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REVIEW ARTICLE

REVIEW ON "NON-ALCOHOLIC FATTY LIVER DISEASE"

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ABSTRACT

The term "Fatty Liver" or "Non-Alcoholic Fatty Liver Disease" refers to the presence of lobular inflammation and macro vesicular alterations without inflammation (steatosis) in the absence of heavy alcohol consumption. It can be further broken down into two subgroups: NASH (Non-Alcoholic Steatohepatitis) and NAFL (Non-Alcoholic Fatty Liver).Non-alcoholic fatty liver disease (NAFLD) develops in people who drink little to no alcohol when too much fat builds up in the liver cells. Numerous metabolic risk factors, including diabetes and obesity, are linked to NAFLD. Although NAFLD is usually not harmful, in certain cases it can advance to non-alcoholic steatohepatitis (NASH).Metabolic Syndrome, obesity, diabetes, and hyperlipidemia are all frequently linked to NAFLD. NAFLD is present in around 80% of people with metabolic syndrome.

INTRODUCTION

The most frequent cause of liver dysfunction in the west is non-alcoholic fatty liver disease (NAFLD).(1) In the absence of a secondary cause like alcohol or drugs, macrovesicularsteatosis in 5% of hepatocytes is what constitutes non-alcoholic fatty liver disease (NAFLD). With a 25% prevalence worldwide, NAFLD is one of the main causes of chronic liver disease. (2) The majority of people with NAFLD also have other metabolic disorders, such as insulin resistance, type 2 diabetes (T2D), hypertension, abdominal obesity, and dyslipidemia. As a result, cardiovascular illnesses are the leading cause of death in people with NAFLD, regardless of other comorbidities(3). Grading and staging of NAFLD-Staging and grading of NAFLD is based on the amount of fat accumulation, the presence of necrosis and inflammation, along with the distribution and degree of fibrosis, in addition to the cellular and molecular details of these conditions.

Macro vesicular steatosis

A.Grade 0: none
B.Grade 1: up to 33 percent (%)
C.Grade 2: 33 %-66 %
D.Grade 3: >66 %

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Necro-inflammatory activity: Grade 1 (mild) ≤66 %, zone 3 ballooning occasionally found, sporadic acinar neutrophils (PMN) ± lymphocytes, minimal inflammation of porta Grade 2 (moderate) Definite Zone III ballooning & occasional presinusoidal fibrosis, intra-acinarPMNs,portal and intra-acinar inflammation. Grade 3 (severe) Pan-acinarsteatosis, widely distributed with PMNs, ballooning, intraacinar and portal inflammation. Stage 1 focal or extensive presence of Zone III presinusoidal/peri- cellular fibrosis;

- Stage 2 Zone III presinusoidal/peri –cellular fibrosis with focal or extensive periportal fibrosis
- Stage 3 Zone III presinusoidal/peri –cellular fibrosis and portal fibrosis with focal or extensive bridging fibrosis
- Stage 4 Cirrhosis (4,5)

A liver biopsy is the gold standard for diagnosing any type of liver inflammation, including damage. Liver biopsies can be very helpful in the diagnosis of NAFLD and related illnesses, and their results can range from more severe types of non-alcoholic steatohepatitis (NASH) to lipid deposition as droplets in the hepatocyte. The US guidelines for NAFLD management describe NAFLD as a) no alcohol, drug, or viral-induced steatosis and b) steatosis with 5% fat infiltration in imaging or histology. Patients with NAFLD may exhibit increased liver enzyme levels (6).

Pathogensis: The presence of hepatic steatosis is necessary for the histological diagnosis of NAFLD. Currently, a variety of common pathogenic pathways, including lipotoxicity, oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress, have been hypothesised and characterised for the change from basic steatosis to NASH. Simple hepatic steatosis and, more commonly, liver cell destruction with associated inflammation and/or fibrosis are pathological characteristics of NASH (7). Contrary to popular belief, adipose tissue has an endocrine function and secretes hormones (adipokines) like leptin and adiponectin.Adipokine imbalance brought on by obesity-related adipocyte hypertrophy and/or insulin resistance may have significant effects on the liver in addition to the adipose tissue itself (8).Another peptide made in adipose tissue, leptin, may be crucial in the emergence of insulin resistance. Insulin receptor substrate is dephosphorylated by leptin, which causes both peripheral and hepatic insulin resistance (9). Through the actions of AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC) signalling, circulating adiponectin controls hepatic fatty -oxidation. Together, these anomalies enhance adipocyte fat loss and encourage ectopic fat growth.

