Management of Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes: A Call to Action

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REVIEW

Traditionally a disease of hepatologists, nonalcoholic fatty liver disease (NAFLD) has recently become a major concern for a broad spectrum of health care providers. Endocrinologists and those caring for patients with type 2 diabetes mellitus (T2DM) are at center stage, as T2DM appears to worsen the course of NAFLD and the liver disease makes diabetes management more challenging. However, the nature of this relationship remains incompletely understood. Although the increasing prevalence of NAFLD is frequently attributed to the epidemic of obesity and is often oversimplified as the "hepatic manifestation of the metabolic syndrome," it is a much more complex disease process that may also be observed in nonobese individuals and in patients without clinical manifestations of the metabolic syndrome. It carries both metabolic and liver-specific complications that make its approach unique among medical conditions. Diabetes appears to promote the development of nonalcoholic steatohepatitis (NASH), the more severe form of the disease, and increases the risk of cirrhosis and hepatocellular carcinoma. Patients and physicians face many uncertainties, including fragmented information on the natural history of the disease, challenges in the diagnosis of NASH, and few pharmacological agents with proven efficacy. However, recent advances in diagnosis and treatment, combined with the risk of serious consequences from inaction, call for health care providers to be more proactive in the management of patients with T2DM and NASH.

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver condition of adults in developed countries (1,2). According to current guidelines, the diagnosis is based on the following criteria (3,4): *1*) the presence of hepatic steatosis (>5% of hepatocytes determined by histology or >5.6% determined by nuclear magnetic resonance techniques); *2*) no significant alcohol consumption (defined as ongoing or recent alcohol consumption of >21 drinks/week for men and >14 drinks/week for women); and *3*) no competing etiologies for hepatic steatosis. Histologically, it covers a wide spectrum of liver disease ranging from isolated steatosis (without or with only minimal inflammation) to severe nonalcoholic steatohepatitis (NASH), characterized by inflammation, cell necrosis (ballooning), perilobular fibrosis, and eventually cirrhosis.

By mechanisms that are still incompletely understood, patients with type 2 diabetes mellitus (T2DM) are particularly susceptible to more severe forms of NAFLD (5,6) and have a higher progression to hepatocellular carcinoma (7,8). Moreover, the coexistence of NAFLD and T2DM results in a worse metabolic profile (9) and a

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higher cardiovascular risk (5,10). Many questions remain regarding the intricate relationship of NAFLD and T2DM, as well as the natural history and clinical implications of NAFLD in patients with prediabetes or T2DM. This review will focus on the appropriate management and treatment of these complex patients based on current evidence.

WHY SHOULD HEALTH CARE PROVIDERS CARE ABOUT NAFLD?

Based on a recent publication assessing the 2011–2012 National Health and Nutrition Examination Survey data (11), the prevalence of prediabetes and T2DM among U.S. adults were 38.0% and 14.3%, respectively. Moreover, among those adults ≥65 years of age, the prevalence of diabetes was 33.0%. Even in the best-case scenario (considering a prevalence of NAFLD among these patients of only 50%, rather than between ~65% and 70% as current evidence suggests) (Fig. 1), this implies that 84 million people in the U.S. live with prediabetes or T2DM and NAFLD. Of these, a significant number of patients already have NASH or are likely to develop this complication in the absence of any preventive intervention (12). However, only a few patients receive a diagnosis of NASH or are ever treated in the clinic (13). There are many reasons for this: *1*) patients and clinicians are unaware of NASH as a potentially serious medical condition; *2*) diagnosis is missed due to a reliance on low-sensitivity diagnostic tests (plasma aminotransferase measurements or liver ultrasound); *3*) a confirmatory diagnosis (liver biopsy) is rarely pursued by providers, even in patients who are at high risk of NASH; and *4*) patients and physicians are uninformed that weight loss and medical treatments may reverse NASH. Another argument frequently heard among primary care providers is that NAFLD may not be of great concern because cirrhosis appears to occur infrequently in clinical practice. One must consider, however, that the onset and magnitude of the obesity/T2DM epidemic is a relatively recent phenomenon of the past 2 decades, which, combined with the relatively slow nature of the disease, may give a false sense of comfort to the unaware physician and squander an opportunity for early intervention. Early signs of an impending "epidemic" of cirrhosis come from liver transplant surgeons. They find with increasing frequency cryptogenic cirrhosis, usually attributed to undiagnosed

