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Exploring Non-Alcoholic Fatty Liver Disease: From Genetics To Emerging Therapies

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Abstract – Non-Alcoholic Fatty Liver Disease (NAFLD) is characterized by the reversible accumulation of hepatic lipids without significant inflammation. The rising prevalence of NAFLD across all age groups has been strongly associated with lifestyle-related conditions, such as obesity and type 2 diabetes mellitus. A comprehensive understanding of the diverse pathophysiological mechanisms underlying the onset and progression of NAFLD is crucial for developing targeted interventions. These may include pharmacological therapies designed to inhibit pathways driving hepatic dysregulation and steatosis. Recent advancements have also highlighted the growing importance of non-invasive diagnostic tools utilizing simple biomarkers, which offer ease of application and accessibility. Alongside these tools, ongoing research into novel pharmacotherapies, combined with lifestyle modifications such as diet and exercise, as well as surgical interventions, when necessary, holds promise for improving patient outcomes and quality of life. This review summarizes key diagnostic approaches and management strategies for NAFLD, emphasizing their potential in addressing this global health challenge.

Keywords – NAFLD, Diabetes, Obesity, Steatosis, Noninvasive.

INTRODUCTION

The most common liver disease in the world is non-alcoholic fatty liver disease (NAFLD) [1]. According to current consensus, NAFLD is a catch-all term for a number of illnesses where more than 5% of hepatocytes with metabolic risk factors exhibit steatosis [2]. NAFLD encompasses a range of conditions, from non-alcoholic fatty liver (NAFL), a benign condition, to non-alcoholic steatohepatitis (NASH), which is a more severe condition [3].

As the prevalence of obesity and metabolic syndrome increases globally, NAFLD has emerged as a significant public health concern, requiring effective management strategies and novel therapeutic approaches.

METHODS

To conduct a comprehensive review of the literature on non-alcoholic fatty liver disease (NAFLD), a systematic search was performed across several electronic databases, including PubMed, Scopus, and Web of Science. The search strategy incorporated a range of keywords and MeSH terms related to NAFLD, such as "non-alcoholic fatty liver disease," "epidemiology," "risk factors,"

"pathophysiology," "diagnosis," "management," and "outcomes," among others. This approach ensured a thorough identification of relevant studies up to July 2024.

The inclusion criteria for selecting articles encompassed peer-reviewed articles, systematic reviews, meta-analyses, and clinical guidelines that addressed various aspects of NAFLD. These included studies that provided epidemiological data, explored risk factors, detailed pathophysiology, and evaluated diagnostic methods, management strategies, and patient outcomes. Additionally, relevant literature discussing the global burden of NAFLD, including prevalence rates and disparities among different populations, was included. Articles that covered the histopathological spectrum of NAFLD, including conditions such as steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), were also considered. Studies discussing imaging techniques, biomarkers, non-invasive scoring systems, and insights into the molecular mechanisms, genetic predisposition, and environmental factors contributing to NAFLD were included. Furthermore, literature on lifestyle interventions, dietary modifications, pharmacological therapies, and surgical options for managing NAFLD, as well as the association between NAFLD and other metabolic conditions like obesity, type 2 diabetes, and dyslipidemia, were reviewed. All articles had to be relevant to the review's objectives and contribute to a comprehensive understanding of NAFLD.

Conversely, articles were excluded if they were non-peer-reviewed, such as conference abstracts, editorials, or letters. Articles not specifically addressing NAFLD or its related conditions, those with outdated or irrelevant information, and those not published in English or lacking sufficient translation were also excluded. Additionally, studies with significant methodological flaws or biases that could affect the reliability of the results were not considered for inclusion. This rigorous selection process ensured that the final review was based on high-quality, relevant evidence, contributing to a thorough and up-to-date understanding of NAFLD.

DISCUSSION

Genetic contributions to NAFLD

Current genetic studies have highlighted the role of different gene variants in the development of NAFLD, using both single candidate gene approaches and genome-wide association studies (GWAS) [4]. Specifically, the rs738409 C > G mutation in the Patatin-like Phospholipase domain-containing 3 (PNPLA3) genes has been identified as a significant factor influencing the amount of fat in the liver. This mutation is mainly associated with decreased triglyceride hydrolysis and elevated lipogenesis linked to the I148 M allele [5,6]. Furthermore, because the TM6SF2 E167K variant inhibits neutral lipid mobilization for the hepatic assembly and secretion of very low-density lipoprotein (VLDL), it has been linked to the susceptibility to NAFLD [7].

Even Though more loci, including PPP1R3B, GCKR, NCAN, and LYPLAL1, have been linked to NAFLD through GWAS studies, the overall amount of genetic risk explained by these loci is still relatively small [8]. This is probably because common tag SNPs (single nucleotide polymorphism) are so common, and it is difficult to detect rare or low-frequency risk variants. Re-sequencing the coding region of target genes offers a promising method to address these limitations [9]. It allows for the identification of non-genotyped risk alleles and a better understanding of the multigenic architecture of NAFLD, allowing for the assessment of the individual and collective contributions of various variants to the risk of this complex condition [10]. This approach has previously been used with success in a variety of situations involving genotyping subjects with clearly defined phenotypes [9].

