Understanding the Burden of Nonalcoholic Fatty Liver Disease: Time for Action

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The prevalence of nonalcoholic fatty liver disease (NAFLD) in the United States is 38%, having increased by 50% within the past 3 decades. The estimated NAFLD prevalence among people with type 2 diabetes is 55–70%. The presence of type 2 diabetes is associated with a higher likelihood of progression of NAFLD to fibrosis development, liver transplant, and death. Cardiovascular disease is the main cause of mortality among people with NAFLD, and the risk of death is significantly higher in people with both NAFLD and type 2 diabetes. NAFLD carries high patient and economic burdens but low awareness among both the general public and health care providers. This article reviews the epidemiology of NAFLD and discusses the need for appropriate risk stratification, referral for specialty care, management of cardiometabolic risk factors, and treatment of the disease. The authors present a call to action to raise awareness of NAFLD and address its increasing burden in a systematic and efficient manner.

Nonalcoholic fatty liver disease (NAFLD) was first recognized in the 1980s, when its natural history was not entirely clear but its histological features were similar to alcoholic fatty liver disease. The main differentiating characteristics were the lack of excessive alcohol consumption and its close association with metabolic comorbidities, including type 2 diabetes, high cholesterol, hypertension, and obesity (1). In the past 4 decades, an enormous amount of research has been undertaken, providing a better understanding of this important form of chronic liver disease.

However, before continuing our discussion, it is important to acknowledge that a new name for NAFLD has been proposed. The proposed new term is "metabolic dysfunction–associated steatotic liver disease" (MASLD), which would fall under the broader category of steatotic liver disease. The name change was recommended as a way to increase awareness of the disease by decreasing perceived stigma associated with the terms "nonalcoholic" and "fatty liver." Additionally, the "nonalcoholic" component of NAFLD was considered inappropriate when this terminology was used to describe the disease if it occurs in children or in individuals from countries or cultures in which alcohol consumption is prohibited. Given how recently the change to MASLD was proposed, additional research may be needed to determine whether MASLD is simply NAFLD by a different name or whether it is indicative of a different form of the disease. For now, the American Diabetes Association (ADA) has not adopted MASLD. Therefore, for the purpose of this article, we continue to use the term "nonalcoholic fatty liver disease" (2–4).

Our current understanding is that NAFLD is not only a complex liver disease but also part of a multisystemic disease associated with metabolic abnormalities (5–7). In this context, type 2 diabetes has a reciprocal relationship with NAFLD through which the prevalence of NAFLD is higher among people with type 2 diabetes and the incidence of type 2 diabetes is higher in people with NAFLD. In fact, the incidence of NAFLD among individuals with type 2 diabetes is estimated to be 65 cases per 1,000 person-years compared with 44 cases per 1,000 person-years among those without diabetes (8). Furthermore, the incidence of NAFLD is three times higher in people with overweight or obesity compared with those of normal weight (5,7,9–12).

Cardiovascular disease (CVD) is the leading cause of death in both people with NAFLD and those with type 2 diabetes. In people with NAFLD, extrahepatic malignancies and liver-related complications are the other top causes of death (1,5,11,13,14).

Given its close association, NAFLD has been considered the hepatic manifestation of metabolic syndrome, although hepatic steatosis in NAFLD seems to arise more from the liver's lipid toxicity, which results from the presence of insulin

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resistance and/or type 2 diabetes (1,5,6). It has also been shown that the increasing components of metabolic abnormalities can promote more rapid progression of liver disease, leading to a higher risk of mortality (15). Nevertheless, the presence of NAFLD has been shown to be an independent risk factor for increased mortality (16).

Although visceral obesity is its most important risk factor, NAFLD can be present among individuals of normal weight (sometimes referred to as "lean NAFLD") (17). Nevertheless, individuals with lean NAFLD still have underlying metabolic abnormalities such as higher rates of insulin resistance and/or type 2 diabetes (17). In fact, a large number of these individuals who are considered lean based on their BMI still have an abnormal waist circumference, suggesting visceral obesity. In this context, visceral adiposity can lead to hepatic steatosis and may be a driver of adverse outcomes in these individuals (17).

