Review Article

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NAFLD: A BRIEF REVIEW OF THE RECENT GLOBAL EPIDEMIC

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) has become a metabolism-related severe illness, and during the next ten years, it will continue to be a major global liver health concern. According to epidemiological research, the incidence of NAFLD in the general population of India ranges from 9% to 32%, with a higher frequency in people who are obese and have diabetes. NAFLD is most strongly associated with obesity and insulin resistance, increasing the risk of type 2 diabetes, cardiovascular and cardiac diseases, chronic kidney disease, and a causal link in sleep apnea, colorectal cancer, osteoporosis, psoriasis, various endocrinopathies such as polycystic ovary syndrome, as well as liver cancer and a liver transplant. Although liver biopsy is still the gold standard for a conclusive diagnosis, developing non-invasive advanced imaging like USG, biochemical, and genetic tests will undoubtedly give future clinicians a wealth of knowledge and the chance to understand the pathogenesis better and develop targeted treatments. Several drugs and nutritional supplements are now used to treat NAFLD, but none appear to be the "magic cure" for this escalating issue. To better understand this condition and manage NAFLD patients, we have compiled the most recent information on NAFLD epidemiology, risk factors, prevalence, pathogenesis, diagnosis, staging, screening, and treatment in this study.

Keywords: Non-alcoholic fatty liver disease, Diabetes, Insulin resistance, Hepatocellular carcinoma, Liver transplant.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), a hepatic manifestation of metabolic syndrome, is the most common chronic liver disease, and its prevalence is swiftly increasing worldwide. NAFLD denotes a spectrum of disorders that have in common the presence of hepatic steatosis (fatty liver) in individuals who do not consume alcohol or do so in minimal quantities (less than 20 g (2 units per day) in women, 30 g (3 units per day) in men, based on guidelines of scientific associations' recommendations of ethanol per week). NAFLD is often understood to be the hepatic expression of metabolic syndrome, and it has become clear that NAFLD is one of the most common illnesses of modern humanity.

The definition of NAFLD requires that:
(a) there is evidence of hepatic steatosis, either by imaging or by histology and
(b) there is no cause for secondary hepatic fat accumulation, such as significant alcohol consumption[1].

RISK FACTORS

While the exact causes of NAFLD aren't well understood, researchers currently believe these may all play a role, like:

a. Genes,
b. Dietary imbalance,
c. Disturbed digestive system functioning
d. Sedentary lifestyle
e. Environmental factors

While some people with NAFLD have no prior risk factors, some lifestyle factors can trigger the likelihood of getting NAFLD.

Genes

Patatin-like phospholipase domain-containing protein3 (PNPLA3, also called adiponectin) is a 481 amino acid protein expressed significantly in hepatocytes[2]. It functions as a triglyceride hydrolase (which suggests catabolic lipase activity) and acetyl-CoA-independent trans-acylase (which suggests anabolic lipogenic activity)[3]. The most commonly studied variant of PNPLA3 is rs738409, altering wild-type cytosine to guanine. This SNP is associated with increased hepatocellular triglyceride accumulation (up to two-fold greater than wild type) and the development of NAFLD[4]. However, the presence of rs738409G has been associated with NAFLD susceptibility and degree of steatosis across many ethnic groups. Several studies indicate that the rs738409 GG genotype is associated with the development and progression of NAFLD in Asian cohorts, including Chinese, Japanese, Korean, and Indian populations. Thus, PNPLA3 I148M has been identified as an ethnic NAFLD risk factor.

Dietary imbalance

The close association between NAFLD and obesity highlights the role of excess dietary intake in NAFLD. The prevalence of NAFLD steeply increases with increased body mass index (BMI) and waist circumference throughout age, sex, and ethnicity, in a manner largely resembling the prevalence of metabolic syndrome (MetSyn)[5]. Increased dietary volume may result from various factors, including frequent dining out, larger portion sizes, and the spread of all-you-can-eat restaurants. Eating out versus at home typically consumes more energy during a meal[6]. Increased calorie consumption from larger meal portions leads to obesity and NAFLD. A high-energy diet is characterised by fried foods, fast food, and eating out. Obesity and NAFLD may readily and significantly increase energy consumption from a high-energy diet.