Role of cellular senescence in NAFLD

The role of cellular senescence in the onset of NAFLD has attracted a lot of attention in the last ten years. It has been suggested recently that cellular senescence plays a role in the development of NAFLD [11]. The term "cellular senescence" refers to a decrease in the ability of cells to divide and proliferate [12]. Repeated cell division, strong mitogenic signals, telomere shortening, DNA damage, and protein aggregation are examples of factors that induce senescence [13]. Senescent cells proliferate in tissues, as a person ages chronologically [14]. The immune system eliminates senescent cells, has an active metabolism, and is not susceptible to apoptosis. The liver is vulnerable to damage due to its involvement in the metabolism of toxins and its vulnerability to infectious agents. Senescence could serve as a defense mechanism in this situation by limiting damage and encouraging regeneration [15]. Research suggests that in patients with varying stages of NAFLD, cellular senescence, particularly in hepatocytes, may regulate inflammation and fat accumulation [16]. Senescence is considered protective in the context of mutations because it prevents the

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unrestricted proliferation and spread of potentially malignant cells [17]. Furthermore, senescence is a crucial maturation process that guarantees controlled and coordinated growth [18]. Nevertheless, senescence is a highly complex and adaptable phenomenon that can have unfavorable effects depending on the environment [15].

Senescent cells secrete proinflammatory cytokines and proteases; this phenomenon is known as the senescence-associated secretory phenotype (SASP) [19]. A 2008 study demonstrated that SASP matrix metalloproteases prevent fibrosis after hepatic injury. [20]. However the SASP has been linked to impaired normal adipogenesis in individuals with obesity which leads to an inflammatory state with an elevated risk of type 2 diabetes mellitus [21].

In the study evaluating telomere dysfunction among patients with NAFLD and cryptogenic cirrhosis (CC), it was found that patients with NAFLD exhibited shorter telomere length and increased cellular senescence compared to both CC patients and healthy controls. Additionally, telomerase reverse transcriptase (hTERT) mRNA expression was significantly reduced in NAFLD patients, suggesting telomere dysfunction and possibly playing a role in the observed cellular senescence [22]. In another study researchers found a strong correlation between the onset of NAFLD and telomere shortening in a 6-year study involving 70 patients with type 2 diabetes mellitus. Of the patients involved, 21 did not develop NAFLD, whereas 39 did. Initially, there was no notable difference in telomere length between the two groups. However, over the course of the study, telomeres notably shortened in the NAFLD group compared to the non-NAFLD group [23]. These findings suggest that telomere shortening and hence senescence may play a pivotal role in the progression of NAFLD in individuals with type 2 diabetes mellitus.

Mitochondrial Dysfunction in NAFLD

Mitochondrial dysfunction is regarded as one of the hallmarks of NAFLD progression [24]. Mitochondrial homeostasis is imperative for the normal functioning of mitochondria, and it is maintained by mitochondrial biogenesis and mitophagy [25]. As the powerhouse of hepatocytes, mitochondria play a major role in oxidative metabolism and the normal functioning of the liver. Within the mitochondria, glucose undergoes oxidation via the tricarboxylic acid cycle (TCA) and fatty acid undergoes oxidation via beta oxidation. The electron transport chain (ETC) is found in the inner mitochondrial membranes; it utilizes the electrons provided by mitochondrial substrates NADH and FADH2 (produced from the TCA cycle and beta oxidation) to form ATP by oxidative phosphorylation [26]. Reactive oxygen species (ROS) are produced during electron transport in the ETC mainly through complexes I and III, they are managed by antioxidant pathways mediated by enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and reductase [27].

In NAFLD patients, it is seen that there is an elevation of oxidative anabolic pathways in mitochondria. During the initial stage of disease, there is an increase in fatty acid oxidation, oxidative phosphorylation, and a 2 fold increase in the TCA cycle, which leads to a rise in TCA cycle intermediates; hence gluconeogenesis is also elevated [28,29]. It was determined in a study that, compared to the mitochondria of healthy subjects, there were nearly five times more increased mitochondrial respiration in patients with NAFLD [30].

This flexibility of the mitochondria to adapt to a high energy state is subsequently lost as the disease progresses, and as a result there is a decrease in the mitochondrial reactions [31]. Uncoupling between the mitochondrial reactions β-oxidation, citric acid cycle, and oxidative ETC leads to the loss of mitochondrial homeostasis [24]. The fat metabolism becomes dysregulated owing to the reduction in the fatty acid oxidation capacity, which leads to an elevation of free fatty acid levels within the hepatocytes [32]. The increased and continuous presence of FFAs can put the ETC in a state of overdrive, leading to oxidative stress due to the overproduction of ROS [33]. ROS, due to its proinflammatory nature, induces the activation of many factors responsible for inflammation, such as activator protein-1 (AP-1), nuclear factor-κB (NF-κB) , nucleotide-binding oligomerization domain-like receptor family, and pyrin domain-containing 3 (NLRP3), which leads to the production of inflammatory cytokines such as IL-1β, IL-6, and TNF-α [34]. By transmission electron microscopy, several changes in the mitochondria of patients with NAFLD were noted, such as the loss of the inner mitochondrial membrane, cristae, and paracrystalline inclusions, appearance of swollen mitochondria with a loss of mitochondrial granules [35,36]. Alteration mitochondrial mechanisms like mitophagy [37], mitochondrial fission, and fusion were defective in NAFLD causing ultrastructural changes in the mitochondria α was known to be one of the major inflammatory cytokines responsible for such morphological changes in the mitochondria [38,39].