NAFLD can lead to cirrhosis, hepatocellular carcinoma (HCC), liver transplantation, and death. From the spectrum of NAFLD, patients with nonalcoholic steatohepatitis (NASH; also known as metabolic dysfunction–associated steatohepatitis) are predisposed to progressive liver disease. In this context, ~20% of people with NASH may progress to end-stage liver disease. The presence of hepatic fibrosis, especially in the setting of type 2 diabetes, can be an important predictor of adverse outcomes. In fact, the presence of stage 2 fibrosis is a predictor of mortality (i.e., high-risk NAFLD) (13,18–24). It is important to recognize that NAFLD can progress directly to HCC without first transitioning into cirrhosis. However, the rate of HCC is significantly higher among people with cirrhosis than those without cirrhosis. Therefore, screening for NAFLD-related HCC is reserved only for people with cirrhosis (25–27).

In the past decade, NAFLD and NASH have been recognized as the leading indications for liver transplant in the United States. In fact, NASH is the top indication for women, individuals >55 years of age, and those with diabetes (28–30). Nevertheless, individuals with NAFLD/NASH have added challenges both pre- and post-transplantation given their high rate of comorbidities (e.g., obesity, diabetes, and hypertension), which not only extends their waitlist time, but also increases waitlist mortality (31). In addition, people with NASH are at higher risk for developing post-transplant diabetes, chronic kidney disease, myocardial infarction, and recurrence of NAFLD. Therefore, an extensive work-up that includes cardiology, bariatric surgery, nephrology, and nutrition consultations is needed, and strict follow-up post-transplant, with an emphasis on diet and exercise, is required, with close monitoring for post-transplant immunosuppression (31).

The following sections will present information on the burden, natural history, and outcomes of NAFLD.

Global Epidemiology

The latest estimates suggest that the period prevalence of NAFLD (2009–2019) among adults was between 23 and 32% (32,33). The wide variation of prevalence rates is the result of different measures being used to estimate prevalence. The lower rate of 23% comes from the Global Burden of Disease 2019 report, which was inclusive of 204 countries around the world (32). The higher prevalence rate is from the most recent meta-analysis (33). In fact, the prevalence of NAFLD from studies published between 2016 and 2019 was 38%, representing an increase of >50% within the past 3 decades (33). The global prevalence of NASH, which is the more progressive form of NAFLD, is between 5 and 7%, but among people with type 2 diabetes, the estimated prevalence is more than seven times higher, at 37%, and the estimated prevalence of advanced fibrosis is 17% (33,34). Additionally, the overall pooled global incidence of NAFLD for the 1994–2014 period was reported to be 48.89 per 1,000 patient-years; however, for only the 2010–2014 survey period, the pooled incidence rate was 59.11 per 1,000 patient-years (95% CI 39.64–87.26 per 1,000 patient-years), an increase of 58% from the earliest time period of 1994–2006 (33).

NAFLD is also more prevalent in males than females, but NASH seems to be more prevalent in postmenopausal females (35). Although NAFLD has been considered a disease of older adults, given the epidemics of obesity and type 2 diabetes among youth, the prevalence of NAFLD in children and young adults (ages 6–29 years) has been reported to range from 10 to 20%, representing an increase of ~40% since the early 2000s. Here, too, NAFLD seems to be more prevalent among males and is driven primarily by obesity and hypertension (36).

Natural History

NAFLD is a complex liver disease that can progress and regress, hindering a full appreciation of its natural history (10). Nonetheless, Figure 1 presents the natural history of NAFLD, including the impact of metabolic comorbidities. Other factors can also influence the development and progression of NAFLD, including a number of genes (e.g., *PNPLA*, *TMSF2*, *MBOAT7*, *GCKR*, and *HSD17B13*) as well as environmental factors (e.g., lack of access to affordable nutrient-dense foods and/or safe areas to perform physical activity and areas high in air pollution), gut dysbiosis, and race/ethnicity (5–7,10).

