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Risk Prevention and Health Promotion for Non-Alcoholic Fatty Liver Diseases (NAFLD)

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Abstract: Non-alcoholic fatty liver disease (NAFLD) is a serious clinicopathological condition that is recognized as the most frequent chronic liver disease, affecting 14%-30% of the world's population. The prevalence of NAFLD has rapidly grown and is correlated with the growth in obesity and type 2 diabetes, among other factors. NAFLD often results in long-term complications including cardiovascular disease, liver cirrhosis, and liver fibrosis. This paper provides an updated overview of NAFLD with a focus on epidemiology, etiology, pathophysiology, screening, complications, and pharmacological therapies to identify effective risk prevention and health promotion.

Keywords: NAFLD; fatty liver disease; metabolic syndrome

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1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease (CLD) [1]. A clinically heterogeneous disease, NAFLD may increase hepatic and non-hepatic morbidity and mortality, resulting in health-care expenditures, impaired quality of life, and massive economic losses [2–5]. Untreated hepatic steatosis progresses in 15-20% of patients to non-alcoholic steatohepatitis (NASH), inciting lobular inflammation, hepatocyte ballooning, and fibrogenesis [6]. Ultimately, NASH is associated with cirrhotic liver and hepatocellular carcinoma (HCC) [7–10]. Globally, HCC is the cause of death for over 800,000 people annually and is the third leading cause of cancer deaths [11].

Growing evidence has demonstrated that NAFLD is not confined to liver-related morbidity and mortality but instead exists as a multisystem disease, impacting numerous organs and regulatory pathways [12]. NAFLD has been strongly associated with obesity and type 2 diabetes (T2D), yet also occurs in individuals with normal weight, particular in Asian populations [13–16].

Cardiovascular disease (CVD) is the leading cause of death in NAFLD patients, followed by chronic kidney disease, T2D mellitus (T2DM), liver-related complications, and extrahepatic malignancies [17–20]. Cirrhotic patients commonly experience liver-related events, whereas non-cirrhotic patients experience vascular events and non-hepatic cancer [21].

NAFLD is a largely underdiagnosed liver condition and is nearly absent on global and national public health agendas. The lack of noninvasive tools for diagnosis and pharmacotherapeutic agents has limited the awareness of its prevalence, resulting in minimal global and national non-communicable disease (NCD) actions and efforts [22]. Further evidence-based public health mechanisms to combat the NAFLD epidemic and develop novel management options are necessary to improve life expectancy, quality of life, and healthcare resource use for patients with NAFLD.

The goal of this narrative review is to analyze risk prevention and health promotion strategies for NAFLD. By investigating NAFLD with a focus on epidemiology, etiology, pathophysiology, screening, complications, and pharmacological therapies, this paper aims to facilitate a comprehensive understanding of NAFLD and identify avenues for further research. This analysis will help clinicians partner with patients to combat the rapid growth and negative impact of NAFLD.

2. Growing Concern of NAFLD

NAFLD is a form of fatty liver disease characterized by the over-accumulation of fat droplets (macrovesicular steatosis) in greater than 5% of hepatocytes that is not caused by alcohol or drug use [23,24]. NAFLD is a broad term for liver disease that includes two notable subtypes: non-alcoholic fatty liver (NAFL) and NASH. Steatosis without hepatocellular damage or inflammation is isolated or simple steatosis, also known as NAFL [24]. NASH, which has a global prevalence of 59.1% among patients with biopsied NAFLD, is identified in liver biopsy findings by steatosis with ballooning and lobular inflammation [24,25]. Most patients with NAFLD only have NAFL, but NAFL can progress into NASH or vice versa [24]. Both conditions, but especially NASH, can progress to liver injury, progressive fibrosis, cirrhosis (compensated or decompensated), and/or HCC [24,26,27]. NAFLD affects 25% of adults worldwide [28]. Accordingly, NAFLD represents a significant global disease burden that is increasing alongside rates of obesity, diabetes, and population aging [25]. Based on a 2016 meta-analysis, the three regions with the highest prevalence worldwide were the Middle East, South America, and Asia, with 31.79%, 30.45%, and 27.37% prevalence, respectively, compared to 24.13% in North America [28]. By 2030, the global prevalence of NAFLD is estimated to rise to 33.5%, with the median age of people with NAFLD increasing from 50 to 55 years from 2015 to 2030 [25].

NAFLD is the most common cause of death in individuals with CLD and is associated with several comorbidities [29]. In the United States (U.S.), NAFLD is a growing cause of cirrhosis, HCC, and liver transplant [30]. More specifically, NAFLD is the fastest growing cause of HCC in the U.S., and NASH is the second leading cause of HCC requiring liver transplantation in the U.S. [29,30]. A recent analysis of NAFLD in the Medicare population concluded that HCC and cirrhosis were the leading hepatic causes of mortality in patients with NAFLD and found that diabetes, hypertension, hyperlipidemia, and CVD (in order of highest to lowest prevalence) were the most common extrahepatic diseases affecting those with NAFLD [31]. NAFLD has also been associated with increased risk of chronic kidney disease [32]. Of these manifestations, cirrhosis and CVD are the leading causes of death in patients with NAFLD, followed by diabetes and hypertension [29,33]. These hepatic and extrahepatic manifestations of NAFLD are associated with increased healthcare use and expenditure, which pose significant burdens to the U.S. healthcare system [34]. The estimated total country cost of the population with NAFLD in the U.S. is estimated to be $95.9 billion, whereas the mean total country cost in Germany, France, the United Kingdom, and Italy is estimated to be $36 billion [2]. Further, a recent retrospective, cross-sectional analysis estimated the total country cost of NASH only, excluding costs of concomitant conditions, to be almost $82 billion in the U.S. and $21 billion in France, Germany, Italy, Spain, and the UK [3]. These financial burdens coupled with the rising incidence and mortality rate of NAFLD underscore the serious present and future impact of NAFLD on world health [33].

