD and NASH are associated with the following:

- Obesity or being overweight
- Insulin resistance is a condition in which your cells do not absorb sugar in response to the hormone insulin.
- Hyperglycaemia (high blood sugar) indicates prediabetes or type 2 diabetes [5].

These combined health issues appear to promote fat accumulation in the liver. For some people, excess fat acts as a toxin to liver cells, causing inflammation and NASH, which can lead to scar tissue build-up in the liver [6].

Symptoms

NAFLD usually produces no symptoms. When this occurs, they may include:

- Fatigue
- Upper right abdomen pain or discomfort [7]

NASH and advanced scarring (cirrhosis) can cause the following signs and symptoms:

- Swelling in the abdomen (ascites)
- Enlargement of blood vessels just beneath the skin's surface Enlargement of the spleen
- Red palm trees
- Skin and eye discoloration (jaundice) [8]

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Pathophysiology

Obesity is the most common complication of NAFLD, caused by an imbalance between high energy intake (overnutrition) and energy expenditure. Overeating high fat and sugar foods has been linked to the activation of opioid and dopamine receptors in the nucleus accumbent, a brain area responsible for the development of cravings [9]. Furthermore, when compared to glucose, the macronutrient fructose increases cerebral blood flow to areas of the brain responsible for motivation and reward while failing to reduce satiety. Although these pathways have not been specifically studied in NAFLD patients, it is possible that they contribute to obesity in NAFLD patients as well [10,11]. The activation of reward centres in response to certain macronutrients is accompanied by a systemic decrease in gut-derived hormones that promote satiety (e.g., glucagon-like peptide 1 (GLP-1)) and an increase in gut-derived hormones that stimulate hunger (e.g., ghrelin). These changes are linked to an increase in circulating triglyceride levels and are thus linked to NAFLD pathogenesis [12]. The regulation of the aforementioned hormones by nutritional status is one common link. However, due to the inherent difficulties of human nutrition research, it is unknown to what extent specific macronutrients increase NAFLD susceptibility. High saturated fat, low fibre, and carbohydrate-rich diets have all been linked to an increased risk of NAFLD, but there is little direct evidence in humans [13]. Data from pre-clinical studies show that sucrose and fructose-rich diets are steatogenic, possibly through the promotion of intestinal dysbiosis or the dysregulation of key lipid metabolic pathways and hormones. Studies show that a high fructose diet and a high soda intake (and thus consumption of high fructose corn syrup) increase the risk of NAFLD in humans [14, 15].

Hyperinsulinemia and insulin resistance are both important in the pathophysiology of NAFLD. Pancreatic beta cells secrete insulin primarily in response to circulating glucose levels under normal conditions. Insulin stimulates esterification of fatty acids and storage in lipid droplets while inhibiting the opposing process of lipolysis in several metabolic tissues, including adipose tissue. Insulin has three primary actions in hepatocytes: it promotes glycogen storage, inhibits gluconeogenesis, and activates key regulators of de novo lipogenesis [16]. Insulin resistance causes 1) increased adipocyte lipolysis and high circulating free fatty acids available for subsequent hepatic uptake, 2) decreased hepatic glycogen storage, and 3) increased gluconeogenesis in NAFLD patients. Hyperinsulinemia may develop in response to systemic insulin resistance (or prior to the development of insulin resistance36), enhancing hepatic de novo lipogenesis pathways. The overall result is increased intra-hepatic lipid accumulation (steatosis) and enhanced triglyceride secretion in the form of very-low density lipoprotein.The increased lipid load circulates to adipose tissue, further reducing adipocytes' ability to store these lipids in lipid droplets. The inability of hepatocytes to accommodate neutral lipids within lipid droplets exposes [17]. The inability of hepatocytes to accommodate neutral lipids within lipid droplets exposes the cells to lipotoxic bioactive lipids. Lipotoxicity impairs insulin signalling further, causes oxidative damage, and promotes inflammation and fibrosis via a variety of mechanisms [18]. These downstream effects are thought to be responsible for the progression of NAFLD patients from NAFL to NASH, as well as the development of fibrosis and hepatocellular carcinoma (Figure 1).