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ROS directly induces DNA damage by shortening telomeres, thus accelerating cellular senescence [40]. Calcium levels within the mitochondria increase as a result of ROS injury, leading to the formation of mitochondrial permeability transition pores in the inner mitochondrial membrane. This alters the mitochondrial equilibrium, causing a collapse of mitochondrial membrane potential and leading to mitochondrial swelling and eventually cell death [41].

Insulin resistance and NAFLD

Insulin resistance and NAFLD shares an interdependent and bidirectional relationship meaning that the presence of one can multiply the risk of developing the other [42]. Individuals with type 2 diabetes mellitus have a much increased risk of developing liver steatosis, leading from steatosis to steatohepatitis, cirrhosis and sometimes eventually to hepatocellular carcinoma [43–45]. The prevalence of NAFLD in people with type 2 diabetes mellitus has been reported to be 55.5% [46]. Based on various observational and clinical studies, it was found that patients with liver steatosis had a 2 fold risk of developing diabetes over a median of 5 years [47,48].

In normal individuals during fasting, white adipose tissue undergoes lipolysis producing fatty acids which become the main source of fuel in the periphery. After a meal, insulin spike leads to inhibition of lipolysis and utilization of consumed glucose as the primary source of energy. In patients with insulin resistance, this physiological response is lost, leading to chronic and excessive lipolysis and hence, an increased level of free fatty acid (FFA) [49]. In NAFLD, FFAs constitute 60% of hepatic triglycerides, while hepatic de novo lipogenesis (DNL) makes up 26% and the rest comes from dietary sources [50]. DNL, which is usually under 5%, is almost 5 times increased during insulin resistance in NAFLD [51]. Increased DNL is mediated by Srebp-1c (sterol regulatory element-binding protein-1c), and increased levels of insulin have been shown to be a potent inducer of Srebp-1c. Therefore, an increase in upregulation of Srebp-1c is seen in hepatic steatosis [52]. This can further activate various genes responsible for the production of enzymes like acetyl-CoA carboxylase, fatty acid synthetase, and stearoyl-CoA desaturase leading to subsequent hepatic lipogenesis [53,54].

An adipokine that has been shown to be linked with NAFLD and insulin resistance is Adiponectin. This hormone is involved in glucose homeostasis and is responsible for enhancing insulin sensitivity by inhibiting gluconeogenesis [55]. Adiponectin plasma levels have been found to be low in patients with obesity, insulin resistance, and NAFLD [56]. Studies indicate that Adiponectin can also decrease the activity of Acetyl-CoA carboxylase and fatty acid synthetase thereby enhancing fatty acid oxidation and decreasing lipogenesis [57,58]. This hormone also has anti-inflammatory characteristics because adiponectin antagonizes TNF-α which is involved in hepatic inflammation [59]. Due to its protective nature, adiponectin could be studied as one of the agents to control liver steatosis and inflammation in future therapeutic research.

NAFLD between sexes

Liver is a sexually dimorphic organ expressing receptors for both androgen and estrogens, which can play a direct or indirect role in either promoting or protecting against NAFLD, in both males and females [60,61]. The prevalence of NAFLD is more common among men (22–42%) than in women (13–24%) [62]. In men, the prevalence was uniform among all age groups whilst in women the prevalence increased with age, especially among postmenopausal women [63]. This was attributed to the decreased levels of circulating estrogen [64].

Both testosterone and estrogen were indicated to have certain effects in the development of NAFLD. Various studies show that in males, the male sex hormone, testosterone helps in preventing liver fat accumulation via reduced lipid production, increased fatty acid oxidation and reducing the oxidative stress, and hence lowering the overall hepatic inflammation [65,66]. While in women, elevated testosterone levels as seen in PCOS, leads to an increased risk of NAFLD [67].

Estrogen levels were seen to be protective against NAFLD among both males and females. To learn the importance of estrogen in NAFLD, various animal studies were conducted using rodents, which revealed that estrogenic effects were mediated through ER-α receptors, and deletion of these receptors in female and male mice lead to an increased presence of fatty liver [68,69]. Hepatic estradiol signaling can reduce insulin resistance and hepatic gluconeogenesis by reducing liver fat accumulation, hepatic lipid transport and de novo hepatic lipogenesis. Complete deletion of ERα leads to a pathway of upregulation of hepatic steatosis genes

and downregulation of hepatic lipid export genes leading to NAFLD [70]. This could explain why estrogen deficiency during menopause is one of the major risk factors for developing NAFLD.

DIAGNOSTIC METHODS

INVASIVE

Biopsy

Liver biopsy is the best method available to determine and confirm liver diseases. Biopsy also plays a vital role in being one of the chief diagnostic tools for the development of new potentially beneficial drugs and also for determining pertinent patients in clinical trials [71]. Due to its unparalleled efficiency in diagnosing liver disease, it is also the standard against which all the other noninvasive tests are compared [72].

