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NON-ALCOHOLIC FATTY LIVER DISEASE IN DIABETIC AND NON-DIABETIC PATIENTS

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ABSTRACT

It's very uncommon for people with NAFLD and T2DM to have one or the other, and this may have a negative impact on their health. Having NAFLD with T2DM raises the chance of developing diabetic complications (including macro- and micro vascular problems) and of having a more severe NAFLD (including cirrhosis, hepatocellular carcinoma and mortality). Currently, the primary goal of NAFLD treatment is to decrease patient's observable metabolic risk. Glycemic management and weight reduction optimization are critical for slowing disease development. As soon as cirrhosis develops, it's critical to monitor for problems and take steps to prevent further liver damage. NAFLD patients presently have few treatment

choices for changing their condition. While there are published data on the best oral hypoglycaemic medication or injectable treatment for people with diabetes and NAFLD, most of these data come from retrospective series and well-designed randomised double blind placebo controlled trials with gold-standard end goals are few. As a result, it is difficult to make general findings that can be applied to all people with NAFLD and diabetes. Here, we have summarised and analysed the existing evidence in an effort to assist readers become more knowledgeable when it comes to dealing with patients who have NAFLD and T2DM both co-occurring.

Keywords: NAFLD, NASH, Diabetes, Insulin resistance, Diabetes complications

1. INTRODUCTION

NAFLD, or non-alcoholic fatty liver disease, is becoming more common. In many areas of the globe, it has overtaken cirrhosis as the most prevalent form of chronic liver disease. It covers a broad range of conditions, each with their own set of clinical consequences. In the absence of other secondary reasons of hepatic fat accumulation such substantial alcohol use, prolonged use of steatogenic medications, or another known chronic liver disease, NAFLD implies there is evidence of liver steatosis by imaging or histology. In obese individuals, NAFLD affects 40 to 50 percent, and in those with type 2 diabetes, it increases to 70 percent (T2DM). In its basic form, recognised as isolated steatosis or NAFL (non-alcoholic fatty liver), there is triglyceride collection of ≥5% without proofs of hepatocellular injury in the form of hepatocyte ballooning or evidence of fibrosis. NAFL is now linked with a low risk of liver morbidity, despite the fact that its natural history is yet unknown and it may develop to a more serious illness. The liver may be regarded as a "mirror" of metabolic health because of its association with insulin resistance and, specifically, adipose tissue dysfunction, and with an elevated risk of cardiovascular disease in obese people with steatosis (CVD). Steatosis of less than 5% is linked to hepatocyte damage with necrosis ("ballooning") and lobular inflammation, with or without fibrosis, in the more severe type known as non-alcoholic steatohepatitis (NASH) (1).

Steatohepatitis is often a disease that worsens over time in people with type 2 diabetes, especially when fibrosis develops and progresses to cirrhosis. Hepatic fibrosis is graded according to the presence or lack of fibrosis (stage F0), mild fibrosis (stage F1), moderate fibrosis (stage F2, including zone 3 sinusoidal fibrosis and periportal fibrosis), or "advanced" fibrosis (stages 3 or 4) (cirrhosis). NAFLD is linked with a higher long-term mortality rate when it has

fibrosis as its most prominent histological characteristic. As a result of their fibrosis, individuals are more likely to develop hepatocellular carcinoma (HCC) (2). A greater prevalence of HCC has been associated with type 2 diabetes mellitus, which has been shown to accelerate the development of NAFLD into more severe forms. However, unlike the other micro and macro vascular consequences, NAFLD is an under-recognized complication of T2DM in clinical practise (3).

Isolated steatosis and NASH, regardless of any metabolic comorbidities, may raise the risk of CVD and be the most frequent cause of mortality in individuals with NAFLD. Researchers have discovered an association between NAFLD in T2DM and metabolic alterations that raise the risk of atherosclerosis and cardiovascular disease. This knowledge is critical for endocrinologists and primary care doctors (4, 5).

2. EPIDEMIOLOGY

NAFLD affects 24% of the global population, according to current estimates. South America has the greatest incidence (31%), followed by the Middle East (32%), Asia (27%), the United States (24%), and Europe (23 percent). Africa, on the other hand, had the lowest mortality rate (14 percent). From 2005 to 2015, studies show an increase in the frequency of NAFLD and a parallel rise in the incidence of NASH. Metabolic syndrome (MetS) is present in 42% of NAFLD patients, which supports the metabolic basis of the disease (6). There are a number of metabolic diseases that are included in the Metabolic Syndrome (MetS), including abdominal obesity and diabetes mellitus. MetS and metabolic diseases linked to it are very common all over the globe. When compared to the general population, individuals with MetS had a substantially higher frequency of NAFLD (43.2 percent). Another finding showed that individuals with five MetS anomalies were more likely to have advanced hepatic fibrosis than people with mild to moderate steatosis, with a frequency of 30.3%. (7).

