Nonalcoholic Fatty Liver Disease (NAFLD)

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ABSTRACT
Background: Nonalcoholic fatty liver disease is the most frequent cause of liver disease across the world. Its pathophysiology is considered multifaceted and is controlled by numerous mechanisms comprising environmental, metabolic, genetic, and gut microbial factors. Diagnosis of nonalcoholic fatty liver disease poses a challenge owing to its subtle and non-specific presentation.
Methodology: we conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE from January 1987 to March 2017. The following search terms were used: fatty liver disease, nonalcoholic liver disease, chronic liver disease, diagnosis and management of liver pathology
Aim of the work: In this study we aimed to understand about the pathophysiology, diagnosis, management and prognosis of nonalcoholic fatty liver disease.
Conclusion: More studies must be done to formulate a more definite and reliable diagnostic method. General practitioners and specialists must be informed of the possible manifestation sings to keep higher degree of suspicion. Once NAFLD is established, frequent follow-up and proper management can reduce complications and improve prognosis**.**
Keywords: nonalcoholic fatty liver disease, chronic liver disease, liver disease in adults

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most frequent cause of liver disease globally with ranging from 25% to 45%, increasing in association with obesity and diabetes. Most recent estimates suggest that 68% of adults in US are overweight or obese; from the expected prevalence of 75 to 100 million individuals in the United States are likely to have NAFLD [1]. NAFLD was first described in 1980 and is classified into categories based on histology: (1) nonalcoholic fatty liver, which comprises patients with isolated hepatic steatosis and patients with steatosis along with mild and nonspecific inflammation, and (2) nonalcoholic steatohepatitis, which varies from the former by the further presence of features of hepatocellular injury which could occur with or without fibrosis. Nonalcoholic steatohepatitis is defined as the progressive subtype of NAFLD; nevertheless, data suggested that hepatic steatosis with inflammation has a distinct and more progressive natural history than hepatic steatosis [2].

METHODOLOGY

• Data Sources and search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed and EMBASE from January 1987 to March 2017. The following search terms were used: fatty liver disease, nonalcoholic liver disease, chronic liver disease, diagnosis and management of liver pathology

• Data extraction

Two reviewers have independently reviewed the studies, abstracted data and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.
The study was done after approval of ethical board of King Abdulaziz University.

PATHOPHYSIOLOGY

Nonalcoholic steatohepatitis is a multifaceted disease that is controlled by numerous mechanisms comprising environmental, metabolic, genetic, and gut microbial factors. Even though the presence of steatosis is necessary for nonalcoholic steatohepatitis, the specific mechanisms that cause one patient to grow nonalcoholic steatohepatitis and others to have isolated steatosis only are not well defined [2].

Presently, the development of NASH is believed to be through a two-step process. The first step includes buildup of fat in liver cells, which is typically associated with insulin resistance, fatty acid metabolism dysregulation that leads to steatosis and central obesity with triglyceride buildup inside the liver. The second step causes hepatocyte inflammation and necrosis, which causes cirrhosis and fibrosis in patients with NAFLD. Visceral adipose tissue produces numerous signals that alter lipid and glucose metabolism, which causes hepatic fat accumulation, and makes a proinflammatory milieu that triggers cellular injury in the liver as well as other tissues. The failure to quell injurious processes, for example oxidative stress, dysregulation of unfolded protein response causes endoplasmic reticulum stress, apoptosis, and lipotoxicity contribute to liver damage, progressive fibrosis eventually leading to cirrhosis, and the progression to hepatocellular cancer in some patients [3].

Risk Factors include [4]:
- Obesity (central)
- Dyslipidemia
- Hypertension
- Metabolic syndrome
- Type 2 diabetes

DIAGNOSIS

Nonalcoholic fatty liver disease is the most widespread form of liver disease in the United States and is the most frequent cause of elevated liver chemistry test results. The majority of patients remain asymptomatic or can have nonspecific symptoms such for example fatigue, but some report pain in the right upper quadrant of abdomen. Consequently, the diagnosis of NAFLD is habitually made incidentally on imaging while testing for an unrelated condition. There are no distinctive physical examination findings, but central obesity and hepatomegaly are usually seen. Acanthosis nigricans associates with insulin resistance, which is more pronounced with progressive disease, and the occurrence of a dorsocervical hump has been related to the presence of nonalcoholic steatohepatitis precisely [5].