3. Metabolic Dysfunction-Associated Fatty Liver Disease

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a new name and definition proposed in recent years for the previously described NAFLD. The reason for the proposed change is because NAFLD is not fully descriptive of the metabolic abnormalities commonly seen in this disease pathology. The diagnosis of NAFLD was based on the presence of hepatic steatosis in the absence of alcohol use [35]. MAFLD offers a more comprehensive definition and diagnostic criteria which account for the metabolic abnormalities common in this disease process. To diagnosis MAFLD, the proposed criteria require evidence of hepatic steatosis as well as one of the following: overweight or obese, T2DM, and/or evidence of metabolic dysfunction [35]. Metabolic dysfunction is defined as at least two of the following parameters: increased waist circumference, elevated blood pressure, elevated cholesterol, prediabetes, insulin resistance, and/or elevated C-reactive protein [35]. Although there is an overlap between patient's who meet diagnostic criteria for NAFLD and MALFD, observational studies demonstrate an increase in the number of patient's identified when using the diagnostic approach of MAFLD as compared to NAFLD [36]. As a result, utilizing the comprehensive diagnostic criteria associated with MAFLD may allow for a more sensitive method to diagnosis patients and provide care early in the disease process.

4. Epidemiology

The prevalence of NAFLD in the U.S. is estimated to be 24% [37]. Most patients are diagnosed with NAFLD in their 40 s or 50 s, and prevalence is greatest in patients aged 70–79 (34.0%), followed by patients aged 60–69 (28.9%) [28,38]. In general, NAFLD appears to be more common in males than females [14]. A recent review found that NAFLD incidence and prevalence was higher in men than in premenopausal women (≤age 50–60 years) [14]. A systematic review on racial and ethnic disparities in NAFLD found that NAFLD was more prevalent in Hispanic patients and lower in Black patients when compared to White patients [39]. Similarly, Hispanic patients were more likely to be diagnosed with NASH compared to White patients (relative risk 1.1; 95% CI, 0.98–1.21) [39].

During the COVID-19 pandemic, social distancing mandates and the closure of non-essential businesses placed an enormous strain on patients' physical health. A retrospective study of 973 patients found that alcohol use and food consumption increased during the pandemic, and this was associated with a corresponding increase in incidence of NAFLD [40]. In addition, NAFLD may aggravate a COVID-19 infection. In a case-control study conducted in 2021, the prevalence of pre-existing NAFLD in hospitalized COVID-19 patients was found to be significantly higher than in patients without COVID-19 [41]. Further, patients with NAFLD were more likely to experience severe COVID-19 compared to patients without NAFLD [42].

Up to 80% of patients with T2D combined with obesity have concurrent NAFLD [15,16]. The rise of diabetes and obesity compounded with the aging population in the U.S. will lead to an increased prevalence and mortality of NAFLD. Estes et al. estimated that the prevalence of NAFLD will increase to 100 million in the U.S. [25].

5. Pathophysiology of NAFLD

The liver synthesizes lipid molecules, such as triacylglycerol. Fatty liver occurs when the metabolism of lipids within the liver is impaired, also called steatosis, which is caused by increased creation or reduced metabolism of triglycerides and fatty acids. Most fatty acids that accumulate in the liver and are taken into the liver cells are non-esterified fatty acids from the blood plasma. The liver metabolizes these fatty acids through fatty acid oxidation in mitochondria and the production of very low-density lipoproteins. Interference with either of these processes could contribute to NAFLD. Genetic polymorphisms have also been shown to affect the progression of NAFLD. Polymorphisms in the IL-6 and the IL-1β have been shown to increase the severity of NASH, while mutations in the HFE

gene have been associated with worsening fibrosis of the liver and advancing NASH progression [42]. Specific alleles have also been associated with progression and fibrosis [43].

NAFLD has several known risk factors including obesity, diabetes, insulin resistance, and sedentary lifestyle. Food intake regulating peptides like leptin and ghrelin may be related to its pathophysiology. Leptin, an appetite suppressing peptide, has been shown to affect hepatic metabolism and NAFLD [43]. Glucagon-like peptide-1 and its receptor agonist may be a treatment to slow disease progression [44].

The proposed pathophysiology for NASH involves two stages. The first one is fat deposition in the liver and progressive resistance to insulin perpetuating a vicious cycle. The next stage involves oxidative stress and oxidation of the deposited fatty acids in the liver. This is initially characterized by inflammation, which progresses to fibrosis and eventually cirrhosis [45,46].

6. Screening for NAFLD

While the U.S. Preventative Task Force has not made any screening recommendations for NAFLD, the 2016 European Associations for the Study of the Liver, Diabetes, and Obesity guidelines recommended screening for high-risk patients greater than 50 years old with cardiovascular risk factors, obesity, T2DM, metabolic syndrome, or persistently abnormal liver enzymes [46]. The 2022 American Association of Clinical Endocrinology guidelines recommended screening for the aforementioned high-risk populations and those with previous hepatic steatosis on imaging [47]. In 2016, the American Association for the Study of Liver Diseases (AASLD) recommended against routine screening even in high-risk populations [47,48]. AASLD's practice guidance is primarily based on cost-effectiveness analysis and uncertainties in diagnostic testing and long-term management. However, recent studies using Markov models in hypothetical patients with NAFLD and T2DM have shown the value and cost-effectiveness of NAFLD screening with transient elastography compared to non-screening [49]. A large disease burden remains undetected but finding an adequate screening test that balances sensitivity and specificity to avoid an overabundance of false positives continues to pose a challenge.

The AASLD does, however, advise a high index of clinician suspicion for patients with T2DM [50,51]. Individuals with central obesity, insulin resistance, and metabolic syndrome are also at an increased risk of NAFLD [50]. The prevalence of NAFLD increases to 75% in people with diabetes and obesity, with an increased likelihood of developing complications of NAFLD [50]. These groups are increasingly vulnerable to other conditions as well. NAFLD is known as the liver manifestation of metabolic syndrome, and people with metabolic syndrome are concomitantly at risk for CVD [51]. Identifying and monitoring these populations is important to prevent the progression of future disease and comorbidities.