Over the course of a four-year cohort trial, individuals were monitored for signs of NAFLD recurrence and found to have greater visceral adipose tissue levels, rather than simply fat under the skin, with an adjusted hazard ratio of 2.23 (95 percent CI 1.28–3.89). Two recent meta-analyses looked at the link between type-2 diabetes (T2D) and non-alcoholic fatty liver disease (NAFLD). There were a total of 35,599 people with T2D who were included in twenty-four studies, and 20,264 of them had been diagnosed with NAFLD. The prevalence of NAFLD in T2D patients was 59.67 percent (95 percent confidence interval 54.31–64.92), and it was even higher in those who were obese (95%

CI 65.51–88.14). (8). In another meta-analysis, obtained combining data from 80 studies (49,419 individuals), a global NAFLD prevalence of 55.5% (95% CI 47.3–63.7) was found among patients with T2D; in Europe, a prevalence of 68% (95% CI 62.1–73.0) was found, followed by West Asia (67.29%; 95% CI 60.39–73.61%), South Asia (57.87%; 95% CI 52.87–62.68%), Latin America (56.83%; 95% CI 34.05–76.98%), East Asia (52.04%; 95% CI 45.37–58.55%), United States (51.77%; 95% CI 31.33–71.64%) and Africa (30.39%; 95% CI 11.64–67.09%) (9).

NAFLD risk is greatly influenced by a combination of metabolic and gender variables. However, most research didn't make a clear distinction between pre- and post-menopausal women, leading to a slew of conflicting conclusions. Recent studies have shown that males are more likely than pre-menopausal women to have advanced fibrosis. Contrary to this, when women after menopause are examined, both sexes show comparable levels of fibrosis severity, indicating that oestrogen may act as a protective factor against severe liver damage. (10). NASH was also shown to be more common in men than in women in a study of obese people around the age of 41. NAFLD is more common in the elderly; in fact, most patients were diagnosed between the ages of 40 and 50. NASH and fibrosis are also more common in those who are older. NAFLD is now the most prevalent cause of liver disease in children, with symptoms ranging from steatosis to NASH and fibrosis as a consequence of the rising obesity incidence (11).

3. NATURAL HISTORY

Only a small percentage of NAFLD patients proceed to cirrhosis or liver-related mortality due to the wide range of disease severity and outcomes. An analysis of paired biopsy studies including 150 NAFL and 261 NASH patients found 33.6% had fibrosis advancement during 2145.5 person-years of follow-up, whereas 43.1% had a stable and 22.3% had better fibrosis stage in a systematic review. In NAFL patients, 39.1% of fibrosis progressed while 8.3% improved; in NASH patients, 34.5% of fibrosis progressed while 26.7% improved (12).

In the progression group, around 20% of the patients showed fast fibrosis progression. There were 12.8% who recovered from NAFL and 41.9% who advanced to steatohepatitis in another paired biopsy research that included 446 patients over an average time span of 4.9 years. About one-fourth of the individuals with steatohepatitis had it cleared up by this time. Thirty-four percent of patients had progressing fibrosis, whereas 33 percent had regressed. Fibrosis regression was linked to lower insulin levels, lower aspartate aminotransferase (AST) baselines,

and changes in alanine aminotrans-ferase (ALT). Fibrosis progression is linked to metabolic syndrome, baseline NAFLD activity score (NAS), a lower decrease in NAS, baseline AST, and changes in AST (13). Patients with NAFLD or NASH were shown to have an annual HCC incidence rate of 0.44 and 5.29 per 1000 person-years, respectively. 2 NAFLD liver-specific mortality had an adjusted hazard ratio of 2.60. It is crucial to know where you are in the fibrosis process (14).

4. PATHOLOGY OF NON-ALCOHOLIC FATTY LIVER DISEASE

Adipose tissue located in the abdomen and other organs of the body functions as an active endocrine organ. Due to obesity's adipose tissue growth and inflammatory response, the normal polypeptides—adipokines—found in this tissue are altered. For the most part, adipokines are bad for the liver because they either promote inflammation or fibrosis, or they stop protecting the liver by inhibiting these processes altogether. Ectopic fat deposition in the liver is a result of and a sign for systemic insulin resistance and the metabolic syndrome's constellation of cardiovascular risk factors. At present, deriving a diagnosis of metabolic syndrome requires the presence of three or more features: aberrant glucose levels (>110mg/dl), hypertension (>130/85 mmHg), dyslipidemia (fasting triglycerides >150mg/dl; HDl 102 cm for men and >88 cm for women) (15).

NAFLD is regarded as the metabolic syndrome's hepatic manifestation. A fatty liver is a better predictor of cardiovascular disease than higher levels of peripheral or visceral fat. NAFLD with metabolic syndrome patients had a greater prevalence of advanced histologic characteristics than NAFLD patients without metabolic syndrome. Patients with advanced NAFLD are at greater risk of dying from liver-related causes. NAFLD individuals with diabetes and/or NASH have a higher risk of liver-related death, while epidemiological research show that patients with steatosis alone are more likely to experience the effects of cardiovascular or non-hepatic cancer associated diseases (16).

Patients with non-cirrhotic NAFLD and cirrhosis have a higher risk of developing hepatocellular carcinoma (HCC), which is linked to metabolic abnormalities and cirrhosis' accelerated cell turnover. The well-documented variations in the incidence of NAFLD and NASH across ethnic groups, as well as the distinct histopathological presentations of NAFLD and NASH in children, are two hotly debated research topics. NAFLD and NASH are more common among Hispanic, Caucasian, and Asian people than among

African-Americans, according to many studies (17).

Indeed, all studies to far have indicated that African Americans had an exceptionally low reported incidence of NAFLD, regardless of how people were gathered and/or NAFLD defined. African Americans may have varying levels of visceral adiposity in relation to their BMI. Hispanic people had a higher frequency of this allele than African Americans, while another allele was associated with African Americans' lower incidence of fatty liver, according to a recent genome-wide association analysis (18).