In most cases, NAFLD develops when there are alterations in glucose and lipid metabolism, as well as in the presence of

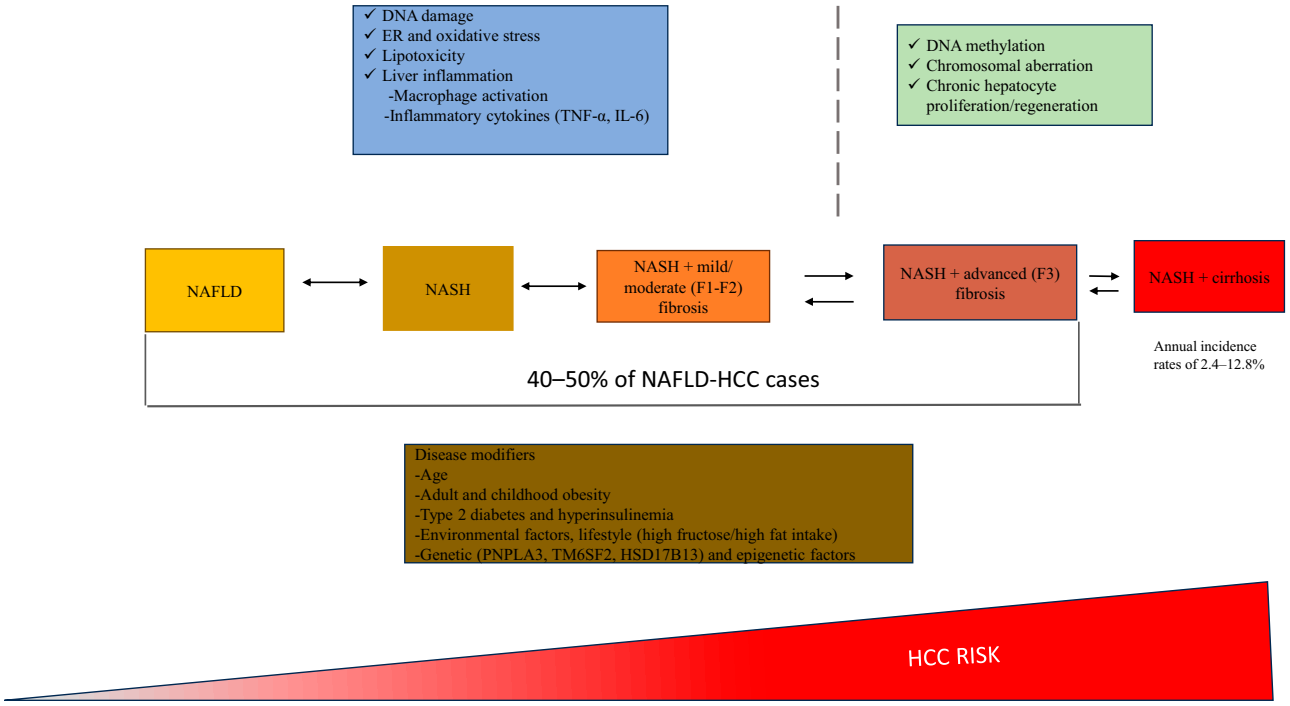

FIGURE 1 Natural history of NAFLD. F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α. Reprinted with permission from Pais R, Maurel T. Natural history of NAFLD. J Clin Med 2021;10:1161.

insulin resistance (IR)—hence its close association with type 2 diabetes. Specifically, individuals with NAFLD and type 2 diabetes are insulin resistant at the level of the muscle, liver, and adipose tissue. These states contribute to ectopic fat accumulation, worsening of IR, lipotoxicity, impaired β-cell function, and excess free fatty acids (FFAs). The excess FFAs cause inflammation, mitochondrial dysfunction, increased oxidative stress, and uncoupled oxidative phosphorylation, which then activates a fibrogenic response in hepatic cells that can promote disease progression to NASH and cirrhosis. Chronic hyperglycemia (glucotoxicity), if present, can also add to hepatocyte dysfunction and death. Because lipotoxicity and glucotoxicity are generally both present, the combination leads to further IR and impaired insulin secretion in type 2 diabetes (Figure 2) (37,38).

IR and type 2 diabetes have also been shown to be associated with accelerated disease progression (38,39). In fact, a recent U.S. natural history study involving >5,000 community members with NAFLD (median follow-up of 6.4 years [range 1–23 years]) found that the presence of type 2 diabetes increased the risk of progression to cirrhosis by three times (hazard ratio 3.0, P = 0.003) (40). This study also indicated that people with NAFLD spent roughly 15 years in an NAFLD state in which 14% died of another cause and 3% progressed to cirrhosis, at which point another 8% died within the next 2 years. Individuals who entered the study with a Fibrosis-4 (FIB-4) score >1.3 at the time of diagnosis were at the highest risk of disease progression. The investigators concluded that, among adults with compensated NASH cirrhosis, the risk of progression to decompensation or death was 10% per year, and, among adults who incurred a decompensation event, the risk of progression to liver death was 32% per year. In this context, the overall probability of death was 22%, of which 26% was from cancer, 20% was from CVD, and 6% was liver-related. This risk of death was higher than the expected rate of death for a similar-aged cohort (40).