Once cirrhosis develops, different findings including palmar erythema, spider angiomata, gynecomastia, or prominent upper abdominal veins may be seen. In patients with decompensated cirrhosis, these manifestation become more pronounced and further features may be noticed, for example ascites, icterus, nail changes also known as Terry or Lindsay nails, splenomegaly, and asterixis.

Less awareness of risk for progression, along with the lack of a reliable diagnostic and screening test, tells why the development of progressive nonalcoholic steatohepatitis goes unobserved until cirrhosis occurs. Until such tests are available, general health practitioners and specialists, who see a patient population with a high prevalence of nonalcoholic steatohepatitis such as endocrinologists and cardiologists, must to be aware of risk factors for disease progression in order to do early intervention [6]. Between patients with NAFLD, those experiencing nonalcoholic steatohepatitis are more likely to develop cirrhosis compared to those with only hepatic steatosis. The occurrence of features of the metabolic syndrome which is central obesity, hypertension, insulin resistance, high hypertriglyceridemia, and low amount of high-density lipoprotein cholesterol is related to higher risk of nonalcoholic steatohepatitis. Studies showed that 66% of patients older than 50 years with obesity or diabetes had nonalcoholic steatohepatitis with advanced fibrosis. Even though metabolic risk factors are related to more advanced disease, progression speed differs considerably even among patients with nonalcoholic steatohepatitis, with some undergoing minimal progression over ten years, while others progressing to advanced fibrosis or cirrhosis in less than 5 years [7].

Liver biopsy

Liver biopsy is invasive, has a possibility of severe complications, and is imperfect by sampling error. Despite these risky outcomes, liver biopsy is the best method for staging and diagnosing nonalcoholic steatohepatitis. The finding of nonalcoholic steatohepatitis on a patient's first liver biopsy is the chief interpreter for the development and progression of liver fibrosis. In sequence, progression of liver fibrosis is the key determining factor of adverse liver–related outcomes. Consequently, diagnosing nonalcoholic steatohepatitis and cirrhosis have significant prognostic and management suggestions [8].

Diagnosing nonalcoholic steatohepatitis is required prior to starting treatment. Regardless of the presence of aminotransferase elevation, any individual with suspected steatosis and metabolic syndrome, or those with metabolic risk factors, chiefly diabetes, has a great risk for nonalcoholic steatohepatitis and advanced fibrosis which must be considered for biopsy [8].
Furthermore, patients with insistent elevation for over six months in levels of ALT and AST must undergo

liver biopsy for additional evaluation; chiefly patients in whom associated disease (such as autoimmune hemochromatosis) cannot otherwise be omitted. There is no regularly accepted threshold to describe the level of persistent elevation in liver enzyme levels to prompt a biopsy; nevertheless, 1.5 times the upper limit of normal is considered. Noninvasive prediction scores can likewise be used to select patients with a greater probability of nonalcoholic steatohepatitis and advanced fibrosis. Conversely, any evidence indicating progressive liver disease on laboratory testing (such as ratio of AST to ALT >1, hyperbilirubinemia, thrombocytopenia, coagulopathy) or physical examination indication of advanced liver disease must suggest a liver biopsy in order to exclude cirrhosis [9].

If noninvasive imaging, for example transient elastography or MRE is indecisive, then biopsy must be tracked to establish the grade of fibrosis or to conclude the potential benefit of treatment or suitability for a clinical trial. If there is clear indication of cirrhosis by imaging and on physical examination, biopsy is not required. If cirrhosis is existent, laboratory tests evaluating for liver failure would be obtained (e.g., the international normalized ratio and bilirubin level), the patient must be evaluated for signs of hepatic decompensation (which includes ascites, hepatic encephalopathy, and variceal bleeding), and the patient must be screened for hepatocellular cancer as well as esophageal varices [10].