The measurement of blood ALT levels is a common ‘screening' laboratory test for liver disease, although the definition of what constitutes a 'normal' result varies. 79 percent of patients with liver steatosis in the United States had normal ALT levels, according to an imaging-based study of hepatic steatosis in a multicultural community. The assessment of ALT levels in steatohepatitis patients has been found to be less than optimal for the diagnosis of illness or the identification of advanced disease. There have been many studies that show the whole range of liver damage produced by NAFLD is present in individuals with 'normal' ALT levels, including cirrhosis in 8–12% of adults and normal ALT levels in 40% of adolescents with various degrees of fibrosis, according to the researchers. Hepatic steatosis may be estimated using several imaging methods, particularly when the lipid level reaches 30%. (19).

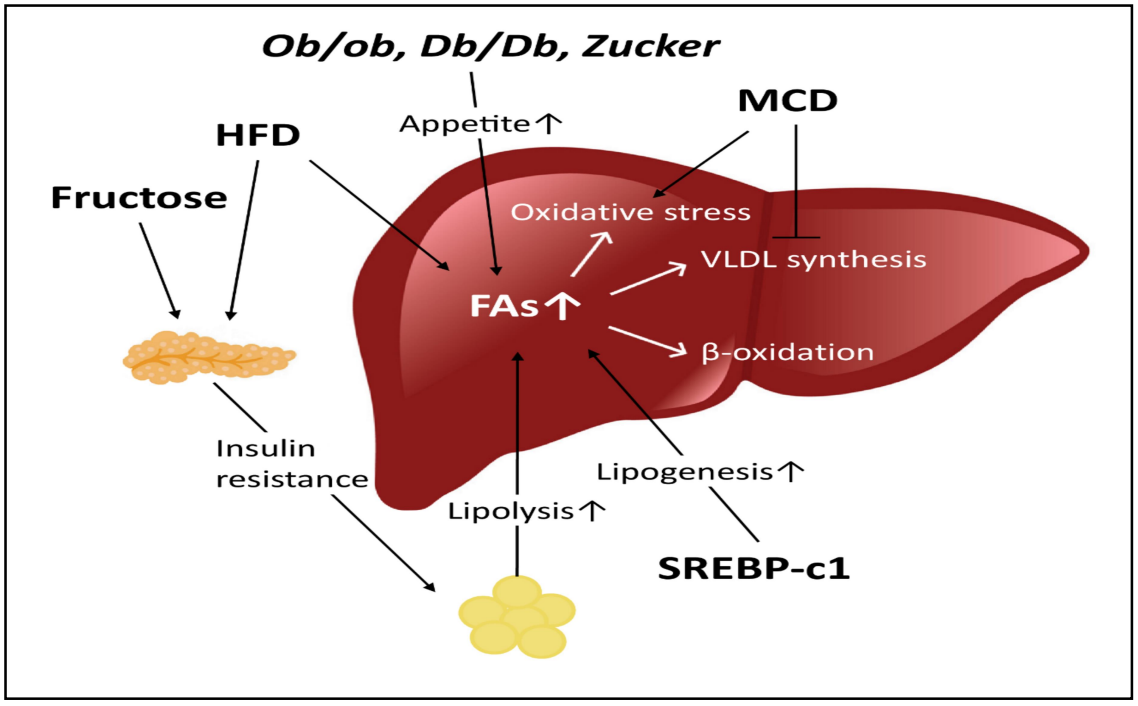

Figure 1: Mechanism of Non-alcoholic fatty liver disease (NAFLD) pathogenesis

5. RISK FACTORS FOR NON-ALCOHOLIC FATTY LIVER DISEAS E IN DIABETIC PATIENT

A. In Diabetic Patient

1. **Metabolic syndrome:**

It is now well accepted that NAFLD is a component of the metabolic syndrome (MS), which has insulin resistance as a core pathogenic feature In spite of having lower BMIs, the research conducted by Petersen *et al*. found that Indians were more likely to develop insulin resistance than other ethnic groups. Between 83 and 98 percent of our patients tested positive for insulin resistance on the insulin tolerance test (ITT) as well as the home obesity and metabolic assessment (HOMA-IR). Researchers think the aetiology of IR is linked to an imbalance between pro-insulin (adiponectin) and anti-insulin (TNF-a) cytokines, especially those produced by adipose tissue (adipokines). TNF-a levels have been shown to be higher in NAFLD, and as NASH progresses, so does the concentration of hepatic TNF-a. To put it another way, Adiponectin increases fat oxidation, reduces hepatic fat production, and suppresses TNF-a, all of which work together to make you more insulin-sensitive. NASH patients have lower levels of adiponectin than those with uncomplicated steatosis, according to research (20).

2. **Obesity**:

A person's weight is a significant risk factor for NAFLD development. According to research, the risk of NAFLD rises in direct proportion to body mass index (BMI). In a large Japanese retrospective research, NAFLD was found in 10.5% of those with a BMI under 23 kg/m2, but only in 8.4% of people with a BMI above 28 kg/m2. NAFLD affects 50–80 percent of the world's obese people. NASH was detected in as much as 80% of severely obese Taiwanese individuals who had laparoscopic bariatric surgery. Only 12–30% of Indian patients were found to be obese in early investigations using international standards for diagnosing overweight and obesity. Most Indian patients with NAFLD were originally believed to be non-obese because of early research, and the term 'lean NAFLD' was coined to describe them. There were 64 overweight and 12 percent of NAFLD patients in a tertiary care centre who met the international criteria for obesity, but the numbers were reversed when we used the Asian-Pacific guidelines, which included more than 100 patients, to find that 20 percent of NAFLD patients were overweight or obese (21).

