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Review Article

Categorization and complication of non-alcoholic fatty liver disease

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ABSTRACT

Non-alcoholic fatty liver disease is the most prevalent liver disease with a global prevalence of 25%. The frequency of non-alcoholic fatty liver disease and the percentage of people with severe liver disease are expected to rise given the ongoing obesity pandemic, the rise in diabetes, and other factors. This will have a significant effect on health care expenditure and the need for liver transplantation, for which non-alcoholic steatohepatitis is already on track to overtake alcoholic steatohepatitis as the most prevalent reason. Non-alcoholic fatty liver disease is characterized by the triglyceride accumulation in the cytoplasm of hepatocytes. Patients with non-alcoholic fatty liver disease who have advanced fibrosis and non-alcoholic steatohepatitis are at much higher risk of negative outcomes, such as overall mortality and liver-specific morbidity and death. It is a multisystemic clinical illness entity that manifests extrahepatic conditions like polycystic ovarian syndrome, type 2 diabetes, chronic renal disease, hypothyroidism, and psoriasis. In fact, cardiovascular disease, cancer, and liver-related problems are the three leading causes of death in non-alcoholic fatty liver disease patients, in that order. Non-alcoholic fatty liver disease is further divided into two subtypes hepatic steatosis and non-alcoholic steatohepatitis ranging from milder to more aggressive form of the disease.

Keywords: Non-alcoholic, Fatty, Liver, Steatohepatitis

INTRODUCTION

Worldwide changes in diet and way of life have resulted in a substantial rising rate of obesity and metabolic disease syndrome, which has considerably increased the prevalence of non-alcoholic fatty liver disease (NAFLD). This condition's presence is indicated by hepatic steatosis in people with only one prior, no or less alcohol consumption.[1] NAFLD is a primary cause of cirrhosis and hepatocellular cancer (HCC) with a global prevalence of 25%. NAFLD involves a spectrum of conditions ranging from hepatic steatosis to non-alcoholic steatohepatitis (NASH), which is characterized by necroinflammation and a faster rate of fibrosis advancement than non-alcoholic fatty liver. Type 2 diabetes raises the risk of cirrhosis and its associated complications, and NAFLD has a

bidirectional relationship with facets of the metabolic syndrome.[2]

NAFLD is characterized by the triglyceride accumulation in the cytoplasm of hepatocytes. NAFLD is expected to surpass hepatitis C and alcoholism as the most common reason for orthotropic liver transplantation within the next 10 to 20 years, as per several gastroenterologists and hepatologists. NAFLD is rapidly becoming one of the most important health problems of present time as it is a considerate comorbidity of metabolic syndrome. NAFLD is closely associated with insulin resistance and is regarded as the hepatic manifestation of the metabolic syndrome. Almost 20–30% of NAFLD patients with simple steatosis are predicted to develop NASH in the future. It is predicted that 7% to 25% of those with NASH will develop cirrhosis.[3]

The majority of cases of NAFLD are incidentally diagnosed in the primary care or hospital settings based on elevated liver enzyme values or hepatic steatosis on imaging. The mortality rate associated to the liver is higher in people with NASH.[4] There are two main categories of NAFLD. The current opinion is that insulin resistance is the main pathophysiological mechanism for the first form of NAFLD, which has a restricted association with metabolic syndrome. The second form of NAFLD has a connection to viral diseases that might cause liver steatosis to develop. This condition may be brought on by infections like hepatitis C and HIV, but it may also be caused by medications including total parenteral nutrition, glucocorticoids, tamoxifen, tetracyclines, amiodarone, methotrexate, valproic acid, vinyl chloride, specific toxins, or inherited or acquired metabolic disorders.[5]

HCC, end-stage liver disease, and liver-related mortality are all more common in NAFLD patients. Although extrahepatic cancers and cardiovascular disease are the two leading causes of death in NAFLD patients, liver-related mortality is only the third. Chronic renal disease, extrahepatic cancers including colorectal cancer, psychiatric issues, gastroesophageal reflux disease (GERD), obstructive sleep apnea syndrome, periodontitis, hypothyroidism, growth hormone insufficiency, and polycystic ovarian syndrome are also extrahepatic complications of NAFLD.[6] The purpose of this research is to review the available information about categorization and complication of NAFLD.

METHODOLOGY

This study is based on a comprehensive literature search conducted on 09 December 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about categorization and complication of NAFLD. There were no restrictions on date, language, participant age, or type of publication.