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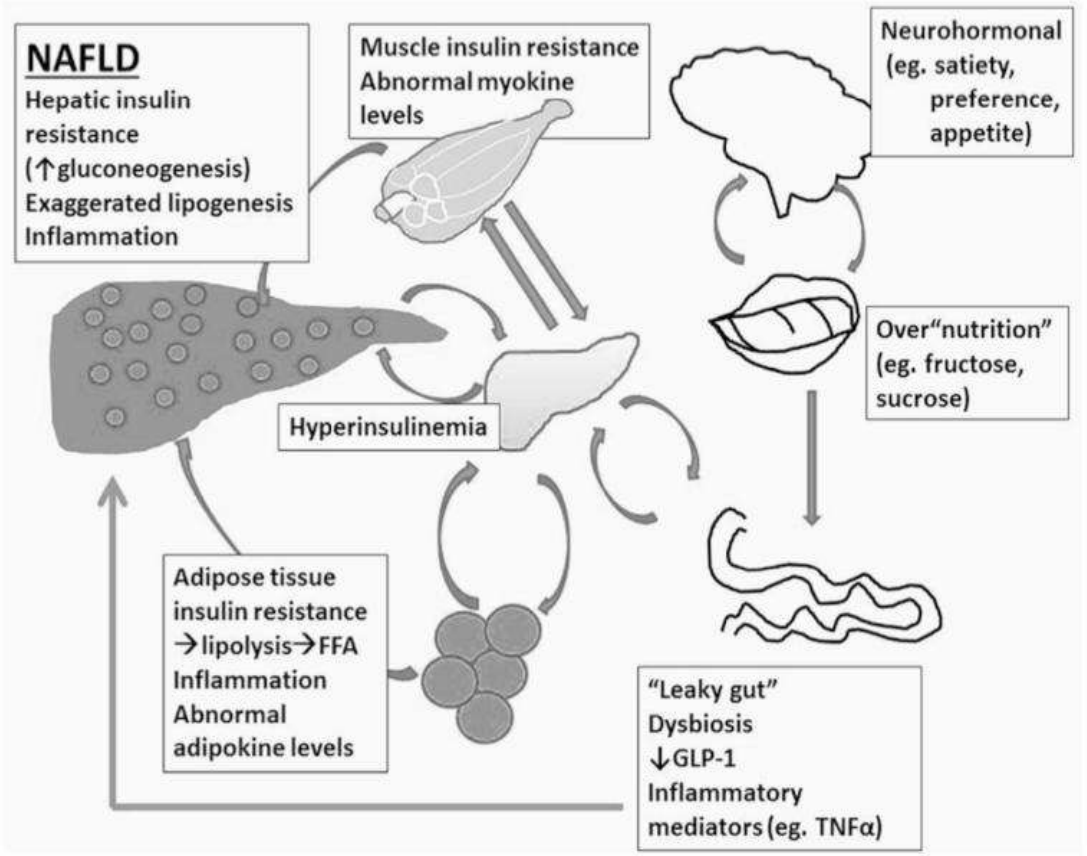

Figure 1: Biochemical changes in NAFLD

Complications

Chronic kidney disease, extrahepatic malignancies (such as colorectal cancer), psychological dysfunction, gastroesophageal reflux disease, obstructive sleep apnea syndrome, periodontitis, hypothyroidism, growth hormone deficiency, and polycystic ovarian syndrome are examples of extrahepatic complications of NAFLD. A suitable screening method for extrahepatic complications has yet to be determined. Because extrahepatic complications can affect multiple organs, collaborative care with respective experts appears to be required for patient management [19].

Diagonosis

Imaging:

Ultrasonography, CT scanning, and MRI scanning are all effective at detecting moderate to severe fatty changes in the liver. When compared to the spleen or renal cortex, hepatic fat has higher echogenicity on ultrasound. The fatty liver is hypodense and appears darker than the spleen on noncontract CT scans. Hepatic vessels appear to be relatively brighter and can be confused with contrast injection. No imaging method can differentiate between simple steatosis and NASH or determine the stage of fibrosis.As BMI increases, the sensitivity and specificity of ultrasonography for detecting fatty infiltration decreases, ranging from 49% to 100% and 75% to 95%, respectively. Each imaging method's sensitivity increases with the degree of fatty infiltration, with at least 33% steatosis optimal for detection [20].

Liver biopsy:

NAFLD is detected 66%-90% of the time by performing a liver biopsy on patients who have persistently elevated liver enzyme levels but no viral serologic markers of chronic liver disease. In this setting, the positive predictive value of fatty changes on ultrasound is estimated to be 92%-96%, while the negative predictive value of a normal scan is estimated to be 55%-87%. 64 Despite this, a clinical diagnosis of NAFLD based on serologic test results and imaging findings is correct in only 53%-83% of cases. A positive ultrasound result in association with metabolic risk factors in the absence of viral serologic evidence of chronic liver

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disease is likely to be sufficient for diagnosis in primary care settings where NAFLD is common.When the diagnosis is uncertain (e.g., in the presence of autoantibodies or elevated iron indices), prior to participation in a clinical trial, or when there is concern of advanced fibrosis, which may alter patient screening and surveillance, a liver biopsy may be useful. The benefits of a biopsy should be weighed against the minor but definite risks of harm [20].