3. **Physical inactivity**:

Many chronic illnesses, including cardiovascular disease, diabetes, stroke, and many kinds of cancer, may be reduced in incidence and death by engaging in

regular physical exercise. Sedentary activities like watching TV or using a computer account for more than half of the typical person's awake hours. Sedentary behaviour, even when supplemented with physical exercise, has been linked to a host of health problems. An increasing number of epidemiological studies have shown a link between sedentary behaviour and a variety of negative health outcomes including obesity and diabetes. These research also found links between sedentary behaviour and metabolic syndrome, cardiovascular disease, and cancer. Even among individuals who engaged in high levels of moderate to vigorous physical activity, this link was still seen, suggesting that regular involvement in high levels of physical exercise may not completely protect against the hazards associated with extended periods of sedentary behaviour (22).

4. Obstructive sleep apnea

Obstructive sleep apnea (OSA) occurs when the pharynx collapses during sleep, obstructing the airway completely or partially. In recent years, there has been some evidence linking OSA to diabetes, metabolic syndrome, and cardiovascular disease. Obesity increases the risk of obstructive sleep apnea from 4 percent to 35 percent - 45 percent in the general population. There was a significant difference in insulin resistance and steatosis among OSA patients with and without BMI in the Tanné research. Patients with severe OSA were reported to have greater necrosis and fibrosis scores (on liver biopsy), as well as more insulin resistance. A change in gas exchange (repeated hypoxemic and hypercapnic events) known as chronic intermittent hypoxia is thought to be the pathogenic mechanism behind this association. This can lead to an increase in proinflammatory cytokines, endothelial dysfunction, oxidative stress and metabolic dysregulation, all of which can lead to insulin resistance. OSA, it turns out, may be a factor in NAFLD progressing from steatosis to NASH. OSA was also shown to hasten the progression of NAFLD to NASH in animal studies. Research have shown that persistent intermittent hypoxia may cause liver damage, inflammation, and fibrogenesis, with an interesting link found between OSA and NASH in a number of the studies conducted (23).

A. In Non-Diabetic Patient:

1. Age

The prevalence of NAFLD rises with increasing age, despite the fact that age is not a factor in the development of NAFLD. Hepatic steatosis is more common as people become older because of increased insulin resistance and the prevalence of metabolic syndrome. Most Asian and Indian research indicates that NAFLD is more prevalent in the fourth and fifth

decades of life (younger than the Western data). Males have a bimodal age distribution with peaks at 40–49 years, whereas females have a [50 year] bimodal age distribution (24).

2. **Gender**

Most research on NAFLD in the Asia-Pacific area show that males outweigh women, with the exception of a greater incidence of NAFLD in post-menopausal women (when estrogens protective effect against hepatic steatosis diminishes). NAFLD was more common among men of Asian descent than Caucasian descent in a recent multi-ethnic research conducted in the United States. NAFLD is more common in men than in women in Asian nations, with males accounting for 13.3% of cases in China and females accounting for 2.7%, while for males and females in Korea, the figures are 21.6 and 11.2 percent, respectively. In our clinical practise, 70% of NAFLD patients are men, which is comparable to Japanese statistics showing that 61% of NAFLD patients are men. There may be a genetic component to the male predominance in Asian patients with NAFLD, which may be explained by the differences in lifestyles experienced by Asian women in Western versus Eastern settings. However, the recent discovery of Apo C3 polymorphisms in Asian Indian men with NAFLD raises the possibility of a genetic component (25).

3. **Ethnicity and genetics**

Asians, particularly Indians, are more likely than other ethnic groups to develop insulin resistance and NAFLD. The incidence of NAFLD in individuals with newly diagnosed chronic liver disease was examined by Weston *et al*. Of the 742 patients, 333 (or 47.7 %) had NAFLD that was either confirmed or strongly suspected. Whites, Hispanics, Asians, and African Americans made up 59 and 45 % population, whereas 10 and 28 %, 16 and 18 percent, and 9 and 3 % were found in the NAFLD subgroup. A greater percentage of Hispanics than Asians or Whites or African Americans was seen in the NAFLD group. Despite their lower BMI, Asian Indians have the greatest fasting serum insulin and insulin resistance, as assessed by the homeostasis model assessment for insulin resistance (HOMA-IR), compared to other Eastern Asians, Caucasians, Blacks, and Hispanics, according to Petersen *et al*. In contrast to Caucasians, Asian Indians have greater liver triglyceride levels. NAFLD incidence varies greatly across ethnic groups, and this is thought to be due to both lifestyle differences and a high genetic susceptibility. The hemochromatosis (HFE) gene, apolipoprotein C3 (APO C3), melanocortin 4 receptor (MC4R), and patatin-like phospholipase domain-containing protein 3 (PNPLA3) all have

polymorphisms that have been linked to NAFLD.