The CARDIA study examined habitual fast-food consumption in young adults at baseline and after 15 years and analysed the association between fast food diets and weight gain and insulin resistance[7]. Patients with obesity and NAFLD frequently exhibit inappropriate food consumption patterns, such as the propensity to overeat at dinnertime, eat late at night, skip breakfast, and eat too quickly. Obese people typically exhibit night-eating syndrome[8]. There are two types of carbohydrates: simple and complex, and consuming too many simple carbohydrates—like fructose and sucrose—is a crucial contributor to NAFLD. Soft drink consumption, especially that of beverages with sugar, is sharply rising globally[9]. The average daily intake and frequency of soft drinks were at least two times greater in patients with NAFLD than in patients without NAFLD when compared between NAFLD and non-NAFLD cases[10]. The degree of change in liver fat, as assessed by ultrasound, was found to correlate with an increase in the number of soft drink bottles consumed, indicating that soft drink consumption strongly indicated fatty liver[11]. Lipid overconsumption leads to increased calorie intake and body fat build-up. Hepatic steatosis is brought on by increased levels of free fatty acids entering the liver as a result of increased visceral fat. Saturated fatty acid overconsumption is considered to cause type 2 diabetes and insulin resistance. Intake of saturated fatty acids was considerably higher in NAFLD patients than in healthy controls, according to a 7-day nutritional assessment of diet[12].

Moreover, saturated fatty acids and lipids were reported significantly more in NAFLD and NASH patients than in healthy individuals. Over-ingestion of cholesterol has been observed as a critical cause of NAFLD. The dietary records of obese and non-obese NAFLD patients found that cholesterol ingestion was significantly greater in NAFLD patients than healthy controls. Interestingly, non-obese NAFLD patients ingested more cholesterol than obese NAFLD patients, suggesting that dietary cholesterol consumption is crucial for NAFLD onset and progression regardless of weight. Despite high lipid intake, PUFA intake is lower in people with NAFLD than healthy persons[13]. It was also shown that PUFA intake had a role in the development and progression of NAFLD and was much lower in non-obese NAFLD patients than in obese NAFLD patients. These results imply that patients with NAFLD have an imbalanced diet.

Disturbed digestive system functioning

Patients with liver cirrhosis have been reported to have various gastrointestinal problems, including impaired gastrointestinal motility, intestinal permeability, and absorption. These alterations affect nutritional status and can lead to clinical problems such as hepatic encephalopathy and spontaneous bacterial peritonitis, even though they may not be as clinically apparent as other typical symptoms of chronic liver disease. The development of liver fibrosis in alcoholic and non-alcoholic fatty liver disease has also been linked to the disruption of gut barrier function[14]. Patients with cirrhosis frequently have SIBO or small intestine bacterial overgrowth. Overall, advanced disease staging, ascites, and hyperbilirubinemia are risk factors for SIBO in chronic liver disease[15]. Several chronic illnesses, such as chronic liver diseases or Type-2 Diabetes, are characterised by low-grade inflammation, although it is yet unknown which organ systems in the body may be involved in this process. Increased levels of circulating inflammatory markers, such as cytokines, acute phase proteins, and adhesion molecules, have been seen in several NAFLD investigations, particularly in NASH patients[16]. In these metabolic "non-communicable" illnesses, detectable systemic inflammation is typically considered sterile and primarily regulated by innate immune mechanisms[17]. Low-grade chronic inflammation is relevant for NAFLD patients within and outside the liver. Although cardiovascular problems are the leading cause of mortality in NAFLD patients, liver disease-related deaths from atherosclerosis are also common[18]. Therefore, inflammation significantly contributes to patient outcomes both within the liver (liver cirrhosis) and outside the liver (atherosclerosis, cardiovascular complications) in NAFLD.

Sedentary lifestyle

Physical inactivity is linked with increased insulin resistance, metabolic risk, and adiposity in youth. It is well-known that exercise cessation (or reduced daily ambulatory activity) and the initiation of acute, short-term physical inactivity lead to a rapid reduction of systemic and skeletal muscle insulin sensitivity. Both acute and chronic physical inactivity can activate pathologies (insulin resistance and central adiposity) closely related to NAFLD.