An abnormality in insulin activity is known as insulin resistance (IR). In relation to metabolism, IR is the difference between a person and the general population in the incapacity of a specific amount of insulin to metabolise a known amount of glucose. The cornerstone of metabolic syndrome (MS), which is characterised by the presence of at least three of the following symptoms: abdominal obesity, elevated triglycerides, decreased HDL cholesterol, elevated blood pressure, and hyperglycemia, is IR, which is closely related to visceral fat (10). The insulin signal is propagated in healthy persons by the phosphorylation of multiple substrates, including insulin receptor substrates (IRS)-1, -2, -3, and -4, as a result of the binding of insulin to its receptor.. The intracellular PI3K (phosphoinositide 3-kinase) and AKT/PKB (protein kinase B) pathways are heavily implicated in modulating the metabolic effects of insulin and are activated in response to insulin stimulation of IRS-1 and -2.(9). This sets off a series of processes that cause a particular glucose transporter-4 (GLUT-4) to move from an intracellular pool to the cell membrane. Myocytes and adipocytes can transport glucose along a concentration gradient from extracellular space into their cytoplasm with the help of GLUT-4 (12).

Reactive oxygen species (ROS) are produced as a result of oxidative stress and mitochondrial malfunction in NAFLD72 because the increased FFA load might overwhelm the mitochondrial oxidation mechanism that normally occurs in the liver.(14). Free radicals and nonradicals can be distinguished amongst ROS based on their chemical characteristics. The main nonradical species are H2O2, hypochlorous acid (HOCl), peroxynitrite (ONOO), and peroxynitrous acid (ONOOH), while the main free radicals are O2, hydroxyl radical (HO), nitric oxide (NO), nitrogen dioxide (NO2), carbonate radical anion (CO3-), and alkoxyl/alkyl peroxyl (RO/ROO)(12). The most major ROS generator in the pathophysiology of NAFLD is the mitochondria, which are both essential cellular producers of ROS and an organelle in charge of lipid metabolism. The literature is rather inconsistent when it comes to mitochondrial dysfunction, which includes variations in oxygen consumption, ETC complex activity, FAO, and mitochondrial DNA content. These variations suggest that the loss of mitochondrial activity may be a contributing factor to NAFLD rather than its cause (13).

Role of ER stress: The primary location for lipid production in hepatocytes is the ER. All of the main lipid metabolic routes, such as lipogenesis, triglyceride synthesis and storage, apolipoprotein assembly and secretion, and fatty acid oxidation, entail the involvement of hepatocytes. (14). Numerous biological stressors, such as hyperinsulinemia and hyperlipidaemia, can lead to ER stress. Further research into the role of ER stress in NASH is necessary because it is known to have a significant role in alcohol-induced steatohepatitis (11).

Treatment

Lifestyle: NAFLD patients might not be as motivated or change-ready as the general population. altering one's way of life, including one's eating and exercise patterns. The most well-established form of treatment for both NAFLD and NASH is weight loss(17). The biggest decrease in the controlled attenuation parameter, which is a measurement of hepatic steatosis in NAFLD patients, was seen when a low-glycemic-index-MED was combined with either aerobic activity or both aerobic exercise and resistance training after three months.(18). Which exercise method, intensity, and duration are most effective at reducing NASH was the subject of several research. A strong inhibitory effect of vigorous exercise was seen in the development of fatty liver to NASH. modified high-intensity interval training (HIIT), which consists of five cycles of intense cycling, three minutes of rest, and three times/week for 12 weeks demonstrated reduction in liver fat and improvement.(19). The most suggested dietary pattern for NAFLD is the Mediterranean diet, which has been shown to reduce liver fat even without weight loss. The Mediterranean diet is characterised by increased monounsaturated and omega-3 fatty acid intake (40 percent of calories as fat vs. up to 30 percent in a typical low fat diet), and decreased carbohydrate intake, especially sugar and refined carbohydrates (40 percent of calories vs. 50 to 60 percent in a typical low fat diet).(17).