Liver biopsy is never considered as a first line diagnostic tool due to its invasive nature, and is only done when there are multiple coexisting liver diseases and etiologies, and diagnosis would be unfeasible without a liver biopsy [73]. Elevated ferritin level and increased iron saturation level in a patient in suspicion of NAFLD is a typical scenario during which liver biopsy can be considered in order to eliminate other etiologies [74]. Liver biopsy can predict the prognosis of the disease, and based on the results obtained, the extent of liver steatosis and inflammation can be effectively analyzed which can explain the severity of the disease. According to a recent study, biopsy was shown to improve prognosis and lower mortality when compared to those who did not undergo the procedure because early diagnosis provided the advantage of earlier treatment strategies to subdue the disease progression and hence ensure patient survival [75]

There are several risks associated with liver biopsy such as intrahepatic hematoma, hemothorax, pneumothorax and septicemia [76–78]. Liver biopsy can increase mortality from 0.009% to 0.14% and because it measures only one per fifty thousandth of liver, there is a definite risk of sampling error [79,80]. But even despite the disadvantages, liver biopsy continues to be the gold standard in diagnosing NAFLD because its advantages outweigh its risks.

NONINVASIVE

Noninvasive severity scoring techniques for NAFLD

Although liver biopsy remains the gold standard in the diagnosis of NAFLD, noninvasive diagnosis of nonalcoholic fatty liver disease (NAFLD) has been steadily gaining popularity, due to its decreased risk and lower margin of sampling error [81]. Here we have reviewed a few of such modalities that has been established.

Serum/blood-based scoring tests

SteatoTest

SteatoTest (ST) developed in 2005, was a scoring system developed for diagnosing hepatic steatosis. It is a noninvasive scoring system that can be used in patients with metabolic risk factors. ST contains 12 parameters: age, serum alanine aminotransferase (ALT), apolipoprotein A-I, α2-macroglobulin, gamma glutamine transaminases, glucose, total bilirubin, haptoglobin, cholesterol, gender and BMI to calculate NAFLD. In a cohort study done with 744 patients, the estimation of liver steatosis done using StetaoTest was found to be accurate using liver biopsy. The scores produced using ST ranged from 0 to 1.00, with the higher score indicating a higher grade of fat accumulation. This test was useful in discriminating between the mild and moderate grades of disease from the severe forms of hepatic steatosis. SteatoTest was found to have 90% sensitivity with a cut-off point 0.3 and 88% specificity with a cut-off point of 0.7 [82]

A newer version of SteatoTest exists presently, which is the Staetotest-2 which utilizes similar parameters excluding BMI and bilirubin levels, this was found to be better than its first generation counterpart due to its lesser parameters, hence making its use easier.[83,84]

NAFLD Liver Fat Score (NLFS)

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NLFS was one of the initial tools developed to diagnose NAFLD using laboratory results and clinical data among the patients in the Finnish population. The NAFLD Liver Fat Score (NLFS) evaluates hepatic lipid levels by using parameters such as: metabolic syndrome, diabetes mellitus (DM), fasting serum insulin levels (FSI), aspartate aminotransferase (AST), and AST to ALT ratio. NLFS is calculated by:

NLFS: 1.18 x metabolic syndrome (if present 1 point) + 0.45 x DM (if present 2 points; 0, if not) + 0.15 x FSI (mU/L) + 0.04 x AST (U/L) − 0.94 x (AST/ALT) − 2.89

Values ≤-0.64 indicates no NAFLD, Values >-0.64 to <0.16 indicates mild steatosis, Values ≥0.16 indicates moderate to severe steatosis. NFLS can predict NAFLD with specificity of 71% and sensitivity of 86%,with a cut-off point of −0.640 [85]

Hepatic steatosis index

The hepatic steatosis index (HSI) was developed following a large cohort study in Korea. It aimed at providing a cost effective diagnostic method for asymptomatic patients with risk of developing NAFLD 1. HSI consists of four parameters: the ratio of liver enzymes serum alanine aminotransferase (ALT) to aspartate aminotransferase (AST), diabetes mellitus (DM), BMI and gender. This index is calculated by:

HSI: 8 x (ALT/AST ratio) + BMI (+2 if the gender is female, +2 if there is presence of DM)

It is a comparatively easy diagnostic scoring system to detect NAFLD; according to HSI if the value is <30 then hepatic steatosis is absent, and if the value is >36 then hepatic steatosis is present. HSI was found to have a sensitivity of 93.1% and specificity of 92.4% [86].

NAFLD ridge score

Ridge score is an easily computable and highly predictive form of measuring NAFLD severity. The Ridge scoring system consists of 6 parameters: serum ALT, HDL (high-density lipoprotein), Triglycerides, presence of hypertension, hemoglobin A1c and leukocyte count.

Ridge Score: ALT+HDL+Triglycerides+Hba1c+leukocyte count + presence of hypertension

The reference for standard was proton magnetic resonance spectroscopy in NAFLD ridge scoring. The NAFLD ridge score achieved a sensitivity of 92% (86–96%) and a specificity of 90% (86–93%) [87] .