Although the general population is not recommended for screening, patients with a high clinical suspicion are risk stratified based on metabolic risk factors. Many proposed algorithmic approaches for screening proceed with the diagnosis of NAFLD through non-invasive proxies categorized by imaging evidence of steatosis, serum tests (indicating raised liver enzymes), biomarkers, and the exclusion of other causes of liver disease. Although liver biopsy is the gold standard to assess the severity of liver disease, it is invasive and costly. Instead, ultrasonography (U/S) is a widely available and frequently used screening method due to its lower costs for the assessment of hepatic fatty degeneration. However, it is less sensitive for steatosis of less than 20% and does not detect steatosis below 10% of hepatocytes [50]. Other imaging modalities like CT and MRI are more sensitive than U/S but are much more expensive. Once NAFLD is confirmed, it is staged, and fibrosis risk is evaluated via fibrosis measures like Fibrosis-4 (FIB-4), NAFLD fibrosis score (NFS), or AST to platelet ratio index (APRI). The FIB-4 score is preferred as the initial non-invasive test due to simplicity and ease of use, but both FIB-4 and NFS have a high risk of over-diagnosis and a significant percentage of false negatives, with 2-4% in all subjects and 8–9% in high risk cohorts with diabetes and hazardous alcohol consumption

[52,53]. Groups with more advanced staging undergo ultrasound-based transient elastography (FibroScan) to detect fibrosis and liver stiffness. Transient elastography is the most widely used method, and a recent meta-analysis demonstrated its sensitivity and specificity and a high accuracy for detecting fibrosis [54].

7. Complications of NAFLD

NAFLD often results in long-term complications including CVD, liver cirrhosis, liver fibrosis, and chronic kidney disease (CKD). NAFLD increases the risk of CVD including hypertension, coronary artery disease, and arrhythmias [17]. These conditions increase the risk of long-term cardiovascular events and cardiovascular related mortality. Patients with NAFLD will need close follow-up to diagnose, manage, and treat cardiovascular complications.

The chronic inflammatory state of NAFLD also contributes to the development and progression of liver cirrhosis and liver fibrosis [55,56]. Diabetes and obesity contribute to a chronic state of insulin resistance and oxidative stress, which influences liver cirrhosis pathogenesis. Predictors of cirrhosis development in NAFLD patients include the presence of diabetes, dyslipidemia, renal disease, and CVD [57]. The incidence and prevalence of NAFLD cirrhosis is increasing and is one of the most common indications of liver transplantation [1]. Mortality associated with NAFLD cirrhosis is 31.1% as compared to 12.6% in NAFLD without cirrhosis [57]. One third of patients with NAFLD will develop liver fibrosis within 4–5 years post diagnosis. NAFLD fibrosis is a risk factor for overall mortality and increased risk of liver-related mortality [58]. Among patients with NAFLD, 30–40% will develop NASH, and 40–50% of patients with NASH will also develop liver fibrosis [12]. The development of NASH is predictive of increased progression to liver fibrosis compared to NAFLD. Both liver cirrhosis and liver fibrosis are associated with increased risk of developing HCC, which may impact long term morbidity and mortality [58].

There has been growing evidence in recent literature associating NAFLD with an increased risk of CKD. The pathophysiology of the two is interwoven with mechanisms related to inflammation, oxidative stress, and fibrogenesis [59]. Even after accounting for confounding variables such as the shared risk factors of T2DM, hypertension, and metabolic syndrome, studies have shown a strong association between the presence and severity of NALFD and the increased prevalence and incidence of CKD [60]. A meta-analysis of 13 longitudinal studies found that the risk of incidence of CKD was 80% greater in people with NAFLD [61]. A higher degree of liver fibrosis as defined by NAFLD fibrosis score and fibrosis-4 index is associated with an impaired estimated glomerular filtration rate in patients [35,62,63].

Liver cirrhosis and liver fibrosis in patients with NAFLD are often difficult to diagnose, resulting in delayed diagnosis [58,64]. Patients with NAFLD require close follow-up to screen for risk factors associated with the development of liver cirrhosis and liver fibrosis. Early detection of liver cirrhosis and liver fibrosis may decrease long-term complications and reduce mortality and morbidity in this patient population. Likewise, monitoring patients' renal function closely for earlier detection of CKD in NAFLD patients would help mitigate future complications.

8. Risk Factors and Prevention Strategies

8.1. Obesity

Though obesity as a risk factor for NAFLD is often discussed in conjunction with metabolic syndrome, recent literature identified it as an independent risk factor as well. Pathological development of obesity related NAFLD primarily results from insulin resistant fatty liver overproduction of glucose and very low-density lipoprotein [65]. Cohort studies have found that obese individuals have a 3.5-fold increased risk of developing NAFLD [66]. In several large studies, associations between weight gain, increase of serum triglycerides, and subsequent development of NAFLD have been noted. An analysis of

8817 subjects showed a NAFLD prevalence of 0.4% in the underweight group and 81.9% in the obese group [67]. Patients who developed NAFLD gained significantly more weight than those who did not [68]. However, not all people who are obese develop NAFLD, and not all people with NAFLD are obese. A meta-analysis of 84 studies found that 19.2% of NAFLD patient participants were lean; in the general population, the prevalence of NAFLD in lean individuals is 5.1% [69].