DISCUSSION

The most widespread liver disease in the world today is NAFLD. It is a primary contributor to cirrhosis and HCC and covers a wide range of disorders. In the absence of other causes of fatty liver, it is identified by the presence of steatosis in 5% or more of hepatocytes. The primary recognized risk factor for NAFLD is the metabolic syndrome.[7] The epidemics of obesity and type 2 diabetes mellitus, whose prevalence is not anticipated to decline in the ensuing decades, have an impact on the burden of NAFLD. As a result, the burden of NAFLD-related liver complications and the requirement for life-saving liver transplantation are also anticipated to rise in the near future.[8]

Categories of NAFLD

NAFLD is primarily categorized into two categories, hepatic steatosis and NASH. The accumulation of fat in hepatocytes results in hepatic steatosis through a variety of ways. One process is related to an increase in the availability of free fatty acids to liver cells, either as a result of an increase in dietary fat intake or an increase in adipose tissue lipolysis. Increased de novo hepatic lipogenesis, decreased free fatty acid oxidation, and decreased very low-density lipoprotein secretion are all caused by this increased infusion of lipid particles into the liver cells, and they all contribute to the build-up of fat in the liver.[9,10] NASH is the most frequent cause of liver disease, and its incidence is rising quickly. It is a multi-system disease that also affects the kidneys, heart, and blood vessels, and it is closely related to metabolic syndrome components. NASH develops when the liver is overburdened by a persistent energy surplus. Lipotoxicity, cell death, inflammation, and fibrosis are caused by this energy oversupply. Targeting the underlying causes of excess energy consumption and obesity or using particular anti-inflammatory and antifibrotic medicines are the two major ways to treat NASH.[11]

COMPLICATIONS

Hepatic

Fibrosis

Hepatic stellate cells become myofibroblasts as a result of the chronic liver inflammation characterized as NASH. The extracellular matrix that is produced by these cells causes liver fibrosis. Fibrogenesis is a typical wound healing process that maintains tissue integrity but persistent fibrosis that worsens over time can have a pathogenic nature. This procedure is protracted and frequently asymptomatic. Thus, patients frequently have end-stage liver disease when they first come, such as liver

cirrhosis, decompensated liver disease, or even HCC. Fibrosis has also been established as the most important predictor of outcome in people with NAFLD. Only a small percentage of patients with liver fibrosis are now classified as at risk and subsequently referred for therapy. This is due to the fact that liver biopsy is still the gold standard for the precise identification of liver fibrosis, in addition to the fact that the illness is typically asymptomatic.[12]

Fibrosis has drawn considerable interest in the NASH community as multiple studies have identified it as the primary cause of mortality in NASH.[13] Similarly, results of a meta-analysis showed that in individuals with NAFLD, both with and without adjusting for confounding factors, as well as in patients with reported NASH, fibrosis that has been confirmed by biopsy is linked to an increased risk of mortality and liver-related morbidity. The unadjusted risk increased with increasing stage of fibrosis compared to no fibrosis mortality from all causes; deaths from liver diseases, liver transplants, and other liver-related conditions.[14]

Likewise, results of a prospective study showed that stages of fibrosis F0 to F2 had an all-cause mortality rate of 0.32 per 100 person-years, F3 to F4 had an all-cause mortality rate of 0.89 per 100 person-years, and F5 had an all-cause mortality rate of 1.76 per 100 person-years. With fibrosis stage F0 to F2 versus F3 versus F4, the incidence of liver-related complications per 100 person-years rose. These complications included variceal bleeding, ascites, encephalopathy, and HCC. Stages F3 and F4 of fibrosis were linked to higher mortality and liver-related complication rates.[15]

HCC and cirrhosis

Cirrhosis is a prevalent disease that is a complication of various diseases, including obesity and NAFLD. After a protracted period of inflammation, the healthy liver parenchyma is replaced with fibrotic tissue and regenerating nodules, which causes portal hypertension resulting in hospitalization, a decline in quality of life, and a high fatality rate.[16] As the process of fibrosis progresses on, stellate cells and inflammatory pathways are activated, causing hepatic fibrosis and, in some people, cirrhosis. Additionally, some of NASH individuals may be predisposed to HCC by cirrhosis. While HCC in NAFLD typically develops in individuals with underlying cirrhosis, certain NAFLD or NASH patients may also develop HCC without cirrhosis. Although the precise pathophysiology of HCC in NAFLD has not been fully characterized, both diabetes and obesity appear to be important risk factors. People with HCC caused by NAFLD have a shorter survival time after diagnosis, which may be because NAFLD-related HCC is often detected at a later stage than other liver diseases such viral hepatitis. Additionally, it appears that NAFLD-related HCC develops as a sizable solitary mass that is only marginally to poorly differentiable, making these patients unsuitable candidates for curative resection or liver transplantation.[17]