Fatty liver index (FLI)

Fatty liver index is considered as one of the beneficial and relatively simple tool in the diagnosis of NAFLD, it consist of 4 parameters: triglyceride (TG) body mass index (BMI), gamma-glutamyl transferase (GGT), waist circumference (WC), and is considered as one of the beneficial tools in the diagnosis of NAFLD[88]. Recent studies indicate that increased FLI has been positively correlated to cardiovascular disease due to similar parameters of risk factors [89].

FLI: [e0.953× Loge(TG) +0.139× BMI +0.718× Loge (GGT) + 0.053× WC − 15.745]/[1+e0.953× Loge(TG) +0.139× BMI +0.718× Loge(GGT) + 0.053× WC − 15.745]×100 [88]

According to revised cut off scores.

FLI <20 - no hepatic steatosis (probability to not have fatty liver is >91%),

FLI ≥60 - presence of hepatic steatosis (probability to have NAFLD is >78%) [89]

Lipid accumulation product (LAP) score

LAP is another effective noninvasive scoring system that is low cost and fairly accurate in diagnosing NAFLD. In a cross sectional study LAP was found to be a reliable index in identifying insulin resistance [90] . According to another study conducted in Taiwan, LAP had high diagnostic accuracy for predicting metabolic syndrome. These studies further reinforce the diagnostic accuracy of

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LAP as both metabolic syndrome and IR have been strongly correlated to NAFLD. LAP uses 2 parameters: waist circumference (WC) and triglyceride level (TG).

LAP: (Waist circumference (cm) – 65) x Triglycerides(mmol/L) for males

LAP: (Waist circumference(cm) – 58) x Triglycerides (mmol/L)) for females [91]

Dai et al. had used this scoring in a large cross sectional study which revealed sensitivity and specificity of 77% and 75% in men for a cut-off of 30.5, respectively, and 82% and 79% in women for a cut-off of 23.0 [92].

OWLIVER

This is a diagnostic tool that is based on an algorithm that combines 25 molecularly distinct triglycerides. It measures the fasting blood biomarkers indicative of the level of severity of hepatic steatosis and hence NAFLD. OWLiver measures the levels of the specific triglycerides using an ultra-high performance liquid chromatography-MS. This test is indicated for people with a risk factor of BMI elevated above 25 [93] .2 This test was able to distinguish normal liver, fatty liver and steatohepatitis from each other. In 2018, the OWLiver test was first performed in a cohort study including 467 patients, and this test was subsequently confirmed using biopsy. According to this study OWLiver could distinguish normal liver from a fatty liver by sensitivity of 94% and specificity of 57% [94] .1

NAFLD SCREENING SCORE

NAFL screening score was developed in China based on cross sectional study of data collected from two different hospitals, for screening of NAFLD. The study involved a training cohort group containing 46,493 individuals which was later validated in a cohort with 1996 individuals from another hospital, and this score was also established separately for males and females with different AUROC.1 High accuracy was seen in both the training and validation cohorts. NSS has a sensitivity of 80% and a specificity of 66% [95].

The parameters included in NAFL screening score are age, BMI, fasting plasma glucose levels, uric acid levels, triglycerides, and AST/ALT ratio. The factor which sets this scoring system apart is the inclusion of uric acid levels. This addition brought a significant improvement in the diagnosis of NAFLD. In a cross section study it was determined that elevated uric acid levels were associated with an increased prevalence of hepatic steatosis [96]. Studies indicate that elevated uric acid levels were due to oxidative stress related to IR and decreased excretion of uric acid was a consequence of elevated insulin levels [97,98].

Imaging studies

Ultrasonography (US)

At present, ultrasonography is the first line imaging modality due to its cost effectiveness and widespread availability. Hamaguchi scoring is a semi quantitative method that can be utilized for staging the severity of NAFLD based on the ultrasonographic findings, brightness of liver parenchyma, hepato-renal contrast, vessel blurring and attenuation depth: 1 point is given to each, Mild hepatic steatosis will be ≥2 and moderate to severe steatosis by score ≥4 [99].

Although US is a reliable and fairly accurate modality for the detection of NAFLD, in a meta-analysis conducted it was found out that ultrasonography could detect of mild to moderate hepatic steatosis of 20 to 30% with a sensitivity of 84.8% and specificity of 93.6%, but the sensitivity is fairly lowered to 65% for low grade hepatic steatosis [100]. Another limitation of US is that there is a significant interobserver and intraobserver variability that has to be taken under consideration.[101].

Controlled Attenuation Parameter (CAP)

CAP is a feature of ultrasound-based vibration controlled transient electrography (VCTE) obtained by Fibroscan. This feature was used to assess the quantity of fat within the hepatocytes by the attenuation of the ultrasound beam as it traverses through the liver parenchyma. CAP was specifically designed to target the liver and hence can be simultaneously used for the detection of liver fibrosis along with checking for liver fat content. Research indicates that CAP can detect steatosis levels over 10%, while US

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requires over 20% steatosis for detection [102]. CAP was shown to have decreased efficiency for detection of higher grades of hepatic steatosis hence it could be used for screening for fatty liver disease among high risk patients [103] . Due to the lower risk of sampling error CAP is also considered superior to liver biopsy. Unlike US, CAP is operator and machine independent, hence guaranteeing uniform results [104] .