The dose-dependent relationship between BMI and NAFLD risk is currently debated. In two prospective studies consisting of more than two million patients, Loomis et al. found that the risk of future NAFLD/NASH diagnosis increased almost linearly with increasing BMI from a BMI category of 20–22.5 to a BMI category of 37.5–40 [70]. Specifically, the risk of NAFLD/NASH diagnosis was approximately 5–9 times higher in patients with a BMI of 30–32.5 and up to 10–14 times higher for patients with BMIs between 37.5–40 compared to patients with BMIs of 20–22.5 [70]. In contrast, a cross-sectional study consisting of 3202 patients found that when compared with a reference BMI of 23, the odds ratios for NAFLD were 0.23 for a BMI of 18.6, 0.62 for a BMI of 22, 2.06 for a BMI of 24.5, and 6.09 for a BMI of 28.6, suggesting a J-shaped relation rather than a linear one [71]. Regardless of the shape the dose-dependent relationship takes, evidence suggests that higher BMI is associated with a greater risk of NAFLD. A meta-analysis of 21 cohort studies demonstrated a dose-dependent association between BMI and NAFLD, where each 1-unit increment increase in BMI was related to a 1.2 times greater risk of NAFLD [66].

A randomized controlled trial of 43 adult patients with biopsy-proven NASH demonstrated that a reduction in BMI of 5% was associated with a 25% relative reduction in liver fat [72].

Maintaining a healthy weight has been shown to benefit patient outcomes, and the current cornerstone of NAFLD therapy is weight loss and dietary interventions. Among individuals who underwent lifestyle changes, patients who lost ≥ 5% of their weight had a higher proportion of NASH resolution than those who lost <5% of their weight [73]. Changes in dietary intake had subsequent effects on NAFLD progression. Independent of changes in body weight, hypocaloric high fiber, high protein diets led to a 36%-48% reduction in liver fat as evaluated by magnetic resonance spectroscopy [74]. Dietary intake may also play a role in the development of NAFLD in lean or normal weight patients. Compared to healthy non-obese controls and obese NAFLD patients, normal weight NAFLD patients had unhealthy dietary composition with altered cholesterol and polyunsaturated fatty acid (PUFA) intake [75]. Given the improvements seen from lifestyle interventions, implementing these strategies even prior to a diagnosis of NAFLD may help attenuate risk.

8.2. Diabetes Mellitus

It is well-established that T2D is a significant risk factor for developing NAFLD. In addition, T2D is an important predictor of adverse outcomes in patients with NAFLD [12,15,76]. Studies estimate that patients with T2D have a more than 2-fold risk of developing NAFLD compared to patients without diabetes, and up to 60% of patients with T2D have NAFLD [19,77]. The literature currently supports a bidirectional relationship between insulin resistance and NAFLD [15,77]. Insulin resistance in T2D promotes hepatic lipid accumulation and peripheral adipose lipolysis [78]. Hyperglycemia and hyperinsulinemia activate several lipogenic transcription factors, which favor lipid accumulation over lipid oxidation or export [78]. Conversely, NAFLD worsens peripheral insulin resistance and causes the release of proinflammatory cytokines, which can lead to T2D [19]. A meta-analysis of 33 studies found that patients with NAFLD were at 2x greater risk of developing T2D, and the risk remained significant when controlling for age, sex, dyslipidemia, hypertension, smoking, and physical activity [79].

As diabetic patients are at increased risk of developing NAFLD, preventing T2D can decrease the incidence of NAFLD. The U.S. Preventative Services Task Force (USPSTF) currently recommends diabetes screening via a Hemoglobin A1c level or an oral glucose

tolerance test for all patients age 35-70 who are overweight or obese [80]. In the most recent guidelines published by ADA which also recommends that all patients with T2DM and prediabetes be evaluated for NAFLD [77]. In patients without any risk factors for diabetes, the American Diabetes Association recommends screening for diabetes beginning at age 45 [81]. Patients who are at increased risk for diabetes defined as an elevated HgbA1c, fasting plasma glucose, or abnormal glucose tolerance test, should be offered dietary, physical activity, and smoking cessation counseling. Studies have shown that 150 minutes per week of moderate physical activity is associated with a significantly decreased risk of developing T2D [82,83]. Randomized controlled studies have shown that the Mediterranean diet can significantly reduce the risk of developing T2D [84,85]. According to the American Diabetes Association, providers should also consider metformin initiation in prediabetic patients who are less than 60 years old, have a BMI > 35 kg/m^2, or have a history of gestational diabetes [86].

8.3. Metabolic Syndrome

Metabolic syndrome is an abnormal metabolic profile, characterized by a variety of conditions including obesity, dyslipidemia, insulin resistance, and hypertension [87]. Metabolic syndrome is a risk for the development and progression of NAFLD due to a chronic pro-inflammatory state and resulting state of insulin resistance [87]. Metabolic syndrome is associated with an increase in inflammatory markers such as c-reactive protein, TNF-alpha, and IL-6, which activate inflammatory cascades and interfere with insulin signaling [87,88]. CRP specifically is produced by the liver as an acute phase reactant and upregulates the NF-KB pathway, which results in insulin signaling dysregulation [88]. These inflammatory markers (CRP, TNF-alpha, IL-6) can be used as biomarkers to assess disease severity [88]. Insulin resistance decreases insulin sensitivity and promotes increased free fatty acids [89], which are then deposited in the liver and result in hepatic inflammation [89]. Among patients with NAFLD, 90% will have one characteristic of metabolic syndrome, and a third will exhibit three or more characteristics [90]. Obesity and diabetes are present among almost half of patients with NAFLD and should be the focus when determining prevention strategies to reduce the risk of metabolic syndrome associated NAFLD [87]. Two main prevention strategies for metabolic syndrome include pharmacological therapy and lifestyle modifications. Insulin sensitizing pharmacological therapies such as metformin may decrease insulin resistance and assist in weight loss [91]. Lifestyle modification centered on weight reduction through diet and exercise is another strategy to decrease rates of obesity and insulin resistance [91]. Implementing pharmacological therapy and lifestyle modifications simultaneously may provide additional preventative benefit to patients at increased risk of developing metabolic syndrome.