Extrahepatic complications

Cardiovascular disease

Significant evidence shows that people with NAFLD are significantly more likely to develop hypertension, coronary heart disease, cardiomyopathy, and cardiac arrhythmias, all of which increase cardiovascular morbidity and death. The progression of NAFLD from simple steatosis to fibrosis and end stage liver disease does not occur in the great majority of people due to its varied natural history. However, those with severe fibrosis and/or NASH as well as those with concurrent type 2 diabetes are more at risk for cardiovascular disease.[18] Greater liver disease severity has been linked to a higher risk of both fatal and non-fatal cardiovascular events. NAFLD has been linked to the emergence of several cardiovascular manifestations, including left ventricular dysfunction, atherosclerosis, abnormalities of the cardiac conduction system, and ischemic stroke, according to several epidemiological and clinical studies, indicating that its involvement may not depend on the presence of conventional cardiovascular risk factors.[19]

Chronic kidney disease (CKD)

CKD and NAFLD may be related, and this have recently gained significant scientific study. The presence and severity of NAFLD, which is defined as a decreased estimated glomerular filtration rate and/or proteinuria, are significantly linked to CKD, according to growing clinical evidence, and NAFLD also predicts the onset and progression of CKD independently of traditional cardiorenal risk factors. Additionally, according to experimental data, NAFLD itself may exacerbate both systemic and hepatic insulin resistance, lead to atherogenic dyslipidemia, and release a number of proinflammatory, procoagulant, prooxidant, and profibrogenic mediators that are crucial to the onset and development of CKD. These results have a clinical relevance that individuals with NAFLD may benefit from more rigorous monitoring or early treatment measures to lower their chance of developing CKD.[20]

GERD

Patients with GERD have a roughly two-fold higher chance of developing NAFLD than people without GERD. The apparent correlation may not be causal, but rather the outcome of underlying risk factors that are present in both cases. The main characteristic of metabolic syndrome is central obesity, which is related to both GERD and NAFLD. Visceral fat is a well-known contributor of insulin resistance, which is the main pathogen responsible for NAFLD. It has been proven that the development of GERD and esophageal regurgitation are both caused by increased abdominal pressure caused by the build-up of visceral fat. Additionally, human visceral adipose tissue is known to produce a number of proinflammatory cytokines, and an increase in these cytokines is linked to a decrease

in esophageal sphincter tone, which may raise the risk of GERD. The esophagus muscle layer suffers from increased oxidative stress brought on by inflammation. Another aspect of the metabolic syndrome is hypertriglyceridemia, which is frequent in NAFLD patients. It's interesting to note that studies have suggested that triglycerides may influence the tone of the lower esophageal sphincter and may perhaps be the common cause of both GERD and NAFLD. Additionally, a malfunction of the autonomic nerve system may relate NAFLD to GERD. Studies have shown that autonomic disturbances were more common in NAFLD patients.[21]

Cancer

Malignancy is one of the top two causes of death in NAFLD, far outpacing liver-related mortality, which affects approximately 1% to 2% of patients, according to large population studies. Among the extrahepatic cancers, patients with NAFLD have an over 2-fold higher incidence of stomach, pancreatic, and colon cancers, with a tendency for younger age at diagnosis in the latter two.[22] An extensive portion of evidence demonstrates that individuals with metabolic syndrome have a higher overall risk of cancer, particularly in the gastrointestinal tract. NAFLD is typically regarded as the hepatic manifestation of metabolic syndrome. In this situation, NAFLD may either actively mediate some pathogenic mechanism, as in the case of liver cancer, or share common risk factors, such as obesity and type 2 diabetes. Colorectal cancer has been consistently linked to NAFLD. Although the processes behind the connection between NAFLD and the risk of neoplasms are not fully understood, they most likely result from the mutual influence of NAFLD and metabolic syndrome. The relationship between NAFLD and colorectal cancer has been most thoroughly researched in the literature. Nearly all of the investigations revealed that individuals with NAFLD had a higher prevalence of colorectal lesions than patients without hence, clinicians shall be vigilant for any indications of malignancy among NAFLD patients.[23] The rising prevalence of NAFLD critically demands for further research to focus on development of effective therapeutic and preventive strategies to curb the burden of disease timely.

CONCLUSION

NAFLD is a global epidemic that is on the rise associated with significant morbidity and mortality. Effective management strategies are therefore necessary for the optimal outcomes of patients, also development of preventive measures can be beneficial in addition to counselling population to adapt healthy lifestyles including moderate physical activity to prevent obesity, NAFLD and its associated complications.

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