Magnetic Resonance based methods

There are 2 magnetic resonance-based techniques: magnetic resonance spectroscopy (MRS) and Magnetic resonance imaging - estimated proton density fat fraction (MRI-PDFF). Research indicates that MRI-PDFF and MRS have stronger correlation with histopathologic steatosis assessment as compared to US and CT [105].

MRS is considered as one of the accurate methods for quantification of fat [106]. In magnetic resonance spectroscopy (MRS), the proton signals corresponding to water and fat, obtained from a specific area of interest, during a single breath hold of approximately 20 seconds, are represented as distinct peaks in a high-resolution spectrum. Liver fat fraction can then be calculated using the peak area under the water and fat curves within the spectrum [107]. Research indicates that MRS showed better diagnostic accuracy than CAP in the detection and staging of hepatic steatosis [108]. However, the use of MRS is limited in a clinical setting as it can only measure fat in a particular region of interest at a specific time [109].

MRI-PDFF, a novel biomarker, PDFF measures the concentration of lipids within the cells of hepatocytes and is strongly correlated to the severity assessment of fatty liver. PDFF can be calculated as the ratio of the signal from the triglycerides to total signals from the triglycerides and water [110]. MRI-PDFF eliminates the biases that are seen with conventional MRI techniques such as the T1 bias, T(2) decay, eddy currents, and multi frequency signal interference effects of protons in fat [107,109]. Unlike MRS, this method allows fat mapping of the entire liver. In a meta-analysis, MRI-PDFF demonstrated reproducibility, maintaining consistent results across various manufacturers and varied magnetic field strengths.[111].

Using randomized control trials it was proven that MRI-PDFF has a high correlation with MRS and is more sensitive in comparison to histology-determined steatosis grade in liver fat quantification [112].

TREATMENT STRATEGIES FOR NAFLD

Pharmacological treatments:

Although research are still ongoing and no medications has yet been approved for the treatment of fatty liver several drugs have been found to have a positive effect in reducing hepatic fat levels, few of those are mentioned below

Pioglitazone

Pioglitazone belongs to the class of drugs called thiazolidinediones, they are peroxisome proliferator–activated receptor γ (PPARγ) agonists. Thiazolidinediones are used for controlling hyperglycemia in patients with type 2 diabetes mellitus [113]. As mentioned previously, insulin resistance (IR) is one of the chief factors in the pathogenesis of NAFLD so the treatment of IR can be one of the beneficial means of treating hepatic steatosis [114] . Pioglitazone is effective for the treatment of hepatic steatosis because it acts on PPARγ involved in glucose metabolism along with PPARα receptor which is involved in lipid metabolism thus improving glucose sensitivity and lipid metabolism [115]. Research indicates that Pioglitazone can alter liver histology by improving hepatocyte ballooning, steatosis and inflammation thereby improving the severity of liver steatosis [116,117]. In a meta-analysis involving various randomized clinical trials, pioglitazone was shown to reduce plasma ALT and AST levels, increase the plasma HDL levels, improve γ-glutamyltransferase level and also bring a significant reduction to Hba1c levels [118,119].

GLP 1 Receptor Agonists

Glucagon-like peptide 1 receptor agonists (GLP1 RA) are drugs that are homologous to GLP 1 hormone which is produced by the enteroendocrine L cells [120]. GLP 1 being an incretin type hormone, can cause an enhanced release of insulin from the pancreatic beta cells in response to glucose in blood and can also inhibit glucagon release from the alpha cells, hence it is used for therapy in type 2 DM [121]. These drugs cause early satiety, delayed gastric emptying and postprandial fullness leading to decreased appetite

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and hence significant weight reduction [122]. GLP1 RA leads to decreased fatty acid accumulation within hepatocytes through autophagy dependent lipid reduction, and also inhibits abnormal ER stress response [123,124]. Ghosal et al conducted a meta-analysis which showed that patients treated with GLP1 RA showed reduction ALT, AST, Hba1c and fat content in the liver along with remarkable weight reduction [125].

A randomized clinical trial conducted among women with PCOS, showed that the treatment with Liraglutide for 26 weeks led to 5.6% reduction of body weight and 44% decrease in liver fat content thus lowering the initial prevalence of hepatic steatosis [126]. In a phase 3 clinical trial comparing various GLP1 RA, subcutaneous semaglutide showed the best results in weight reduction and Hba1c levels, although with significant gastrointestinal adverse effects [127]

Vitamin E

For patients with NAFLD, vitamin E supplementation offers a possible therapeutic option. Vitamin E is a lipid-soluble antioxidant, has the most evidence for its ability to provide a therapeutic benefit through prevention of free radical accumulation [128]. A number of studies have been carried out to investigate the possible function of vitamin E based treatment in NAFLD patients. In patients with non-alcoholic fatty liver disease, these clinical trials investigated the effectiveness of vitamin E monotherapy as well as dual therapy in combination with other possible therapeutic agents [129–131].

The study conducted in China found that both lifestyle intervention and vitamin E (100 mg/day) improved liver function and insulin resistance in obese children with NAFLD. Vitamin E treatment led to significant reductions in ALT levels, supporting its use in NAFLD management [129]. Another study compared vitamin E plus vitamin C with ursodeoxycholic acid (UDCA) in treating patients with fatty liver disease. Both treatments significantly reduced serum AST and ALT levels after six months, with vitamin E and C showing a slightly higher, but not statistically significant, efficacy in normalizing ALT levels compared to UDCA [130].