3.1 HFE gene mutations:

Iron and HFE gene alterations may have a role in the development of NAFLD, although the evidence is mixed. NASH patients of Anglo-Celtic ancestry had more C282Y heterozygosity than controls in an Australian multi-ethnic research, however the higher heterozygosity was not associated with disease severity or fibrosis in those individuals. No HFE gene mutations were identified in patients with NAFLD/NASH in a Japanese research. Serum iron levels were normal in patients with NAFLD, according to our findings (abnormal serum iron, ferritin and transferrin saturation in 3, 7 and 8 percent, respectively, of a total of 60 patients). A total of 67% of our 30 patients exhibited negative iron Perls' staining on liver biopsy, with only 20% having 1 + or 2 + iron staining and 13% having negative iron. Only 4 (13 %) of 30 patients were discovered to be heterozygotes for the H63D gene mutation, and none of the patients possessed the C282Y HFE gene mutation. Patients with NAFLD are more likely to have iron excess and HFE gene alterations, suggesting that these conditions are an ethnic phenomena (26).

3.2 APO C3 polymorphisms:

An APO C3 polymorphism may or may not have a role in NAFLD. This is up for debate. Among healthy, non-obese Asian Indian men, 38 percent developed NAFLD and significant insulin resistance due to the APO C3 polymorphisms (C-482T and T-455C), whereas none of the APO C3 wild-type homozygotes had NAFLD. NAFLD affected 9 out of every 100 non-Asian Indian men and 0 out of every 100 Asian Indian men. Other variables may be to blame for the higher incidence of NAFLD (38 vs. 9 %) in Asian males than in non-Asian males, as shown in the study with variant APO C3 alleles. There is no evidence that APO C3 polymorphisms are linked to NAFLD or IR in other populations, including European Americans, African Americans, and Hispanics. In comparison to other Asian populations, Asian Indians are less likely to be obese, which may allow for a greater phenotypic expression of the APOC3 polymorphism. Larger sample numbers across ethnic groups are required in future research to elucidate the function of APOC3 in NAFLD aetiology (27).

3.3 Melanocortin 4 receptor (MC4R):

Polymorphism of genes genetic variation in the melanocortin 4 receptor (MC4R) gene has been linked to both obesity and metabolic syndrome. Among 2,684 Indian Asians in a UK genome-wide association analysis, researchers found 318,237 SNPs associated with insulin resistance. The waist circumference was 2 cm larger in

homozygotes with the risk allele of rs12970134 near the MC4R gene, and the HOMA-IR was 10% higher than in wild-type individuals. Indian Asians had substantially higher rs12970134 risk allele frequencies than Europeans (36 % vs. 27 %, p = 10-50). (28).

3.4 PNPLA3 polymorphisms:

A G-to-C change that results in the replacement of isoleucine with methionine at codon 148 (I148 M; rs738409) and a G-to-T change that results in the substitution of serine with isoleucine at codon 453 have both been identified as single nucleotide polymorphisms associated with NAFLD (S453I; rs6006460). The I148 M allele is linked to NAFLD in a variety of ethnic groups, regardless of BMI or diabetes status, and a link has also been discovered in Asian nations for countries with Asian populations (29).

4. Central obesity

Insulin resistance and NAFLD are more closely linked to central obesity, which is a measure of visceral adiposity. The odds ratio for developing fatty liver was 1.89 in subjects who were normal weight but centrally obese in a Japanese study compared to controls (normal weight but not centrally obese). The odds ratio increased to 2.57 in obese but not centrally obese individuals and to 5.64 in those who were both overweight and centrally obese. In light of these findings, it's possible that NAFLD may develop in thin, centrally obese individuals, and that risk rises when weight gain and central obesity are combined. Despite having a lower BMI, individuals with NAFLD had greater levels of visceral adipose tissue, according to Indian research. While lean patients had a smaller volume of total and subcutaneous adipose tissue, when adjusted for BMI, their visceral adipose was comparable to that of overweight and obese NAFLD patients, our research revealed. We compared subcutaneous and visceral adipose tissue volumes in lean and overweight/obese patients (30).

5. Diet, smoking and life style

NAFLD has been linked to a high-fat diet as a risk factor for the development of the disease. It has been shown that dietary changes may decrease metabolic syndrome by restricting calorie intake and manipulating dietary macronutrients, such as carbs, fat, or enrichment with monounsaturated fatty acids. Metabolic syndrome and consequent NAFLD are more likely to develop in those who follow a Westernized diet pattern that includes plenty of red meat and refined grains, sweet pastries, and sugar-sweetened drinks. Cigarette smoking was shown to be a risk factor for the development of NAFLD in a retrospective analysis of 2029 individuals. Tobacco smoking increases a person's risk of insulin resistance development. A study

of American teenagers found that both passive and active smoking were significant risk factors for metabolic syndrome (31).

In terms of lifestyle, fitness and sedentary behaviour have been linked to an increased risk of NAFLD and NASH development; the severity of NAFLD also increases with decreased physical activity. Clinical practise recommendations developed by the EASL, EASD, and EASO suggest that a complete NAFLD screening test include an evaluation of physical activity patterns. Diet and exercise are also part of the NAFLD treatment plan to combat obesity and insulin resistance. Studies have examined the impact of a well-balanced diet combined with progressive weight loss on NAFLD biologic markers in a number of different ways. The majority of studies have demonstrated improvements in serum liver enzymes, reduced hepatic fatty infiltration, decreased hepatic inflammation, and lower fibrosis levels with progressive weight loss via diet, with or without exercise (32).

Even with little or no weight reduction, and activity levels that are below those advised for obesity treatment, exercise has a demonstrable benefit on hepatic fatty infiltration. For those with NAFLD who have low cardiorespiratory fitness and cannot handle vigorous, high-intensity aerobic exercise, resistance training improves the condition (as opposed to the therapeutic effects of aerobic exercises such as jogging) (33).