Hepatic steatosis

The diagnosis and grading of hepatic fat content can be useful in that it can calculate future progression to diabetes and other cardiovascular risk factors. Ultrasound is an economical diagnostic tool that has a high sensitivity of 93% if steatosis is greater than 33%; nevertheless, sensitivity is poor for steatosis less than 30%. Newer ultrasound methods that can more precisely quantify fat may be able to overcome this drawback. An important caution with ultrasound is that distinguishing features of hepatic steatosis, like increased brightness and vascular blurring, can also be detected in the setting of fibrosis and thus could symbolize fibrosis and even early cirrhosis along with steatosis [11].

The controlled attenuation parameter is good new techniques that may be capable to quantify steatosis at lesser degrees; nonetheless, this technique needs further validation. Computed tomography does not considerably improve sensitivity if steatosis is slight and carries the shortcomings of amplified cost and exposure to radiation. Magnetic resonance imaging, as well as magnetic resonance spectroscopy, is able to notice the presence of hepatic fat more than 5.56% (which is the defining threshold) with a precision that is nearly 100%. Both are costly and magnetic resonance spectroscopy has inadequate availability (mostly in academic medical centers) [12].

Predictive assays that use easily available parameters, for example those used to calculate the fatty liver index (which include body mass index, level of triglycerides, waist circumference, and amount of γ-glutamyltransferase), could be used. Due to inconstant performance across ethnic groups, a US fatty liver index was established using data from the National Health and Nutrition Examination Survey and performance features were compared with ultrasound-detected hepatic steatosis findings. Performance characteristics were the least promising for non-Hispanic blacks. Generally, to rule in fatty liver, a cutoff of 30 or higher had a sensitivity of 62%, a specificity of 88%, and a negative likelihood ratio of 0.43, and a positive likelihood ratio of 5.2. To eliminate hepatic steatosis, a cutoff of less than 10 had a sensitivity of 86%, a specificity of 48%, a negative likelihood ratio of 0.28, and a positive likelihood ratio of 1.7 [13].

Nonalcoholic steatohepatitis

Current techniques can sufficiently measure hepatic steatosis; nevertheless, it is more clinically applicable and challenging to recognize patients with nonalcoholic steatohepatitis. The main drawback of imaging studies remains in their incapability to discriminate nonalcoholic steatohepatitis from isolated hepatic steatosis. Developing MRI techniques may make this likely in the future. Nonalcoholic steatohepatitis rests largely underdiagnosed due in part to an over-reliance on raised levels of ALT and aspartate aminotransferase (AST). Even though high levels of ALT and AST have adequate specificity in the appropriate clinical setting, their sensitivity makes them defective to categorize those with nonalcoholic steatohepatitis. In patients with the metabolic syndrome, those who have ultrasound results of hepatic steatosis (regardless of elevated levels of ALT and AST) are at risk for nonalcoholic steatohepatitis [14].

Several separate and combinations of clinical and laboratory considerations have been studied in an effort to noninvasively diagnose nonalcoholic steatohepatitis. Nonetheless, the available data are basically restricted to pilot analyses in heterogeneous

groups of patients. Of the clinical and laboratory factors, the best studied is cytokeratin 18, which is a breakdown metabolic product resulting from caspase 3–mediated apoptosis of hepatocytes. Grouping of cytokeratin 18 with other markers may additionally improve its performance characteristics; though, reported developments in diagnosis are modest and need to be authenticated in outside cohorts [15].

The most reliable biomarkers are limited to the clinical research setting and are short of sufficient accuracy to substitute or considerably limit liver biopsy to diagnose nonalcoholic steatohepatitis. New biomarkers would be required to (1) be evaluated in different populations, (2) be beneficial for longitudinal evaluation, and (3) accurately quantify response to therapy. Because current biomarkers have imperfect utility, liver biopsy remains the most trustworthy method to diagnose patients with nonalcoholic steatohepatitis [16].