Although rates varied, these results were similar to other recently published natural history studies in which CVD and cancer were the leading causes of death (41–46). Studies have suggested that the most likely underlying mechanisms through which NAFLD increases the risk of CVD and its complications are exacerbation of hepatic and systemic IR, promotion of atherogenic dyslipidemia, induction of hypertension, and triggering of proatherogenic, procoagulant, and proinflammatory mediators (45,46).

Given the proinflammatory state associated with NAFLD, individuals with NAFLD had a higher mortality rate during the coronavirus disease 2019 (COVID-19) pandemic compared with those without NAFLD. In a single-center study of almost 5,000 inpatients with COVID-19, those with

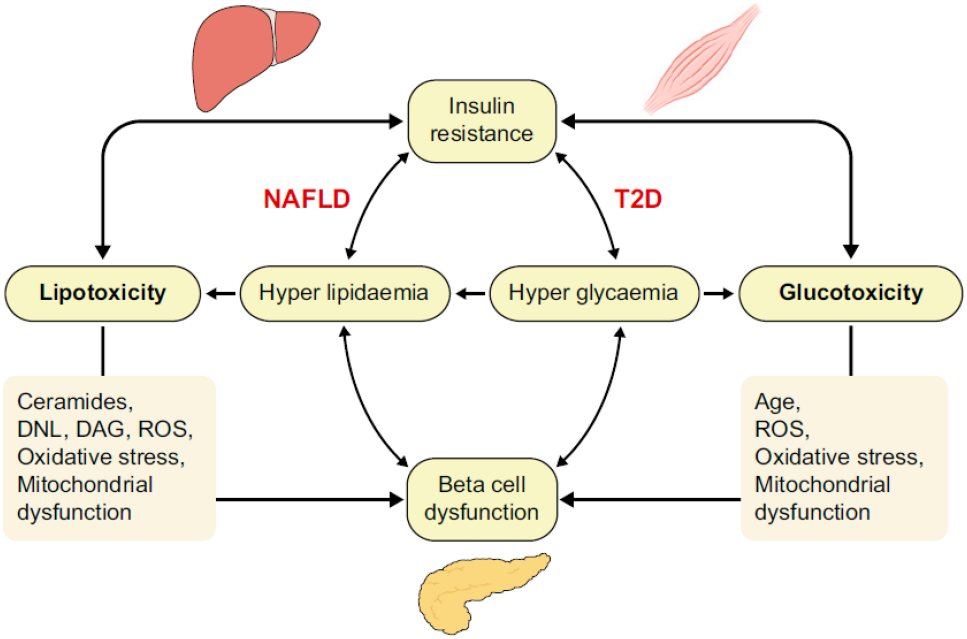

FIGURE 2 Relationship between lipotoxicity and glucotoxicity in the development of NAFLD. DAG, diacylglycerol; DNL, de novo lipogenesis; ROS, reactive oxygen species; T2D, type 2 diabetes. Reprinted with permission from Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: mechanisms and treatment options. JHEP Rep 2019;1:312–328.

NAFLD were sicker on admission (i.e., with hypoxemia and febrile), requiring more hospital resources. Researchers determined that the independent predictors of mortality included being at high risk for fibrosis, having multiple comorbidities, being older, and having morbid obesity (47). Interestingly, in a gene-based study, people with leukemia, NAFLD, type 2 diabetes, psoriasis, or pulmonary arterial hypertension were at higher risk for adverse outcomes of COVID-19 (48).