6. DIAGNOSIS

Screening for non-alcoholic fatty liver disease is not recommended in the general population. It usually is considered after an incidental discovery of unexplained elevation of liver enzyme levels or when hepatic steatosis is noted on imaging (e.g., ultrasonography).

A. History and physical examination

Patients with non-alcoholic fatty liver disease are often asymptomatic, but symptoms may include right upper quadrant pain, jaundice, and pruritus. Common causes of liver injury, such as alcohol and drug use, must be excluded. The history should explore diet, physical activity, change in weight (usually an increase, such as 40 lb. [18 kg] over two to three years), and an assessment for associated conditions (e.g., diabetes, hypertension, hyperlipidemia, obesity, sleep apnea). Physicians should assess risk factors for viral hepatitis, including intravenous drug use, blood transfusion, and sexual activities. Risk factors for non-alcoholic steatohepatitis include age older than 45 years, an aspartate transaminase (AST) level greater than the alanine transaminase (ALT) level, diabetes, insulin resistance, low albumin level (less than 3.6 g per dL [36 g per L]), low platelet count

(less than 100 × 103 per μL [100 × 109 per L]), metabolic syndrome, obesity, and portal hypertension on imaging. The patient's family history should be checked for cardiovascular and metabolic disorders, and chronic liver disease. It may be appropriate to evaluate for the presence of hereditary or less common conditions that may initially present with liver test abnormalities. Vital signs should be obtained, including blood pressure, weight, BMI, and waist circumference. Physical examination often is unremarkable, but may include elevated blood pressure, central obesity, and hepatosplenomegaly (34).

B. Laboratory studies

Laboratory studies may be used to examine factors for insulin resistance and metabolic syndrome, to evaluate liver injury, and to exclude other causes of liver disease. No single laboratory test is diagnostic for non-alcoholic fatty liver disease. Liver enzyme levels have low sensitivity and specificity, and do not predict clinical outcomes. Although elevated liver enzyme levels (i.e., AST and ALT levels) occur more commonly in patients with non-alcoholic steatohepatitis compared with hepatic steatosis, not all patients with non-alcoholic steatohepatitis have elevated AST or ALT levels. Tests to exclude viral hepatitis and hemochromatosis should be performed routinely. Additional laboratory evaluation should be considered in patients with chronically elevated liver enzyme levels or in those with a family history of cirrhosis. These tests include measurement of antinuclear antibody, smooth muscle antibody, α1-antitrypsin, ceruloplasmin, and thyroid-stimulating hormone levels (35).

C. Imaging

Imaging tests look for liver and spleen abnormalities, as well as steatosis in the liver. They don't include anything else. However, they are unable to detect fibrosis or inflammation. It is recommended that ultrasound be used as a first imaging tool to evaluate and identify moderate to high levels of fat in the liver. However, despite the fact that ultrasonography is a non-invasive, low cost, and radiation free procedure, there is some variability among and between observers when using it. The physical habitus of a patient may also affect the accuracy and reliability of the test. Ultrasonography may be unreliable if there is hepatic fibrosis because it cannot tell the difference between fibrosis and steatosis. Patients are exposed to ionising radiation during an unenhanced computed tomography scan, which is an excellent technique for evaluating liver anatomy. When it comes to hepatic attenuation, fat content is directly proportional to those changes. The sensitivity and specificity of contrast-enhanced computed tomography

are reduced, and there are also hazards associated with the use of contrast media. Non-alcoholic fatty liver disease may be accurately assessed by magnetic resonance imaging, which is one of the most accurate imaging modalities. Hepatic steatosis may be measured by magnetic resonance imaging, which is non-invasive and does not expose patients to radiation. Despite this, its use is restricted due to the expensive cost and wide range of findings produced by various systems (36).

D. Non-invasive tests for liver fibrosis

Collagen deposits in the liver as a consequence of inflammatory cytokines and liver damage, leading to fibrosis. Patients with non-alcoholic fatty liver disease may avoid liver biopsy if non-invasive diagnostics for fibrosis are available. In order to diagnose advanced fibrosis, doctors may use a commercially available set of serologic markers with a 47% sensitivity and 90% specificity. Non-invasive indicators were shown to be accurate at predicting progressive fibrosis in 285 obese individuals in a validation study. Magnetic resonance elastography and several other grading methods are also used as additional testing (37).

E. Liver Biopsy

Although a liver biopsy may not influence therapy choices, it is still the gold standard for diagnosing and determining steatosis, inflammation, and fibrosis stage. One test differentiates between hepatic steatosis and non-alcoholic steatohepatitis by performing a liver biopsy, although this procedure is controversial in those with non-alcoholic fatty liver disease because of the risks associated with it. Clinical conditions that are out of the ordinary need liver biopsy (e.g., patients with normal BMI or highly elevated liver enzyme levels). More than 5% of hepatocytes have hepatic steatosis, which is described as hepatic intracellular fat. Non-alcoholic steatohepatitis findings include hepatocyte ballooning, Mallory hyaline, and perivenular mixed lymphocytic and neutrophilic inflammatory infiltration. Hepatocyte necrosis, apoptosis, and fibrosis may also be present, and these conditions may be classified according to their severity. Though it comes with certain risks and expenses (such as the potential for mistake in sample), liver biopsy is an option that should only be used when absolutely necessary (38).