SGLT2 inhibitors

SGLT-2 inhibitors, also known as glucose-lowering agents, have been shown to decrease serum uric acid levels and aid in weight loss. Even non-diabetic patients with heart failure and chronic kidney diseases have benefited from them. In addition to their ability to lower blood sugar, SGLT-2 inhibitors are strong anti-inflammatory and antioxidant drugs that show promise in the treatment of NAFLD [132]. Numerous clinical investigations have demonstrated SGLT-2i's benefits for NAFLD patients [133–135].

The study published in 2021 revealed tofogliflozin's potential as a treatment by showing a significant reduction in hepatic steatosis in patients with NAFLD. Furthermore, liver enzyme levels improved in tofogliflozin-treated patients, supporting the effectiveness of SGLT-2 inhibitors in the treatment of nonalcoholic fatty liver disease [136]. Another study showed that in Korean patients with type 2 diabetes mellitus and NAFLD, the addition of SGLT2 inhibitors resulted in significantly lower body weight and ALT levels when compared to other oral antidiabetic drugs [134]. Based on its ability to reduce weight and improve liver enzyme abnormalities, SGLT2 inhibitors may be a useful therapeutic option for managing T2DM-associated NAFLD.

FXR ligands

Farnesoid X receptors (FXR) are part of the nuclear hormone receptor family [137]. FXRs are highly expressed in bile acid-metabolizing tissues such as the liver, and have been linked to liver cirrhosis [138,139]. Numerous gain and loss-of-function studies have shown that FXR regulates lipid and glucose metabolism, as well as the inflammatory response. Activated FXR promotes lipid and glucose homeostasis while inhibiting inflammation [140,141]. FXR's properties suggest that it is an ideal target for NAFLD treatment.

The study published in 2010 discovered that decreased expression of farnesoid X receptor (FXR) in patients with NAFLD was linked to increased levels of liver X receptor, sterol regulatory element binding protein 1C (SREBP-1C), and hepatic triglyceride synthesis [142]. The FLINT study, a randomized multicenter clinical trial using FXR agonist obeticholic acid showed to improve hepatic fibrosis, hepatocellular ballooning and liver fat fraction [143]. This suggests that FXR plays an important role in regulating lipid metabolism, and that FXR activation could be a viable therapeutic target for treating NAFLD by restoring proper lipid balance.

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FGF19 mimetics and FGF-21 mimetics

Novel endocrine messengers known as fibroblast growth factors 19 and 21 (FGF19 and FGF21) control several facets of energy homeostasis [144]. FGF19 and FGF21 have emerged as pivotal therapeutic targets for NAFLD. The metabolic actions of FGF19 and FGF21 primarily involve their binding to βKlotho (KLB) and subsequent activation of FGFR1c and FGFR4 signaling pathways in the liver [145]. Research into FGF19 mimetics and FGF21 mimetics as treatments for NAFLD highlights their potential to modulate metabolic homeostasis through targeted receptor interactions. Studies indicate that these endocrine factors bind specifically to KLB, facilitating downstream activation of FGFR1c and FGFR4 signaling pathways crucial for regulating bile acid synthesis and lipid metabolism [144,146]. Research indicates that pharmacological administration of recombinant FGF19 improved dyslipidemia and hepatic steatosis, while FGF21 based drugs have shown to improve liver damage due to plasma bile acid levels along with hepatic steatosis [147].

The clinical application of FGF19 and FGF21 analogues in treating NAFLD faces challenges, particularly in achieving consistent metabolic outcomes across diverse patient populations. While rodent models have provided foundational insights into their therapeutic potential, variability in individual patient responses underscores the need for further clinical research to optimize their efficacy and safety profiles. Despite promising preclinical evidence, the therapeutic efficacy of FGF19 and FGF21 analogues in humans remains a subject of scrutiny in clinical trials. Variability in patient responses and concerns over gastrointestinal side effects associated with FGF administration highlight ongoing challenges in translating rodent-based findings to clinical practice, necessitating continued research into their mechanisms of action and optimization of treatment protocols [147]

SURGICAL TREATMENT

Bariatric surgery

Bariatric surgery (BS) has shown to be greatly beneficial in patients with NAFLD due to its potential to reverse the multitude of causes leading to fatty liver such as obesity, type 2 DM and hypertriglyceridemia. In a meta-analysis conducted among patients with NAFLD it was seen that there was improvement in more than 75% of patients after BS, among which the majority had a complete regression of hepatic steatosis [148]. BS was found to improve liver function by reducing plasma ALT, AST and GGT levels [149,150]. Histopathologically BS has been shown to improve lobular steatosis, ballooning, fibrosis and inflammation of the liver, due to its direct effect on weight reduction [151].