Finally, given the association of sarcopenia with type 2 diabetes and obesity, the role of sarcopenia in people with NAFLD is now being explored (49–52). Although sarcopenia, defined as the loss of muscle mass and strength generally associated with the elderly, is highly prevalent in people with end-stage liver disease, the prevalence of noncirrhotic sarcopenia is high among those with NAFLD. The exact pathophysiological mechanisms explaining sarcopenia's impact on NAFLD outcomes is unclear; however, the common features of both sarcopenia and NAFLD (i.e., IR, low vitamin D levels, inflammatory myokines, and physical inactivity) lead to increased proteolysis, myosteatosis, increased oxidative stress, and decreased uptake of glucose in the muscle, in turn leading to poorer outcomes (49–52). In fact, the presence of sarcopenia in people with NAFLD is linked with an almost twofold higher risk for all-cause mortality, a threefold higher risk for cardiac-related mortality, a twofold higher risk for cancer-related mortality, and an 11% higher risk for significant hepatic fibrosis. Indeed, the interaction of NAFLD and sarcopenia accounted for 55% of significant hepatic fibrosis cases (52). In this context, assessment for sarcopenia and NAFLD in people with type 2 diabetes is important for its prognostic and therapeutic implications.

Patient-Reported Outcomes, Economic Burden, and Awareness

In addition to adverse clinical outcomes, NAFLD and NASH are also associated with impairment of patient-reported outcomes (PROs) such as health-related quality of life and work productivity, which can further worsen with progression to advanced liver disease (53–56). In addition, people with NAFLD report high levels of fatigue and have higher rates of anxiety and depression compared with the general population (56,57). These factors most likely help to explain patient reports of low physical activity, lower physical functioning scores, and decreased work productivity (57,58).

Numerous economic studies from around the world have found that there is a tremendous economic burden associated with NAFLD and NASH, especially when advanced liver disease is present (12,59–64). Additionally, the presence of type 2 diabetes, CVD, and renal impairment can increase costs substantially (12,61). Furthermore, costs increase with advanced liver disease and the requirement for liver transplantation, contributing to approximate overall lifetime costs of NASH in the United States of $223 billion in 2017 (60). These

costs were most likely underestimated given that they are not inclusive of lost worker productivity, an important direct cost of NAFLD. Another study suggested that NAFLD among people with type 2 diabetes in the United States can lead to a $55.8 billion 20-year cost, 65,000 liver transplants, 1.37 million cardiovascular-related deaths, and 812,000 liver-related deaths (12).

Despite the clinical, PRO, and economic burdens of NALFD, awareness of the disease remains low, not only among the general public, but also among health care providers (65,66). Addressing this gap in awareness is especially important for those involved in the care of people with type 2 diabetes who see a large number of patients at risk for progressive NAFLD.

Reasons for the low awareness of NAFLD may include a lack of appreciation of the NAFLD disease burden, as well as a perception that there is no NASH-specific treatment available. Although there are no approved pharmacological therapies for NASH with fibrosis, there are a number of interventions that can be implemented to either prevent the development of NAFLD or treat NAFLD and stop its progression to more advanced stages. These include lifestyle modification and highly effective treatments approved for the treatment of type 2 diabetes and obesity, the two most important drivers of the NAFLD-related disease burden (67).

Diagnosis and Risk Stratification of High-Risk NAFLD

Although lifestyle modification can be recommended to all people with NAFLD, specific treatment and clinical management should be recommended to those considered to have high-risk NAFLD (stage F2 or higher) (41,67).

Historically, liver biopsy was used to determine the stage of fibrosis. Given the shortcoming of liver biopsy, the use of noninvasive tests has become increasingly popular (68). The use of noninvasive tests is especially important in primary care and endocrinology practices where a large number of patients at risk for progressive NAFLD (those with type 2 diabetes or other components of metabolic syndrome) are treated. In this context, the presence of fibrosis can be determined with the use of simple serum markers such as the FIB-4 score, which can be followed by the Enhanced Liver Fibrosis assessment or vibration-controlled transient elastography to assess liver stiffness. These tests have been used to develop practical algorithms that can be implemented easily in the clinic to determine whether patients require referral to a specialist (gastroenterology or hepatology) or whether they can be managed in the primary care setting. A full discussion of these algorithms and tests is beyond the scope of this article. However, the American Association of Clinical Endocrinology and the ADA, as well as others, have developed appropriate guidelines to help clinicians in these settings (69–71).