7. TREATMENT

Preventing further liver damage and fibrosis is a major aim of treatment. Patients-oriented outcomes have not been addressed in treatment trial evaluations, which have focused on disease-oriented outcomes (e.g., lower liver enzyme levels, less fibrosis) (e.g., reduction in morbidity and mortality). Diabetes, hyperlipidemia, hypertension, and sleep apnea are all examples of comorbid diseases that should

be addressed and managed properly. The use of statins is not prohibited in people with non-alcoholic fatty liver disease, and the risk of hepatotoxicity is not higher in these people than in the general population (39).

A. Exercise and weight loss

Patients with non-alcoholic fatty liver disease who are insulin resistant may benefit from lifestyle changes such as a balanced diet, weight reduction, and regular exercise. Despite the lack of a cure, a low-fat, healthful diet may offer other advantages than weight reduction. Normalization of AST levels may be achieved with a 5- to 10-percent weight reduction. Weight reduction was shown to be safe in individuals with non-alcoholic fatty liver disease and to improve liver histology in a meta-analysis of 49 randomised controlled trials. Physical activity and exercise have been proven to decrease steatosis and improve liver enzyme levels independently of weight reduction, therefore patients should be encouraged to do so. Patients with non-alcoholic fatty liver disease have an elevated risk of cardiovascular disease, therefore engaging in vigorous physical exercise may be more beneficial in improving liver function while waiting to evaluate cardiovascular disease. Orlistat (Xenical) helps with weight reduction in the short term and has been linked to improved AST, ALT, and histology of the liver. A Cochrane review concluded that there was inadequate data to determine if bariatric surgery for non-alcoholic steatohepatitis helps or harms patients (40).

B. Pharmacologic therapy

bile acids (such as ursodeoxycholic acid) were found to have inadequate evidence to support their usage, antioxidant supplements, metformin (Glucophage), or thiazolidinediones in individuals with non-alcoholic fatty liver disease who did not have diabetes. According to another meta-analysis of 49 randomised controlled trials, thiazolidinediones (particularly pioglitazone [Actos]) reduced steatosis and inflammation, but were linked to a weight gain of 4.5 to 11 lbs. and an increase in edoema of 4 to 10 % in patients (66 to 75 percent of patients). Metformin, simvastatin (Zocor), antioxidants, pentoxifylline (Trental), telmisartan (Micardis), and L-carnitine all had findings that were inconsistent and heterogeneous in this meta-analysis. Vitamin E and pioglitazone improved AST and ALT levels in non-alcoholic steatohepatitis patients in a randomised controlled study, however fibrosis did not improve. Fibrates, statins, and omega-3 fatty acids all improve AST levels somewhat, but they don't provide any additional health benefits above diet and exercise alone. Pentoxifylline was shown to lower AST and ALT levels in a

comprehensive analysis of two randomised trials and four prospective cohort studies, however the research did not evaluate changes in patient morbidity or death (41).

C. Lifestyle management

Patients with NAFLD are still managed mostly via dietary and activity changes in their lifestyle. Lifestyle change is beneficial, but it may be tough to adopt, therefore the goal should be to lose weight gradually but consistently over a period of six to twelve months. Individuals are often advised to limit their calorie consumption by 500-1000 kcal/day while also meeting with a dietician on a regular basis. NAFLD has been related to simple carbohydrates in the diet, particularly fructose. Glucose homeostasis and liver free fatty acid metabolism are influenced by carbohydrate intake, thus carbohydrate restriction has been investigated in the past. A number of studies show that a weight loss of 7 to 10 percent is linked to a decrease in inflammation in the presence of NAFLD and is thus established as an objective. While exercise on its own hasn't been shown to be helpful, it may improve biochemical and histological features of NAFLD when combined with dietary modifications like brisk walking for 30 to 45 minutes per day. The results of a 12-week weight loss programme involving dietary restriction and aerobic exercise on 169 obese, middle-aged men show that MVPA (moderate to vigorous physical activity) of at least 250 minutes per week reduces VAT severity, lipid peroxidation, and increases adiponectin levels compared to those who do not exercise (42).

D. Bariatric surgery

Several studies have demonstrated that bariatric surgery, when used to treat obesity, reduces the majority of NAFLD's histological characteristics as well as obesity-related T2DM and IR. However, NAFLD is often taken into consideration while deciding whether or not to do bariatric surgery on an overweight patient. Due to weight reduction after bariatric surgery, insulin sensitivity improves in the liver, muscle, and fat, which leads to better metabolic health. After bariatric surgery, the liver, muscles, and fat become more insulin sensitive. As a result, while bariatric surgery is widely accepted as having the potential to enhance overall metabolic health, it is unknown how this improvement in insulin sensitivity occurs (43).