The two most commonly performed forms of bariatric surgeries are Roux-en-Y gastric bypass (RYGB) and laparoscopic sleeve gastrectomy (LSG). Among the two forms mentioned, RYGB is superior due to enhanced ability to reduce plasma lipid levels and improve insulin resistance and hence reduce liver steatosis grade in comparison to SG [152,153]. The proposed hypothesis by which BS could improve insulin resistance was by increasing glucagon-like peptide 1 (GLP-1). GLP 1 is an insulinotropic hormone that can help improve insulin resistance and hence glycemic control in type 2 DM [154]. In a study conducted it was revealed that there was a 10 times increase in GLP 1 secretion in patients who have undergone RYGB in comparison to the other patients [155]. Elevated levels of GLP 1 can help in delaying gastric emptying thus leading to reduced caloric intake. Bile salts levels are also seen to be elevated in patients post-BS [156] . This has also further conferred to improving glucose and lipid metabolism by promotion of insulin secretion and inhibition of triglyceride synthesis respectively [157,158]. All this evidence indicates that surgical management is also a great option that has been shown to be effective in treatment of NAFLD.

NON-SURGICAL

NAFLD AND DIET

The risk of developing NAFLD is 3.5 times increased in people with obesity [159]. Reduction of body weight by a minimum of 10% through lifestyle modification can significantly reduce this risk [160]. Hypocaloric dietary interventions and exercise are the fundamentals of NAFLD treatment since no drug has yet been approved [161]. Mediterranean Diet (MD) and DASH (dietary approaches to stop hypertension) is considered as some of the most effective diet practices that are beneficial in reversing NAFLD.

Mediterranean Diet (MD)

MD is a diet form that is characterized by consumption of food rich in mono and polyunsaturated fatty acids and high percentage of fiber. This diet consist of large amount of plant based foods rich in fiber sources like fruits, vegetables, whole grains, legumes, and olive oil (monounsaturated fatty acid) along with fish and seafood rich in omega 3 fatty acid (polyunsaturated fatty acid), along with moderate consumption of eggs, poultry and dairy products. While red meat and alcohol is consumed in the lowest amount [162]. According to research, fatty liver and MD was found to have an inverse relationship [163]. In a meta-analysis, Haigh et al, concluded that MD and hypocaloric diet was associated with lowered liver enzymes such as ALT and AST, along with reduced fatty liver index and liver steatosis grade [164]. MD practice reduces the risk factors of metabolic syndrome such insulin resistance, waist circumference, LDL and triglyceride accumulation, and hence is protective against type 2 diabetes, atherosclerosis and dyslipidemia which can in turn ameliorate the risk of NAFLD by reducing the level of inflammatory mediators, lipid accumulation and oxidative stress [165–168].

Dietary approaches to stop Hypertension (DASH)

The DASH diet is a specific diet that has been tailored for the treatment and reduction of hypertension. It consists of a diet low in sodium and saturated fats and high in proteins, fibers and minerals [169]. This diet is based on fruits, vegetables, low fat dairy products, whole grains, and reduced consumption of red meat, products with high added sugar content, combined with sodium restriction [170]. In a randomized clinical trial conducted among patients with NAFLD, it showed that 8 weeks of consuming meals as per DASH diet had yielded significant impacts on reducing BMI, aspartate aminotransferase, alanine aminotransferase, highly sensitive c-reactive proteins, total cholesterol, VLDL (very low density lipoproteins), insulin, and serum triglycerides [171]. In another trial Hekmatdoost et al. showed that adherence to this diet had decreased the risk of NAFLD by 30% [172]. Several trials show that the DASH diet can be considered to be protective against type 2 diabetes mellitus, metabolic syndrome, and breast cancer [173–175]. Considering these trials and observational studies it can be said that the DASH diet could be one of the effective tools in patients with a risk of developing or with NAFLD.

CONCLUSION

This comprehensive literature review has synthesized current knowledge on non-alcoholic fatty liver disease (NAFLD), shedding light on its global burden, risk factors, pathophysiology, and management strategies. The findings underscore the multifaceted nature of NAFLD, highlighting its association with various metabolic conditions such as obesity, type 2 diabetes, and cardiovascular disease. Our review confirms that NAFLD presents a significant health challenge worldwide, with prevalence rates and disease severity varying across different populations.

The review emphasizes the importance of early and accurate diagnosis through advanced imaging techniques, biomarkers, and non-invasive scoring systems. Furthermore, it illustrates the critical role of lifestyle interventions, pharmacological treatments, and, in some cases, surgical options in managing NAFLD and preventing its progression to more severe stages such as non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).

By integrating insights into the molecular mechanisms, genetic predisposition, and environmental factors contributing to NAFLD, this paper provides a comprehensive understanding of the disease. The review also highlights gaps in current knowledge and suggests areas for future research, particularly in optimizing diagnostic tools, exploring new therapeutic approaches, and addressing health disparities in NAFLD management.

In conclusion, NAFLD appears to be a vicious cycle of inflammation, lipotoxicity, and steatosis that leads to complex changes in the liver's histological as well as the biochemical characteristics, and addressing this spectrum of disease requires a multidisciplinary approach, combining early detection, effective management strategies, and continued research efforts to mitigate the global impact of this increasingly prevalent condition.

Author's Contribution

N.C and O.C. wrote, reviewed and edited the manuscript. Both the authors critically revised the manuscript and approved the final

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Conflict of interest

The authors declare that there is no conflict of interest in this study.

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