9. Pharmacotherapy

The FDA has yet to approve a pharmacological therapy for NAFLD or NASH. According to the most recent practice guidance from AASLD published in 2018, management of NAFLD should focus on treating liver disease and associated metabolic comorbidities such as obesity, hyperlipidemia, insulin resistance, and T2D. Medications for primarily improving liver disease should only be used in patients with biopsy-proven NASH and fibrosis [92]. Recommended therapies include pioglitazone and Vitamin E. Statins and omega-3 fatty acids should only be used in patients with dyslipidemia and hypertriglyceridemia, respectively, and do not directly treat NAFLD [92]. Statins can be used in NASH cirrhosis but should not be used in decompensated cirrhosis [92]. GLP-1 receptor agonists (GLP-1 RAs) such as liraglutide were considered premature in the 2018 AASLD guidance, but more recent evidence suggests that they benefit patients with NASH and DM [93,94]. The 2022 Clinical Practice Guideline for NAFLD by the American Association of Clinical Endocrinology (AACE) also recommends sodium-glucose cotransporter 2 (SGLT2) inhibitors for cardiometabolic benefit in patients with T2D and NAFLD but not for treating steatohepatitis [94]. A summary of the pharmacological therapies for

NAFLD/NASH with the corresponding mechanism of action and effect on NAFLD is discussed in Table 1.

9.1. Pioglitazone

Pioglitazone is a thiazolidinedione (TZD), a class of drugs used for T2D that improve insulin sensitivity via peroxisome proliferator-activated receptor γ (PPAR-γ) activation in liver, muscle, and adipose tissues [95]. Another mechanism by which TZDs increase insulin sensitivity is through increased adiponectin levels, resulting in elevated glucose uptake and fatty acid oxidation [95]. Increased beta oxidation and decreased de novo lipogenesis in the liver lead to decreased VLDL secretion and gluconeogenesis [96]. Multiple studies have reported an inverse relationship between increased circulating adiponectin and reduced hepatic steatosis [97]. Pioglitazone use has also improved liver function tests [97]. Pioglitazone are associated with side effects of peripheral/lower limb edema as well as weight gain due to increased subcutaneous fat, although visceral fat and intrahepatic fat are decreased, and there is no significant change in circulating leptin [95,97–99]. Risk of fractures is also a potential concern with use, particularly in women [100]. Phase 2 trials with the selective PPAR-γ modulator INT131 in T2D patients demonstrated reduced HbA1c or fasting plasma glucose compared to the placebo, along with less or no fluid retention and weight gain compared to TZDs [97,101,102]. INT131 also stimulates adiponectin, so it may benefit NASH patients, but more research is needed [97].

The 2018 AASLD practice guidance states that 30 mg of Pioglitazone daily improves liver histology in patients with biopsy-proven NASH with and without T2D, but it should only be used in patients with biopsy-proven NASH [92]. The more recent AACE guideline recommends TZD for T2D and biopsy-proven NASH; TZD should also be considered for cardiometabolic benefit in T2D and NAFLD and for diabetes treatment in patients who are highly likely to have NASH based on elevated plasma aminotransferase levels and noninvasive tests [94]. The AACE recommendations are Grade A recommendations with a best evidence level (BEL) 1 [99].

According to a meta-analysis of Pioglitazone therapy in NASH, pioglitazone's effects on liver histology in patients with NASH with or without diabetes have been shown in several randomized control studies, with outcomes of improved advanced fibrosis, fibrosis of any stage, and NASH resolution for up to 24 months of treatment [92]. These significant effects were not observed with rosiglitazone, another TZD [92]. However, a similar meta-analysis did not find a significant difference in fibrosis improvement between TZD and lifestyle changes versus lifestyle changes alone or with placebo [96,103]. The PIVENS trial (pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis) in adults with NASH and without diabetes demonstrated significant reductions in ALT, AST, GGT, hepatic steatosis, and lobular inflammation as well as significant NASH resolution compared with placebo but no improvement in fibrosis scores or significant rate of NASH histological improvement (defined by primary outcome measures) after 96 weeks of 30 mg/day of TDZ [97,104]. The UTHSCSA NASH Trial found a significant reduction in fibrosis only in patients with T2D after 18 months of 45 mg/day of TDZ [98,105]. Given the above findings, TDZs' effects on hepatic fibrosis warrant further investigation.

Two ongoing Phase 4 RCTs are investigating TDZ, empagliflozin (a SGLT2 inhibitor, discussed below), and combination therapy with both drugs in patients with T2D and NAFLD [106,107]. The AIM 2 Phase 2A RCT at the University of Florida is evaluating 15 mg/day pioglitazone in 138 patients with T2DM with biopsy-proven NASH for 72 weeks with a histological primary outcome measure and estimated study completion date of 29 February 2024.

9.2. GLP-1 Receptor Agonists (GLP-1 RAs)

Glucagon-like peptide-1 (GLP-1) is a gut-derived incretin hormone that is naturally released from intestinal L cells into the hepatic portal system after food consumption [108,109]. It has multifactorial effects on the brain, liver, muscle, heart, stomach, and pancreas, including the stimulation of glucose-dependent insulin secretion and reduction of glucagon secretion from the pancreas, as well as delayed gastric emptying [108]. Due to the short-lived endogenous effects of GLP-1, long-acting GLP-1 RAs were developed as a pharmacological treatment to mimic these effects [108]. In patients with T2D, GLP-1 RAs decrease HbA1c and risk of renal diseases and improve cardiovascular outcomes via reduction in systolic blood pressure, LDL, total cholesterol, and triglycerides [110]. GLP-1 RAs are also used for weight loss due to their ability to decrease appetite, increase satiety, delay gastric emptying, increase brown adipose tissue thermogenesis, and modulate gut-to-brain communication [110]. The GLP-1 RA Semaglutide was approved by the FDA in 2021 for obesity management after the Semaglutide Treatment Effect in People with Obesity (STEP) program demonstrated significant weight loss with Semaglutide 2.4 mg/weekly compared to placebo in patients with and without T2D [110–112]. The main adverse events reported with GLP-1 RA use are gastrointestinal complications including diarrhea, constipation, loss of appetite, nausea, vomiting, flatulence, and abdominal pain [113–115]. These dose-related symptoms typically resolve 1–2 weeks after dose titration [113].