Treatment

Treatment of NAFLD is summarized in Figure 3. The primary treatment goal should be to prevent the development of NAFLD by maintaining a healthy weight through the use of diet (the most commonly recognized eating pattern is one that is based on the components of the Mediterranean diet) and physical activity performed at a moderate effort for at least 150 minutes/week (67). These efforts can lower the risk

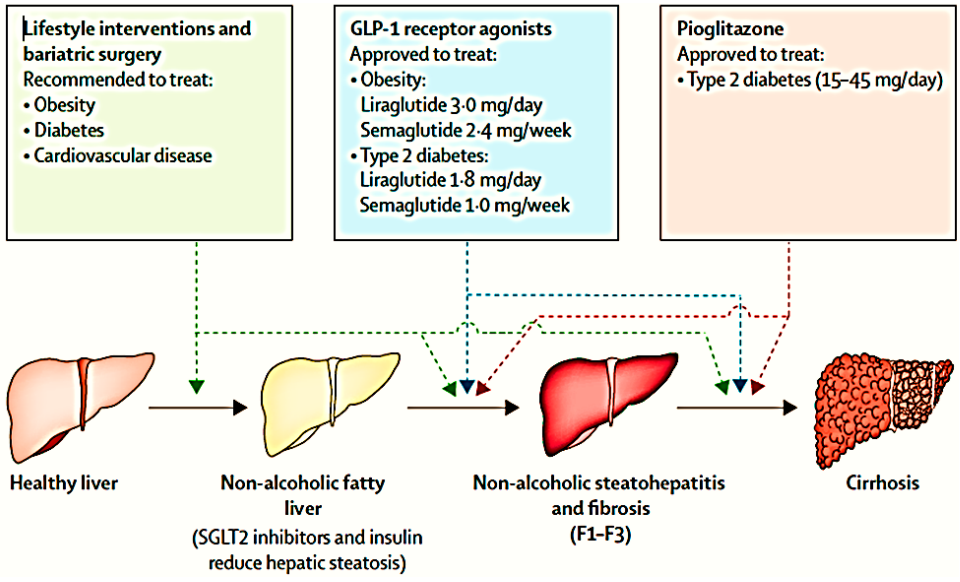

FIGURE 3 Treatment of NAFLD. F1, portal fibrosis without septa; F3, numerous septa without cirrhosis. Reprinted with permission from ref. 1.

of IR, type 2 diabetes, and other metabolic comorbidities (72). However, there are barriers to meeting these goals, including limited access to healthy, culturally appropriate food and a lack of safe spaces in which to perform physical activity (73–75). Therefore, efforts must continue to encourage policymakers to design and reconfigure neighborhoods and public spaces to meet these needs.

Diet

Management of NAFLD requires recognition of both modifiable factors (i.e., diet, exercise, and metabolic risk factors) and nonmodifiable factors (i.e., genetics, age, ethnicity, and sex) associated with progressive liver disease. The majority of people with NAFLD report having an unhealthy eating pattern and a lack of physical activity (76). Therefore, the first step in management of people with NAFLD is to address the modifiable risk factors with the goal of achieving a 5–10% weight loss (or 3–5% for those without overweight or obesity), which can reduce steatosis at the lower percentage of weight loss and reverse fibrosis at the higher percentage (77).

The eating pattern most commonly recognized as providing weight loss and delaying the need for antidiabetic medications is the green-Mediterranean diet, which is a lower-carbohydrate version of the Mediterranean diet that includes plenty of vegetables, poultry, and fish rather than lamb and beef, 28 g/day of walnuts, and other phenol-rich foods such as green tea and Mankai (although availability of this green aquatic plant varies by country) (78,79). For some people, benefits can be realized from other diets (e.g., low-calorie ketogenic, high-protein, anti-inflammatory, and/or whole-grain diets), as long as the principles of healthy eating are followed (79–82). Avoidance of advanced glycation end products, which are generated from high-fat and high-sugar foods, high heat–processed food and beverages, and processed and well-done red meat, is also encouraged (80–82). The consumption of three or more cups of coffee is also recommended because of its antifibrotic and antioxidant properties in the liver, while avoiding sugar-sweetened beverages, fructose-laden products, and ultra-processed foods (e.g., foods that contain hydrolyzed proteins, fructose, high-fructose corn syrup, hydrogenated oil, and cosmetic additives such as flavorings, coloring agents, and emulsifiers) (83–86).

Physical Activity

It is known that physical activity improves both hepatic and peripheral insulin sensitivity and, through associated weight loss, decreases the proinflammatory and oxidative stress markers associated with NASH while improving liver enzymes and decreasing intrahepatic lipids and potentially improving the gut microbiome (87,88). However, the majority of people with NAFLD are sedentary, and those with both NAFLD and type 2 diabetes are the most sedentary and least physically active (76). As a result, individuals with NAFLD and IR or type 2 diabetes who maintain even a short-term reduction in physical activity as assessed by step count have demonstrated deleterious effects on insulin sensitivity and hepatic steatosis (89).