Environmental factors

The relevance of environmental contaminants in inducing NAFLD is underscored by the fact that in recent years the terms "toxicant-associated fatty liver disease" (TAFLD) and "toxicant-associated steatohepatitis" (TASH) have been coined to show the spectrum of fatty liver injury in non-obese people exposed to chemicals and xenobiotics. Furthermore, although nutritional status, co-exposures, and obesity seem to confer amplified susceptibility to TAFLD/TASH, it is interesting to note that the effects of pollutants are not always associated with metabolic alterations; in fact, TAFLD/TASH patients may have a low body fat mass and no IR (insulin resistance). In recent years, the pathogenesis of cardiovascular diseases (CVDs) and MetSyn have been directly linked to PM2.5 exposure, indicating its profound metabolic impact. PM2.5 promotes systemic and pulmonary inflammation, prompting IR incidence. It was recently established that PM2.5 exposure might act synergistically with a high-fat diet in promoting MetSyn, an event associated with inflammation onset that may represent a chief risk factor in NAFLD progression.

PREVALENCE

The prevalence of NAFLD in the Indian population ranges from 5 to 28%. Approximately 2–3% of the general population is estimated to have Non-Alcoholic Steatohepatitis (NASH), which may advance to liver cirrhosis and hepatocellular carcinoma. In India, it is becoming a significant cause of liver disease. Epidemiological studies suggest the prevalence of NAFLD to be about 9–32% in the general Indian population, with a higher incidence among overweight or obese individuals and diabetic or pre-diabetic patients.

PATHOPHYSIOLOGY OF NAFLD

Most NAFLD patients are overweight or obese and have underlying insulin and probably leptin resistance, resulting in dysregulated energy metabolism. The regulation of glucose and lipid metabolism involves a complex interplay between adipose tissue, skeletal muscle, and the liver. The clinical syndrome of NAFLD spans from bland steatosis to steatohepatitis, which can progress to fibrosis and cirrhosis. The pathogenesis, including roles of hormones, nutritional and intestinal dysbiosis, insulin resistance, lipo-toxicity, hepatic inflammation, and genes, are examined. While the knowledge of the pathogenesis of hepatic steatosis has undoubtedly increased over the last decade, many uncertainties remain, and it remains the subject of intense investigation. Hepatic steatosis derives from several possible sources, including (1) increased free fatty acid (FFA) delivery to the liver as a result of dietary fat intake and increased lipolysis within insulin-resistant adipose tissue; (2) increased hepatic de novo lipogenesis (DNL); (3) decreased FFA oxidation; and (4) decreased triacylglycerol (TAG) export from the liver in the form of very low-density lipoprotein (VLDL). The largest contributor to hepatic steatosis in patients with NAFLD has increased FFA influx to the liver (60%), followed by DNL (de-novo lipogenesis).

DIAGNOSIS, STAGING, AND SCREENING

Patients are frequently asymptomatic until liver decompensation develops without incidental discovery; however, if the patient's evaluation reveals markers like insulin resistance, obesity, or characteristics linked to metabolic syndrome, the diagnosis can be made considerably earlier. The assessment of morphological features must be calculated using a predetermined scoring method to give a reliable and consistent evaluation of NAFLD for use in clinical studies. Three histological scoring systems are currently in place: the NASH clinical research network's NAFLD activity score (NASH CRN-NAS), steatosis, activity, and fibrosis (SAF), and the Brunt staging system[19]. It should be emphasised that despite all efforts to generate a scoring system that is consistent and highly repeatable, the classification of NAFLD will always be hampered by observer bias and a lack of complexity that would be required to depict an elaborate disease process.

BMI and visceral adiposity are valuable indicators of NAFLD during the patient's physical examination, although the diagnosis is considerably trickier in slim patients. It sounds like a good idea to screen people at risk of developing NAFLD; however, ultrasound is too expensive and time-consuming to be used for mass screenings of populations, and liver function tests in patients with NAFLD or NASH can be within the normal range.

Non-invasive tests (Biochemical tests and Imaging techniques like USG whole abdomen)

NAFLD is diagnosed by combining clinical features and liver imaging. A thorough review of alcohol drinking history is part of the clinical evaluation, which also looks at metabolic risk factors that may be personal or familial, past medical history (including dietary supplements), and serologic tests. While up to 60% of NAFLD patients with normal ALT can have NASH or advanced fibrosis, and 53% of NAFLD patients with raised ALT do not have NASH or advanced fibrosis, liver enzymes (Liver Functional Tests/LFT) are not always a sole aspect of the diagnostic criteria for NAFLD. Most patients require a clinical history, serologic tests, and radiologic results (ultrasound, CT, or MRI) to determine whether they have NAFLD. Interestingly, incidental radiologic findings of hepatic steatosis are the primary reason for suspicion in most individuals with NAFLD. Although there is significant inter- and intra-observer variability, at least 30% hepatic steatosis is ideal for visualising hepatic steatosis by these popular radiological methods. Conventional radiologic methods cannot detect Steatohepatitis and early fibrosis.