E. Pharmacological management

Insulin sensitizers: Given the important of IR in the pathogenesis of NAFLD, insulin sensitizers such as metformin and thiazolidinedione (TZDs), have been extensively studied in the treatment of NAFLD.

a. Metformin:As a biguanide insulin sensitizer, metformin is often used to treat

people with type 2 diabetes. It works by activating an enzyme in the body called AMPK. Gluconeogenesis and lipogenesis in the liver are reduced, while FFA beta oxidation is increased as a result. But in NAFLD clinical trials, no consistent effect has been seen in patients with NAFLD, thus its usage is restricted to the treatment of patients with NAFLD and concurrent type 2 diabetes (44).

b. Thiazolidinediones (TZDs):Adipose tissue effects of TZDs on NAFLD are likely to be the primary mechanism of action in the disease. In addition to this, TZDs may increase hepatocyte levels of adiponectin and/or sitrulin, which influences key hepatic metabolic regulators including AMPK, Foxo1 (Forkhead box O1), LKB1 (Liver Kinase B1), NAD (Nicotinamide adenine dinucleotide), NADH (Reduced Nicotinamide adenine dinucleotide), PGC-1 In pre-clinical NAFLD models, several medicinal compounds have been shown to have significant effects, increasing fatty acid oxidation and consequently reducing hepatic fat formation. In spite of this, clinical concerns persist regarding the drugs' impact on sodium excretion in the kidneys and intestinal ion transport, which leads to increased plasma volume/fluid retention and exacerbations of pre-existing heart failure. Adipocyte insulin sensitivity is improved by TZDs, as is hepatic steatosis, and subcutaneous adipose tissue shifts ectopic lipid from the muscle and liver (45).

c. Incretin based therapies:A gut-derived neuroendocrine hormone known as incretin, which stimulates glucose-dependent insulin release, decreases glucagon release, and prolongs stomach emptying, is generated by the digestive tract in response to food intake. This means that they may be legally used to treat type 2 diabetes, where they help to regulate blood sugar levels, enhance insulin sensitivity, and help people lose weight. A DPP-4 enzyme degrades GLP-1 rapidly, so drugs targeting GLP-1 receptors with increased resistance (e.g. Liraglutide, Exenatide) and DPP-4 inhibitors have been developed as treatments (e.g. Sitagliptin, Saxagliptin). GLP-1 has a half-life of about 1-2 minutes due to the enzyme dipeptdyl peptidase-4 (DPP-4) degrading rapidly. These drugs show promise in NAFLD, and NAFLD controlled trials are now being conducted based on promising open-label research (46).

d. Lipid lowering drugs Statins:Fibrates and omega-3 polyunsaturated fatty acids (PUFAs) are used to manage dyslipidaemia, which is commonly found in patients with NAFLD. There are no studies to support direct benefit of those drugs in NAFLD, but they will be important in

reducing the concomitant cardiovascular risk (47).

G. Hypertension

Angiotensin II receptor blockers (AIIRB): AIIRB inhibit the proliferation of stellate cells, reducing inflammation and fibrosis, and although early clinical studies with Losartan and Telmisartan have suggested improvements in transaminases and histology in patients with NASH, larger trials have not yet been performed. (48).

H. Anti-oxidants and cytoprotective therapies

a. Vitamin E:PIVENS and TONIC (Treatment of non-alcoholic fatty liver disease in children) were two recently published major randomised controlled studies that looked at the effects of vitamin E, a fat-soluble vitamin, on adult and paediatric NAFLD populations, respectively. In all studies, therapy with 400 IU/day of vitamin E met the primary end goal; nevertheless, long-term safety at this dosage remains a worry since it has been found to increase overall mortality (49).

b. Betaine:Studies have demonstrated that the natural choline metabolite Betaine raises levels of Sadenosyl methionine and lowers oxidative damage. Betaine did not improve steatosis or other histological results in a randomised controlled study when compared to placebo (50).

c. Ursodeoxycholic acid (UDCA):Cytoprotective and antioxidant capabilities provide UDCA, a hydrophilic bile acid, with a unique chemical structure. Patients with biopsy-proven NASH in the two UDCA RCTs failed to see any change in their histology with UDCA alone (51).

d. Pentoxyphylline:The anti-inflammatory effects of pentoxyphylline, a tumour necrosis factor alpha (TNFα) inhibitor, have been studied in NASH patients with liver disease. NAFLD patients with high levels of aminotransferase activity may benefit from Pentoxyphylline due to its ability to decrease aminotransferase activity and improve histological parameters, but these findings need to be validated in bigger investigations (52).

I. Microbiomes

As a result of their potential impact on intestinal microbiota composition and how it interacts with the immune system and gut epithelium, probiotics have generated considerable attention. Lactic acid bacteria (Clostridium/Bacillus gram-positive bacteria and Actinomycetes gram-positive Bifidobacteria) and spore-forming bacteria are typical components of commercial probiotics... (Clostridium Bacillus gram-positive bacteria). In order to defend themselves against gastric non-immunological barriers like acidity and mucosal barriers such as lactobacillus species that generate lactic acid, many

probiotic bacteria, primarily lactobacillus species, produce lactic acid (53).

J. Liver transplantation

NAFLD-related liver damage is curable only by liver transplantation (LT) in the most advanced stages. Patients with this indication had similar post-transplant outcomes to those with other indications, but this is likely because to the narrowness of the patient pool. Post-transplant NASH recurrence is frequent owing to pre-existing metabolic risk factors and immunosuppression with drugs such corticosteroids, although allograft loss is uncommon as a consequence (54).

8. CONCLUSION

NAFLD is becoming more common among children and adults owing to increased obesity rates, and symptoms may range from simple steatosis to inflammation to fibrosis and cirrhosis. We know that liver steatosis results from interactions between food, environment, and the liver and adipose tissues but we still don't know all about how it happens. Having fibrosis is a bad sign since it increases mortality from cardiovascular, hepatic, and malignancy-related causes. There are currently no approved pharmacological treatments, although many late-phase clinical studies are underway, thus this will certainly change in the near future. Because cardiovascular disease is the leading cause of mortality in NAFLD, addressing both of these aspects at once will be difficult.

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