Thus, engagement in physical activity is imperative for people with NAFLD and type 2 diabetes. As previously mentioned, the current goal is to engage in moderate physical activity for at least 150 minutes/week (67,90). Moderate physical activity is defined as any activity during which a person finds it somewhat difficult to carry on a conversation, and vigorous activity is any activity during which a person finds it challenging to carry on conversation (91,92). Another way to help people understand what moderate activity is involves giving a few examples, such as brisk walking, water aerobics, riding a bike on level ground or with few hills, playing doubles tennis, or pushing a lawn mower (93). The addition of resistance training has also been shown to promote a better environment for liver and cardiac health while also addressing the presence of sarcopenia (94).

Therefore, among this population, incorporating physical activity is imperative. However, people may face many barriers to incorporating exercise into their daily routine, including deconditioning resulting from sedentary behavior and the presence of more advanced liver disease or CVD. For this reason, physical activity programs should be individualized and overseen by a professional and should include an accountability component and obtainable goals to help ensure success (95,96). Although Web-based programs are showing promise, especially for people who do not have access to a workout facility, there is no large-study current research on the outcomes of these programs for people with NAFLD and type 2 diabetes, so, at this time, these Web-based programs cannot be recommended for this population (97,98).

Bariatric Surgery

The use of bariatric surgery has also been shown to be beneficial for those who fail to lose weight or maintain a weight loss through lifestyle interventions (99–102). In general, the use of bariatric surgery to lose weight has been found not only to translate into the reversal of hepatic steatosis, NASH, and fibrosis, but also to result in improved management or resolution of type 2 diabetes, dyslipidemia, and hypertension, along with reductions in cardiovascular morbidity or mortality (99–102).

Bariatric surgery procedures fall into two categories: purely restrictive (e.g., laparoscopic adjustable gastric banding and vertical sleeve gastrectomy) or a combination of restrictive and malabsorptive (Roux-en-Y gastric bypass). However, to date, there are no guidelines for the use of bariatric surgery

in the treatment of people with NAFLD or those with NAFLD and type 2 diabetes.

This lack of guidelines is most likely due to the inconsistency of results reported from cross-sectional or retrospective studies, despite the positive outcomes noted (99–102). As a result, a new clinical trial (ClinicalTrials.gov identifier NCT04366999) was registered in April 2020 and is now underway to investigate the effect of bariatric surgery on NAFLD remission in people with obesity (102). The trial will include ~150 people with obesity who will undergo one of the following surgical procedures: sleeve gastrectomy, Roux-en-Y gastric bypass, or one anastomosis gastric bypass. Prospective follow-up will occur at 3 months, 6 months, 1 year, and 2 years after surgery. At the end of the trial, a more definite approach to bariatric surgery in the treatment paradigm for people with NAFLD may be forthcoming (103).

Pharmaceutical Treatment

Management of the metabolic comorbidities associated with NAFLD is also of great importance. Such intervention could potentially help by reversing NAFLD and lowering the risk for cardiovascular-related mortality (104–107). Therefore, identifying, evaluating, and treating diabetes, hypertension, coronary artery disease, and high cholesterol are all essential in the care of people with NAFLD. In this context, the use of statins is considered safe for all patients with NAFLD except for those with decompensated cirrhosis (104–107).

More specifically, several medications used for the treatment of diabetes have shown promise in managing liver disease, including the thiazolidinedione pioglitazone, glucagon-like peptide 1 (GLP-1) receptor agonists, and sodium–glucose cotransporter 2 (SGLT2) inhibitors (108–112). GLP-1 receptor agonists are promising in that, in addition to improving glycemia, they also promote weight loss, improve upregulations of fatty acid metabolism and insulin signaling pathways, improve hepatic steatosis and histological components of NASH if present, and provide good cardiovascular protection; however, long-term studies are still needed. Although SGLT2 inhibitors are also promising for improving hepatic steatosis, liver enzyme levels, BMI, and inflammatory markers, additional studies are needed to assess their safety and side effects (e.g., hypoglycemia, ketoacidosis, and urinary tract and genital infections) (108–111). Pioglitazone has shown promise for yielding histological improvement in people with NAFLD/NASH and type 2 diabetes; however, its use requires familiarity with potential side effects (112). Additionally, there are ongoing clinical trials for medications that can either resolve NASH without furthering fibrosis, reduce fibrosis without worsening NASH, or both (113–115). At this time, none of these agents have been approved, although several are being considered for approval. In this context, the initial surrogate end points must be confirmed with long-term outcomes data (116).