MANAGEMENT
Lifestyle Intervention

Diet and exercise are the backbone treatment for the majority of patients with NAFLD. Weight loss is beneficial and the degree of liver histological improvement is directly relational to the amount of weight lost. In a study of a dietary intervention in patients with biopsy-confirmed nonalcoholic steatohepatitis, a decrease of 10% of body weight was connected to histological benefit. Resolution of NAFLD (as measured by magnetic resonance spectroscopy) was witnessed in 64% of the intervention group compared with only 20% of the control group without weight loss. In another study, lifestyle intervention was linked to histological benefit in patients with NAFLD, the mainstream of whom had nonalcoholic steatohepatitis in the beginning [6].

Even though the ideal diet for patients with NAFLD has up till now to be determined, data propose that dietary composition is essential. A Mediterranean diet is associated with decreased liver fat and improved insulin sensitivity without any change in weight loss [11].

Exercise betters cardiovascular health and decreases peripheral adipose distribution, and hepatic insulin resistance regardless of weight loss. It is not known convincingly if exercise exerts autonomous benefits on NAFLD. Limited data propose that aerobic exercise outcomes in greater reduction in hepatic fat than weight training does and some data recommend that this effect of aerobic exercise on

hepatic and visceral fat may be irrespective of weight loss. The duration and intensity of exercise required to improve NAFLD are also not well defined [17].

Bariatric surgery would be considered for those who are unable to lose weight. Several retrospective studies and one large prospective study with a 5-year follow-up period demonstrated that bariatric surgery could improve or even reverse NAFLD, nonalcoholic steatohepatitis, as well as fibrosis [18].

Vitamin E

Vitamin E, a low-cost potent antioxidant, has been examined as a management agent for NAFLD in many adult and pediatric studies, with fluctuating results. In all trials, vitamin E was well tolerated, and most studies displayed modest improvements in ultrasonographic appearance of the liver, serum aminotransferase levels and histologic results [19].

Lipid-lowering agents

Few small trials evaluated the usefulness of lipid-lowering and cytoprotective medications for NAFLD treatment, with unpredictable results. In one controlled trial, gemfibrozil enhanced liver chemistry in 74% of NAFLD patients in the treatment group, compared with 30% of control subjects with no obtainable histologic data. Thus, in general, lipid-lowering agents are not used for NASH management [20].

Insulin sensitizers

The connotation between hyperinsulinemic insulin resistance and NAFLD offers a logical target for treatment. Two classes of drugs have been presented to correct insulin resistance, which are biguanides (such as metformin) and thiazolidinediones. Metformin, a biguanide that reduces hyperinsulinemia and recovers hepatic insulin sensitivity, decreases hepatomegaly and hepatic steatosis in mice, but results in human studies have been less inspiring, as in human studies, even though ALT was improved and liver size was reduced, metformin was not constantly found to improve liver histology [21].

Ursodeoxycholate

Ursodeoxycholate (UDCA) is a hydrophilic bile acid that is linked with hepatoprotective properties. In one study, UDCA demonstrated improvement in liver enzymes and a reduction in hepatic steatosis. The long-standing benefits of UDCA and the optimum dose of UDCA remain yet to be discovered [19].

Taurine

Taurine is supposed to function as a lipotropic factor and to increase the mobilization of hepatic fat. In another single uncontrolled series, 10 children who

managed with taurine supplements orally had radiologic resolution of their fatty liver [22].

Pentoxifylline
Pentoxifylline antagonizes TNF-α and is orally accessible for long-term use. In two pilot studies, ALT improved after a number of months of treatment at a dose of 400 mg three times in a day. Furthermore, although the drug was well tolerated in one study, 9 of 20 subjects in the other study quit because of the side effects, particularly nausea [22].