GLP-1 RAs have the same AACE recommendations and ratings as TDZ for use in NAFLD [94]. They should be used in individuals with T2D and biopsy-proven NASH, and they should also be considered for treating diabetes when NASH is highly probable, as well as for cardiometabolic benefit in T2D and NAFLD [94]. RCTs with the GLP-1 RAs liraglutide or exenatide in NAFLD patients with or without T2D reported decreased serum alanine aminotransferase (significant in exenatide only), gamma-glutamyl transferase (GGT), and liver fat content, along with reduced body weight, waist circumference, fasting blood glucose, and HbA1c compared to control groups [113]. The D-LIFT trial concluded that dulaglutide, another GLP-1 RA, significantly decreased liver fat content and GGT in patients with T2D and NAFLD when given once weekly for 24 weeks (0.75 mg for 4 weeks, 1.5 mg for 20 weeks) [116]. A recent umbrella review found that GLP-1 RAs were the most effective pharmacological intervention for liver fat reduction when compared to the mixed control group; the effect size was larger than that of SGLT2 inhibitors and omega-3 fatty acids [117]. A 12-month RCT with T2D patients found a more significant reduction in liver fat, plasma triglyceride, and ALT with combined exenatide (GLP-1 RA) and pioglitazone therapy than with TDZ alone, suggesting the benefit of combination therapy with GLP-1 RAs [118].

In terms of liver histology, the LEAN phase 2 study performed liver biopsies after 48 weeks of treatment with 1.8 mg daily of liraglutide and found increased NASH resolution and decreased progression of fibrosis compared to the placebo but no significant improvement in Kleiner fibrosis stage or change in total NAFLD activity score [114]. The mechanism of NASH resolution by liraglutide may be due to its reduction of proinflammatory mediators and hepatic de novo lipogenesis, in addition to its improvement of weight, insulin resistance, and metabolic phenotype [108]. A larger 72-week RCT with Semaglutide in a mixed T2D and non-T2D patient population with biopsy-confirmed NASH and stage F1-F3 liver fibrosis found significantly greater NASH resolution without worsening of fibrosis compared to the placebo, with the largest improvement at 0.4 mg/daily [115]. However, improvement in fibrosis stage was not significantly higher in the treatment group compared to the placebo.

Tirzepatide is a dual GLP-1 RA/gastric inhibitory polypeptide (GIP, also known as glucose-dependent insulinotropic polypeptide) analog that was briefly mentioned in the AACE practice guideline as a new weight loss drug that is being tested for use in NASH [47]. Like GLP-1, GIP is an incretin hormone that stimulates glucose-dependent insulin secretion, resulting in an additive effect when combined with GLP-1 [112]. Other unique

effects of GIP include increased glucose-dependent glucagon secretion and triglyceride storage [112]. Tirzepatide was approved by the FDA for the treatment of T2D on May 13, 2022, shortly after the AACE guideline was published [113]. Tirzepatide's benefits in lowering hemoglobin A1c in patients with T2D have been demonstrated in the SURPASS trial series [113,114]. Other benefits of Tirzepatide include cardiovascular (CV) safety with potential for CV risk reduction, as well as weight loss in patients with obesity/overweight BMI, which is also being investigated in the SURMOUNT trial series [113,115]. CV risk with Tirzepatide versus dulaglutide is being assessed in the ongoing SURPASS-CVOT trial, which has an estimated study completion date of 17 October 2024 (NCT04255433).

As for its effects on NASH-related biomarkers, a phase 2 study of once weekly Tirzepatide (1, 5, 10, or 15 mg) in patients with T2D found significant reductions in keratin-18 (K-18) (10 mg) and procollagen III (pro-C3) (15 mg) and significantly increased adiponectin (10, 15 mg) compared with placebo [116]. ALT (10, 15 mg) was significantly reduced compared with dulaglutide [116]. The phase 3 SURPASS-3 trial demonstrated significant reductions in AST and ALT from baseline to 52 weeks in all three groups (5 mg, 10 mg, and 15 mg) treated with Tirzepatide compared to insulin Degludec [114]. A sub study of the SURPASS-3 trial (SURPASS-3 MRI) in patients with T2D and fatty liver index of at least 60 found a significantly greater reduction in liver fat content (measured by MRI-proton density fat fraction [MRI-PDFF]) and volume of visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (ASAT) at week 52 with Tirzepatide (5 mg, 10 mg, and 15 mg) compared to insulin Degludec [117]. Tirzepatide is being investigated in patients with NASH in the phase 2 SYNERGY-NASH trial, which has a primary outcome measure of percentage of participants with absence of NASH with no worsening of fibrosis on liver histology at 52 weeks (NCT04166773). Similar to GLP-1 RAs, the most frequent adverse events reported with Tirzepatide treatment were mild to moderate gastrointestinal symptoms such as nausea, diarrhea, vomiting and decreased appetite [114]. More studies on Tirzepatide's effects on NASH and fibrosis and its efficacy compared to GLP-1 RAs are needed to support its potential use for treating NAFLD.

9.3. Vitamin E

Vitamin E, a lipid-soluble micronutrient antioxidant, has been researched as a treatment for NASH due to the role of oxidative stress in the progression of NASH and hepatocellular injury [92,119,120]. Excess reactive oxygen species promote lipid peroxidation, leading to inflammation and fibrosis via increased cytokine production [120,121]. Compared to healthy controls, individuals with steatosis and metabolic syndrome have increased lipid peroxidation and serum lipid peroxides and decreased antioxidant levels [120]. In addition to its antioxidant effects, Vitamin E may improve NASH by inducing adiponectin expression, decreasing inflammatory signaling, and regulating macrophage polarization [120]. It also significantly reduces LDL-C and fasting blood glucose levels [121]. Despite these beneficial effects of Vitamin E, there are several safety concerns related to its use. One meta-analysis published in 2005 concluded that greater than 400 IU/day of Vitamin E increased all-cause mortality risk, but it was criticized for flaws in the analysis and later challenged by studies that did not find the same association [92,122–125]. Vitamin E has also been associated with increased risk of hemorrhagic stroke and prostate cancer, although the association with prostate cancer is modified by selenium status and variants in genes related to selenium and Vitamin E [92,126–129].