Nonetheless, interventions are currently available to help prevent or reverse NAFLD, and all stakeholders will need to work together to meet the growing burden of this disease, as summarized in Figure 4.

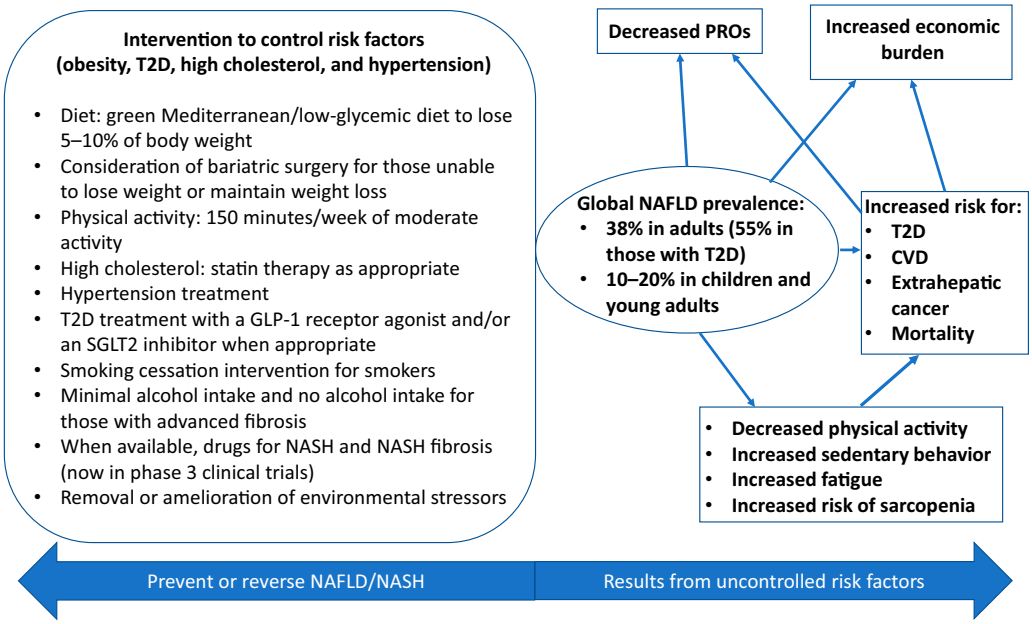

FIGURE 4 Scope of NAFLD. T2D, type 2 diabetes.

Conclusion

NAFLD is a complex, multisystem disease that is increasing dramatically around the world in parallel with increases in the rates of type 2 diabetes and obesity. Today, more than one-third of adults and up to one-fifth of children have NAFLD. Some of these individuals have developed advanced liver disease and HCC.

Based on the sheer number of people with NAFLD, this type of liver disease is rapidly becoming the most common cause of liver mortality and is considered an indication for liver transplantation and a cause of HCC. Given its tremendous clinical, PRO, and economic burdens, NAFLD requires early recognition and aggressive intervention involving a multidisciplinary health care team to facilitate weight loss, increased physical activity, and management of cardiometabolic comorbidities. In the near future, NASH-specific drugs currently under study may also play an important role in the management of patients with NAFLD. Moving forward, multidisciplinary teams of health care professionals must work together to identify, assess, and treat people with high-risk NAFLD, while also working with community leaders and national and international policymakers to advocate for the provision of known treatments and the development of more interventions to reverse the current trends.

DUALITY OF INTEREST

Z.M.Y. has received research funds or served as a consultant to Abbvie, BMS, Genfit, Gilead Sciences, Intercept, Madrigal, Merck, Novo Nordisk, Siemens, Terns, and Viking. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to the study design, literature review, writing, and critical revision of the article. Z.M.Y. is the guarantor of this work and, as such, had full access to all the data included in the review and takes responsibility for the integrity and accuracy of the content.

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