PROBOIOTIC: The World Health Organization/Food and Agriculture Organisation (WHO/FAO) defines probiotics as a "live microorganism that—when administered in adequate amounts—confers a health benefit on the host" (20. Probiotics have been proposed as a treatment for the prevention of chronic liver damage because they inhibit bacterial mucosal adhesion and production of antimicrobial peptides, as well as prevent bacterial translocation and epithelial invasion while reducing inflammation and enhancing host immunity(21).

ANTIFIBROTIC: Based on its effects on improving red blood cell flexibility, lowering blood viscosity, and increasing aerobic glycolysis and oxygen consumption in ischemic TISSUE(22), the methylxanthine derivative pentoxifylline is frequently used in the treatment of intermittent claudication in western countries.It stimulates an increase in cyclic AMP levels and prevents TNF- gene transcription by acting as a non-specific PDE inhibitor(23).In many experimental models of fibrosis, pirferidone has the ability to decrease both the proliferation of fibroblasts and the synthesis of collagen. It decreases the production of extracellular matrix components, the proliferation of activated hepatic stellate cells, and may have anti-inflammatory effects in rats(24).

URSODEOXYCHOLIC ACID: Gallstones made of cholesterol and primary biliary cirrhosis (PBC) can be treated without surgery using ursodeoxycholic acid (UDCA), a secondary bile acid made by intestinal bacteria as a metabolic byproduct(25). A substance called UDCA has effects that are cytoprotective, antiapoptotic, membrane stabilising, antioxidative, and immunomodulatory (27).The two main bile acids in humans, chenodeoxycholic acid and deoxycholic acid, are hydrophobic and, when in excess, can cause direct biliary toxicity by acting as detergents on lipid membranes.Only 1-3% of the entire bile acid pool in humans naturally contains the compound 2 UDCA26).The nuclear receptors in the liver and intestinal cells are activated by bile acids and their derivatives, including UDCA. Bile acids and their derivatives are also used to treat cholestatic diseases by protecting the liver from retained bile acids.(27).

ELAFIBRANOR (GFT505): In mice models of NAFLD, steatosis, inflammation, and fibrosis were demonstrated to be improved by elafibranor, an unlicensed dual agonist of PPAR/ receptors (28).dual PPAR and PPAR ligand. The nuclear hormone receptor superfamily, which includes the ligand-activated transcription factors known as PPARs, has a wide range of genes engaged not only in various metabolic processes but also in cellular function. (29).

DPP-IV INHIBITORS AND SGLT2 INHIBITORS: DPP-IV inhibitor medication is not advised for NAFLD patients outside of their labelled indications due to the unsatisfactory outcomes of all of the studies looking into its effects [30].Although sizable randomised trials are still required to support this hypothesis(32), studies investigating sodium-glucose cotransporter protein 2 (SGLT2) inhibitors have consistently shown a decrease in liver transaminases and an improvement of imaging-based biomarkers. As a result, they may be a treatment option not only for diabetic NAFLD patients but also for those without diabetes.

STATINS AND OTHER LIPID LOWERING AGENTS: Clinicians frequently have to deal with these diseases in NAFLD patients because MetS characteristics including T2DM, hypertension, obesity, and (atherogenic) dyslipidemia are related with NAFLD. Statins, which are known to block 3-hydroxy-3-methylglutaryl-coenzyme Areductase (HMG-CoA), a crucial enzyme involved in cholesterol formation, can be used to regulate abnormal blood cholesterol levels [33]. Statins have pleiotropic qualities in addition to their ability to decrease cholesterol, such as neoangiogenesis, anti-oxidative and anti-inflammatory actions, and enhanced endothelial function [34].Statins may increase aminotransferase levels, however in actual practise, liver damage brought on by this lipid-lowering medication is rarely seen(35).