Vitamin E is considered first-line therapy for nondiabetic individuals with NASH, but it only significantly improves liver histology in patients with both T2D and NASH when combined with TDZ [130,131]. The 2018 AASLD practice guidance states that 800 IU/day of Vitamin E improves liver histology in nondiabetic adults with biopsy-proven NASH and thus can be considered for treatment of these individuals after discussing risks and benefits with each patient [92]. These recommendations are supported by the 2022 AACE guideline, which does not recommend Vitamin E for advanced fibrosis (Grade B; High Strength of Evidence; BEL 1; downgraded due to risk/benefit) [94].

While Vitamin E has been shown to improve steatohepatitis and aminotransferase levels in nondiabetic patients with biopsy-proven NASH, it has only shown modest benefit in T2D patients with mixed results and lack of fibrosis improvement [92,94,104,130]. Further, trials with Vitamin E have been difficult to evaluate due to varying study criteria, unclear formulations, use of other drugs, and limited use of histological data [92]. A 2022 umbrella review of NAFLD treatments found that Vitamin E reduced liver fat (effect size measured by standardized mean difference [SMD]) [SMD = 0.574, $p < 0.0001$], fibrosis [SMD = 0.302, $p = 0.02$], and inflammation [SMD = 0.378, $p = 0.004$] [110]. The PIVENS trial in adults with NASH and without diabetes demonstrated that 96 weeks of 800 IU/day of Vitamin E significantly improved NAFLD activity scores and hepatocyte ballooning scores compared to the placebo but showed no improvement in fibrosis scores or significant NASH resolution [97]. An 18-month RCT in patients with T2D and NASH (VA NASH) showed no significant change with Vitamin E monotherapy (400 IU b.i.d.) in the primary histological outcome, but liver histology significantly improved with combination therapy with 45 mg/day of Pioglitazone [132]. Both the PIVENS and VA NASH trials found improved NASH resolution in the Vitamin E group compared to the placebo, but statistical significance ($p < 0.025$) was not achieved [97,132]. However, a meta-analysis of off-label therapies for NAFLD concluded that Vitamin E significantly improved NASH resolution (3 studies, 263 patients, OR = 2.27 [95% CI: 1.54, 3.35] [133]. Finally, diabetic and non-diabetic NASH patients with bridging fibrosis or cirrhosis who took 800 IU/day of Vitamin E for ≥2 years had significantly higher adjusted transplant-free survival (78% versus 49%, $p < 0.01$) and significantly lower rates of hepatic decompensation (37% versus 62%, $p = 0.04$) [134]. More research is necessary to evaluate the benefits of Vitamin E in NASH patients with diabetes and/or cirrhosis.

9.4. Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i)

SGLT2 inhibitors (SGLT2i) primarily block SGLT2-mediated glucose reabsorption in the kidneys, resulting in glycosuria, glycemic control, and weight loss [132]. Though SGLT2 is also found in the liver, the hepatoprotective effect of SGLT2i are mostly indirect [132]. SGLT2i increases the glucagon/insulin ratio, which contributes to a transition from carbohydrate to lipid metabolism that results in hepatic glycogenolysis and gluconeogenesis, reduction in hepatic triglycerides, stimulation of fatty acid oxidation, and eventual hepatic ketogenesis [133]. Other potential mechanisms of SGLT2i-mediated improvement of NAFLD include lipolysis, reduced glucose oxidation and insulin resistance, and decreased stimulation of carbohydrate response element-binding protein [133]. Among antidiabetic agents, SGLT2i are the most effective at increasing HDL-C and decreasing LDL-C in individuals with NAFLD and T2D, according to a meta-analysis of RCTs [134]. SGLT2i may increase the risk of genital and urinary tract infections, volume depletion, and diabetic ketoacidosis, but they are protective against acute kidney injury and hyperkalemia [135].

As previously stated, the AACE Clinical Practice Guideline for NAFLD recommends SGLT2 inhibitors such as dapagliflozin, empagliflozin, and canagliflozin as adjunctive pharmacotherapy for cardiometabolic benefit in patients with T2D and NAFLD but not for treatment of steatohepatitis (Grade A; High Strength of Evidence; BEL 1) [94]. SGLT2i were not mentioned in the earlier AASLD guidance [92]. They are FDA-approved for treating T2D and heart failure and may be useful in NAFLD due to glycosuria and reduction of hepatic steatosis, which has been demonstrated in several RCTs [94,134]. According to a 2022 umbrella review of NAFLD treatments, SGLT2i were the most effective intervention for reducing GGT and body weight compared with the mixed control group, and like GLP-1 RAs, they improve anthropometric parameters and reduce liver fat [117]. Reduction of LFTs and hepatic steatosis has been demonstrated with dapagliflozin, canagliflozin, empagliflozin, ipragliflozin, Luseogliflozin, and tofogliflozin, with the first three drugs decreasing ALT levels independent of weight loss [132]. A meta-analysis of twelve RCTs testing SGLT2i for treatment of NAFLD (11/12 studies with T2D patients)

found significantly decreased ALT (but not AST), GGT, and absolute percentage of liver fat content measured with magnetic resonance-based techniques compared to placebo/reference therapy [136].

Few studies have evaluated liver histological endpoints after treatment with SGLT2i [94,132,133,136]. One RCT in patients with T2D and NAFLD found that 50 mg/day of ipragliflozin for 72 weeks significantly improved hepatocellular ballooning, NASH resolution, and hepatic fibrosis but not steatosis or inflammation compared to the control group [137]. Liver biopsies were also performed in two small studies evaluating canagliflozin and empagliflozin, both involving a 24-week treatment of nine patients with T2D and NAFLD or NASH [138,139]. The canagliflozin study reported decreased steatosis (7/9 patients), lobular inflammation (3/9), ballooning (2/9), and fibrosis stage (3/9) and histological improvement in all nine patients [140]. The empagliflozin study reported reductions in steatosis, ballooning, and fibrosis that were significantly greater than a historical placebo [141]. Larger RCTs are needed to corroborate these findings.