Treatment

Weight loss:

The effect of weight loss on histological improvement appears to be proportional to the amount of weight lost rather than the method used to achieve it. Indeed, lifestyle interventions such as hypocaloric diet and physical activity, drug-induced weight loss (e.g., orlistat), or weight loss after bariatric surgery appear to have a similar beneficial effect on NASH resolution and fibrosis regression. All patients with NAFLD, regardless of T2DM, should avoid moderate alcohol consumption and, whenever possible, hepatotoxic drugs. Clinicians should also advise patients to avoid smoking and fructose-containing beverages and foods. Physical exercise of various types (for example, aerobic exercise, resistance exercise, or high intensity intermittent exercise) appears to have similar effects on liver fat content.

However, resistance training, high-intensity interval aerobic training, and moderate-intensity continuous aerobic training were all equally effective in reducing hepatic fat content in the Oh et al. study, but only high-intensity interval aerobic training was effective in improving hepatic stiffness and restoring Kupffer cell function. Finally, because patients with NAFLD are more likely to develop cardiovascular disease than those who do not, it is critical to remember that the benefits of exercise extend to the entire cardiovascular system [21].

Bariatric Surgery:

Bariatric surgery refers to surgical procedures that cause weight loss by limiting the amount of food the stomach can hold and/or promoting nutrient malabsorption.

Laparoscopic sleeve gastrectomy, laparoscopic Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, and duodenal switch are the most common bariatric surgery procedures performed worldwide. Inaddition to weight loss, bariatric surgery can improve insulin resistance, obesity, T2DM, hypertension, dyslipidemia, and obstructive sleep apnea. Importantly, bariatricsurgery has been shown to significantly improve all histological features of NAFLD, including fibrosis.

Medicine:

There is no evidence that alternative medicine treatments can cure non-alcoholic fatty liver disease. However, researchers are investigating whether certain natural compounds, such as:

- Vitamin E and other vitamins known as antioxidants, in theory, could help protect the liver by reducing or neutralising the damage caused by inflammation. However, more research is required. Some evidence suggests that vitamin E supplements may be beneficial for people suffering from non-alcoholic fatty liver disease. However, vitamin E has been linked to an increased risk of death as well as an increased risk of prostate cancer in men.
- People with non-alcoholic fatty liver disease who reported drinking two or more cups of coffee per day had less liver damage than those who drank little or no coffee, according to studies. It's not clear how coffee affects liver damage, but new research suggests it may contain compounds that help fight inflammation [22].

Prevention

Choose a healthy diet. Choose a diet rich in fruits and vegetables, whole grains, and healthy fats. Maintain a healthy weight. If you are overweight or obese, reduce your daily calorie intake and increase your physical activity. If you have a healthy weight, work to maintain it by eating well and exercising on a regular basis. Exercise [22]. Exercise on most days of the week. If you haven't been exercising regularly, consult your doctor first.

II. CONCLUSION

NAFLD is a major cause of morbidity and mortality worldwide, owing to cardiovascular and oncologic complications, as well as the fact that it is rapidly becoming the leading cause of end-stage liver disease and liver transplantation. With a 30% prevalence in the United States, it has reached epidemic proportions. While the metabolic syndrome is a common risk factor, there are differences between racial and ethnic groups, indicating a complex interaction of hormonal,

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nutritional, and genetic factors at work in disease pathogenesis. Furthermore, these biologic factors are likely to interact with socioeconomic forces, influencing one's susceptibility to NAFLD and likelihood of progression to advanced stages.

The complexity of NAFLD pathogenesis mirrors the complexity of its management in that NAFLD patients require a multi-system, integrated approach to care. In addition to hepatic health, overall metabolic health must be closely monitored. Providers should aggressively assess and manage risk factors, as well as estimate the risk of fibrosis at presentation and over time. Referral to hepatology can occur at any stage, but is most common when fibrosis is suspected. Because there are currently few approved treatments, the field of treatment options is ripe for innovation. Weight loss can reverse NASH and fibrosis; however, we anticipate that adjunctive pharmacologic and non-pharmacologic therapies for NAFLD patients will be available in the future.

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