Liver biopsy

Liver biopsy remains the gold standard for NAFLD staging due to the limitations of non-invasive diagnostics in NAFLD patients. Nevertheless, liver biopsy is not advised for all patients due to the frequency of NAFLD, the majority of patients' relatively low risk of the illness progressing, the lack of treatment options, the hazards of the biopsy, and the questionable cost-effectiveness of invasive diagnostics.

MANAGEMENT

Cardiometabolic illness (12.7%), non-HCC malignancy (8.1%), and liver disease (including HCC) (6.9%) are the leading causes of death from NAFLD. In NASH patients compared to non-NASH patients, liver-related mortality at age 18 is higher (17.5% versus 2.7%, respectively)[20]. Metabolic and cancer risk factors need to be given extra attention in NAFLD patients due to the risk of death from cardiometabolic and oncologic illnesses. For all patients, it is recommended to examine and treat obesity, hyperlipidemia (despite the use of statins, which increase mortality in NASH and cirrhotics), insulin resistance, and diabetes. Also, based on their age, gender, and family history, individuals are advised to undertake regular cancer screening exams.

Moreover, patients should be co-managed by general care, cardiology, endocrinology, and nutrition. Currently, the main treatment options for NAFLD in its advanced stages are surgical treatments and lifestyle changes (including diet and exercise). When treating NAFLD, medications and dietary supplements that target metabolic diseases like Diabetes, obesity, etc., are also considered.

DISCUSSION

Globally, NAFLD is the main contributor to chronic liver disorders. NAFLD is a medical condition that affects about 25% of the world's adult population, with the prevalence of NAFLD in India ranging from 9% to 32%. It is characterised by excess fat deposits in the liver that are not brought on by heavy alcohol use (20 g (2 units per day) in women and 30 g (3 units per day) in men, according to guidelines of scientific associations recommendations). Early NAFLD detection helps identify those who may have silently progressing fatty liver disease. The most prevalent form of NAFLD is simple fatty liver, which does not cause difficulties. However, if left untreated and undetected, simple fatty liver can advance to Non-Alcoholic Steatohepatitis (NASH), which can cause cirrhosis and liver cancer. NAFLD patients are more likely to develop cardiovascular conditions than non-NAFLD patients. Hence, all NAFLD patients should be thoroughly screened for metabolic complications and treated accordingly.

CONCLUSION

This review focuses on and discusses NAFLD as an epidemic rising quickly globally. In most cases, fatty liver is harmless, but as it progresses and develops into fibrosis, it is not, and it frequently signifies a dismal prognosis. Many risk factors have been advocated for the development of NAFLD, and the pathophysiology of most of these risk factors centres on metabolic dysregulation or insulin resistance. NAFLD is typically asymptomatic and discovered by chance during standard laboratory testing. In most NAFLD patients, diabetes or impaired glucose tolerance will occur. The primary causes of Non-

Alcoholic fatty liver disease are excessive calorie intake and a lack of exercise, leading to obesity and insulin resistance, which cause triglyceride and free fatty acid accumulation in the liver. This indicates that changing an unhealthy lifestyle should be the first defence in preventing and treating NAFLD. The condition can be prevented by adopting a healthy lifestyle and diet. NAFLD is a clinicopathological illness that is becoming more well-recognised and has the potential to proceed to end-stage liver disease if conventional therapy does not establish a successful management strategy. NAFLD is a significant risk factor for Metabolic complications, and there is substantial evidence that it also has a role in the development and progression of T2DM, cardiac disorders, and CKD. To determine whether there are any significant "connecting links" (such as insulin resistance and the activation of inflammatory pathways) that relate NAFLD to the emergence of extra-hepatic diseases, more research is required to understand the biological mechanisms by which NAFLD influences the risk of HCC and other extra-hepatic diseases like cirrhosis and carcinomas. Several drugs and vitamins can already be used to treat NAFLD, but none appears to be the "sure shot cure" for this escalating issue. Gaining a better understanding of the pathophysiological relationships between NAFLD and these extra-hepatic complications will not only aid in the development of new pharmacological therapies for the liver disease itself but will also contribute to a reduction in the global burden of these highly prevalent non-communicable diseases, which, as we now understand, share same grounds with NAFLD.

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