ANTI-PLATELET AGGREGATION AGENTS: There aren't much data from prospective trials on how aspirin affects fibrosis in NAFLD patients. Daily aspirin use was linked to less severe histologic characteristics of NAFLD and NASH, as well as a lower risk for advanced fibrosis progression over time, in a recent observational analysis of individuals with biopsy-proven NAFLD [36]. Studies that suggest platelet-derived GPIb may contribute to the onset of NASH without the involvement of von Willebrand factor (vWF), p-selectin, or Mac-1 (also known as integrin M2, or CD11b/CD18) corroborated this data. These pathways might present a brand-new potential NASH target (37).

METFORMIN: When T2DM is first diagnosed, most patients are given the biguanide metformin as their first line of treatment [33]. In T2DM patients without contraindications (including chronic renal disease stage 4 or 5, advanced heart failure, advanced pulmonary illness, or a history of lactic acidosis), metformin is regarded as safe and effective (with a reduction in HbA1c levels ranging from 0.5% to 1%) [34]. AMP-activated protein kinase (AMPK)-dependent enhancement of hepatic glucose metabolism and enhanced glucose absorption into muscle cells are two mechanisms by which metformin lowers blood glucose levels in experiments [33,34]. Other hypothesised mechanisms for the inhibition of gluconeogenesis by this glucose-lowering substance include changes in cellular energy charge, fructose-1,6-bisphosphatase 1, and modulation of the cellular redox state via direct inhibition of mitochondrial glycerol-3-phosphate dehydrogenase (35).

BIARTIC SURGERUY: Obesity prevalence and its metabolic effects, including nonalcoholic fatty liver disease (NAFLD), have emerged as major health issues. Patients with NAFLD who make lifestyle changes, including weight loss, experience less liver damage. However, in a therapeutic context, there is relatively little commitment to lifestyle adjustments. Long-term weight loss can result from bariatric surgery and metabolic components can be improved.(36,37).Beyond weight loss, bariatric surgery may have additional advantages for the liver. In fact, bariatric surgery can boost levels of the hormone glucagon-like peptide-1 (GLP-1) in the blood, which reduces hunger, slows gastric emptying, and enhances insulin sensitivity [38]. The farnesoid X receptor (FXR), which GLP-1 controls, alters the gut flora and supports NAFLD [39]. In light of these presumptions, current recommendations suggest that bariatric surgery may be an option for patients with T2DM or severe obesity (i.e., a BMI >35 kg/m2) [40].

LABORATORY FINDINGS: Serum indicators including aminotransferases (AST, ALT) are mildly to moderately increased during laboratory tests [30]. However, in patients with NAFLD or other associated disorders, the AST and ALT levels can vary. In other words, NAFLD cannot be present even if AST and ALT levels are increased or normal [41]. ALT elevations are more typical in NAFLD patients than AST elevations. In comparison to ordinary steatosis, NASH typically has higher ALT levels. Patients with NAFLD frequently have raised blood ferritin levels, and 6–11% of them also have elevated transferrin saturation [42]. Alkaline phosphatase (ALP) and coagulation factors are additional interesting markers. ALP can be abnormal and even high in people with NAFLD.

CONCULSION

The management of these patients has grown more challenging due to the expanding obesity pandemic and the increased frequency of concomitant disorders including T2DM and NAFLD. There are several therapy options, however there aren't many high-quality research that compared them with one another. Prospective studies addressing the remaining uncertainties regarding the relationship between insulin resistance, fatty liver, and fibrosis progression should be made accessible soon given the rising popularity of bariatric surgery.Despite significant improvements in our understanding of the epidemiology and aetiology of NAFLD, the only viable

treatment for NAFLD and its severe manifestations is currently weight loss.. A phase 2 trial testing IONIS-DGAT2Rx [78] is the only RCT that has so far included patients with and without T2DM. As a result, the information currently available on new medications (such as OCA, selonsertib, elafibranor, cenicriviroc, or resmetirom) as monotherapy for NAFLD treatment may not necessarily be applicable to all patients with T2DM. However, several glucose-lowering medications, including pioglitazone, GLP-1RAs, and SGLT-2 inhibitors, may be helpful for treating NAFLD in these patients.

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