Betaine
Betaine is a hepatoprotective factor, and liver histology and AST activity were upgraded in ten NAFLD subjects who were given betaine for one year. In a current randomized placebo-control study, 55 NASH patients were treated with betaine (20 g daily). Patients randomized to betaine had a reduction in steatosis grade without a noteworthy change in intragroup or intergroup differences in NAS or fibrosis stage. Furthermore, there was no important change in adiponectin, proinflammatory cytokines, insulin, glucose, or oxidant stress in NASH patients receiving betaine treatment [23].

Losartan
Angiotensin II has been associated to matrix production and hepatic stellate cell activation. In a small pilot study of an angiotensin receptor blocker, losartan, an improvement in ALT was distinguished [22].

Surgical treatment
Bariatric surgery is the principal surgical intervention for NAFLD in patients with a BMI of greater than 40 kg/m^2 or of 35 kg/m^2 with comorbidities. Existing bariatric surgical techniques comprise vertical banded gastroplasty, biliopancreatic diversion with duodenal switch, Roux-en-Y gastric bypass, adjustable gastric banding, and biliopancreatic bypass. Founded on a recent meta-analysis, bariatric surgery is connected to significant histologic enhancements in steatosis, steatohepatitis, and fibrosis, with greater than 50% of patients experiencing complete reversal of their fatty liver disease subsequent to surgery. Even though these results are compelling, these observational studies revealed no relationship between histologic improvement and the extent of weight loss [24].

As with additional causes of cirrhosis, liver transplantation is a practical option for patients with end-stage liver disease because of fatty liver disease. The consequence of liver transplantation in these patients is good, although NAFLD can relapse after liver transplantation [25].

PROGNOSIS
The existence of hepatic fibrosis is the most essential determinant of outcome. Since most patients who progress to advanced stages of fibrosis initially had nonalcoholic steatohepatitis, hepatic morbidity is principally attributable to those with this subtype who have a projected risk of advancement to cirrhosis of approximately 20%. On the other hand, nonalcoholic fatty liver is understood to have a much more benign course with a predictable risk of progression to cirrhosis of less than 4% with the forewarning that a less precise subgroup of patients within the diagnosis of nonalcoholic fatty liver (i.e., those with inflammation who do not meet histological criteria for nonalcoholic steatohepatitis) may be greater than before risk [26].

Clinical risk factors, for example the presence of the metabolic syndrome and its features, along with emerging biomarkers can help select patients for liver biopsy and recognize those at highest possibility of nonalcoholic steatohepatitis and advanced liver disease. Patients with NAFLD overall, and those with nonalcoholic steatohepatitis in specific, are at greater risk of mortality from liver disease (13%), and more normally from cardiovascular disease (25%) and malignancy (28%) [27].

Compared with the common population, patients suffering from NAFLD, particularly nonalcoholic steatohepatitis, have decreased survival that is mainly attributable to cardiovascular disease and malignancy. Cardiovascular-related deaths dominate, accounting for two times as many deaths as those that happen due to liver-related causes. The prognosis of NAFLD is directly reliant on liver histological structures, isolated hepatic steatosis, and nonalcoholic steatohepatitis with or without fibrosis and cirrhosis. The ability to predict the liver-related outcomes becomes more consistent as NAFLD advances to cirrhosis. Once cirrhosis is recognized, several factors, including serum albumin level, and the hepatic venous pressure gradient model for end-stage liver disease score can predict the probability of hepatic decompensation or the development of hepatocellular cancer [28].

Twenty percent of patients with nonalcoholic steatohepatitis will progress to cirrhosis during their lifetime. Decompensated cirrhosis happens in approximately 45% of patients with nonalcoholic steatohepatitis cirrhosis throughout a 10-year period. Even though decompensated cirrhosis can occur in the form of variceal bleeding or hepatic

encephalopathy, the most common appearance is the development of ascites [25].

CONCLUSION

NAFLD is the most common liver disease and is easy to miss due to its late presentation and uncertain diagnostic methods. More studies must be done to formulate a more definite and reliable diagnostic method. General practitioners and specialists must be informed of the possible manifestation sings to keep higher degree of suspicion. Once NAFLD is established, frequent follow-up and proper management can reduce complications and improve prognosis.

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