Ongoing RCTs with histological primary outcome measures include the Phase 3 Dapagliflozin Efficacy and Action in NASH (DEAN) study and the Phase 4 Combined Active Treatment in Type 2 Diabetes with NASH (COMBATT2NASH) study [133,138,142].

9.5. Other Pharmacological Therapies

The 2022 umbrella review of NAFLD treatments also noted that Huo Xue Hua Yu (HXHY) therapy, bicyclol, and silymarin improved liver function compared with the placebo, with HXHY being the most effective pharmacological intervention based on one meta-analysis [117]. However, these treatments were not mentioned in the most recent AASLD guidance or AACE guideline for NAFLD, suggesting that more research is needed to support their efficacy and safety [47,51].

Three other drugs, Elafibranor, Cenicriviroc, and Selonsertib, were previously investigated for use in patients with NASH, but all three Phase 3 trials were terminated due to lack of efficacy [139,143]. The farnesoid X receptor agonist Obeticholic acid (OCA) was not included in the umbrella review due to a lack of clinical trials and meta-analyses, and the AASLD guidance recommended that it should not be used off-label to treat NASH [92,117]. Results from the FLINT and REGENERATE trials indicated that 25 mg daily of OCA significantly improved fibrosis but did not significantly increase NASH resolution compared to the placebo [92,144,145]. Further, liver enzymes and hepatocellular ballooning were reduced, but there is conflicting data for steatosis and lobular inflammation [144,145]. OCA use is associated with pruritus and increased LDL-C, and cases of death and serious liver injury were reported in patients taking inappropriate doses of OCA for primary biliary cholangitis [144–146]. The Phase 3 REVERSE trial evaluating fibrosis improvement with OCA use in patients with compensated cirrhosis due to NASH is currently ongoing.

Table 1. Summary of pharmacological therapies recommended for NAFLD/NASH or under investigation for use in NAFLD/NASH. Results are relative to placebo/control group (varied).

	Mechanism of Action	Effect on NAFLD
* Pioglitazone	Improved insulin sensitivity via PPAR-γ activation in liver, muscle, and adipose tissues and increased adiponectin levels [89]	Reduced liver enzymes [97,133], steatosis [97,147], lobular inflammation [97,147], hepatocellular ballooning [96,97,147]; improved NASH resolution [92]; mixed evidence for fibrosis (possible improvement in T2D patients) [92,96–98]
* GLP-1 receptor agonists (GLP-1 RA)	Mimics effects of gut-derived incretin hormone GLP-1 (released from intestinal L cells into the hepatic portal system after food consumption): stimulation of	Reduced liver enzymes [106,108,109], steatosis [106,109] Semaglutide: reduced lobular inflammation [108]

	glucose-dependent insulin secretion and reduction of glucagon secretion from the pancreas; delayed gastric emptying [101,102]	Semaglutide & liraglutide: improved hepatocellular ballooning and NASH resolution; no significant improvement in fibrosis [107,108]
Tirzepatide	Dual GLP-1/GIP RA [88]: same as GLP-1 RA (above) plus GIP-mediated insulin secretion and unique effects of GIP (increased glucose-dependent glucagon secretion and triglyceride storage) [112]	Reduced hepatic fibrosis biomarkers [116], liver enzymes [114,116], liver fat content [117]
* Vitamin E	Lipid-soluble micronutrient antioxidant; induces adiponectin expression, decreases inflammatory signaling, regulates macrophage polarization [119]	Reduced liver enzymes [97,121,133], steatosis, lobular inflammation, hepatocellular ballooning [121]; conflicting data for fibrosis and NASH resolution [97,132] (improved in some meta-analyses [121,133])
* Sodium-glucose cotransporter 2 inhibitors (SGLT2i)	Block SGLT2-mediated glucose reabsorption in the kidneys, resulting in glycosuria, glycemic control, and weight loss [136]	Reduced liver enzymes [110], steatosis [139,142] (not ipragliflozin [142]), hepatocellular ballooning; improved fibrosis and NASH resolution; no improvement in lobular inflammation [139,142]
Obeticholic acid	Farnesoid X receptor (FXR) agonist; FXR regulates bile acid conjugation and increases expression of FGF-19 on ileal enterocytes with downstream effects of repressed gluconeogenesis and bile acid synthesis via the classical pathway and stimulation of hepatic protein and glycogen synthesis [146]	Reduced liver enzymes, hepatocellular ballooning, fibrosis; conflicting data for steatosis and lobular inflammation; no significant improvement in NASH resolution [144,145]

* Included in 2022 AACE recommendation [47].

10. Conclusions

While NAFLD already affects 25% of adults globally, it is the fastest growing cause of liver mortality. NAFLD-associated prevalence, morbidity, and mortality are expected to increase over the coming years as life expectancy, obesity, diabetes, and metabolic syndrome continue to rise. Subsequent complications including chronic inflammation, cardiovascular events, hepatic fibrosis, and CKD can cause significant concern in afflicted patients. Unfortunately, direct pharmacological treatment options for NAFLD remain elusive, with current clinical guidelines solely recommending supportive management of comorbidities and cardiometabolic disease. Hence, NAFLD prevention or early detection are key points of focus, although routine screening for the general population or high-risk individuals is not advisable. Utilizing the newly proposed MAFLD definition may offer a more comprehensive approach to diagnosis patients with this disease pathology. Accordingly, understanding risk factors and associated prevention measures that can inform public health strategies and patient counseling for those at high risk is crucial. This review provides a current understanding of the NAFLD pathogenesis, epidemiology, and management landscape, along with updated strategies for patient-provider partnership, which may encourage health-seeking behaviors and risk mitigation strategies to reduce NAFLD prevalence and complications.

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