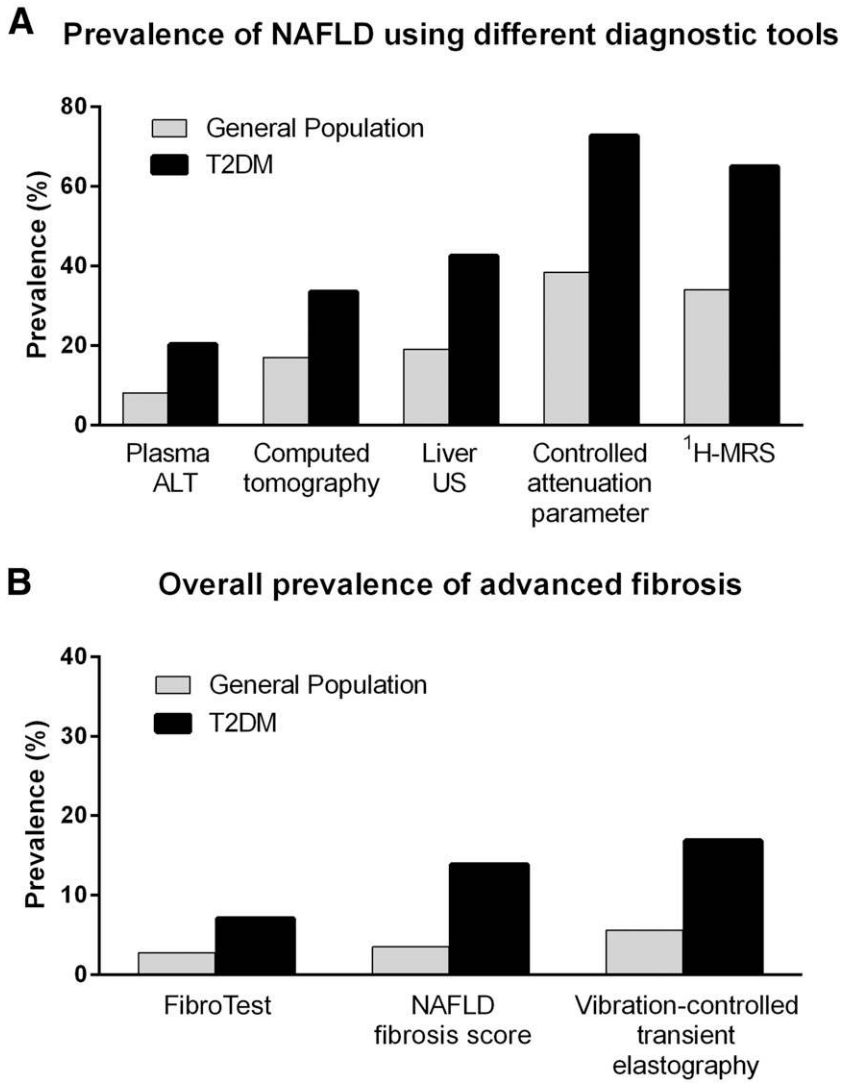

Figure 1—Prevalence of NAFLD (panel *A*) and advanced fibrosis (panel *B*) in the general population and in patients with T2DM according to different diagnostic tools. Note that the presence of T2DM significantly increases the prevalence of NAFLD and advanced fibrosis. Results were extrapolated from the following references: plasma ALT (24,25), computed tomography (26,27), liver ultrasound (US) (28,29), CAP (30,31), liver ^{1}H-MRS (32,35), FibroTest (46,47), NAFLD fibrosis score (48), and vibration-controlled transient elastography (49).

NASH, as a cause for liver transplantation (14). It is estimated that at its current course NASH will soon be the main cause of liver transplantation in the U.S. (15). Of note, the prevalence of T2DM among patients with cryptogenic cirrhosis is much higher than that in patients with cirrhosis of other causes (16). Moreover, with increasing frequency pediatric and adult hepatology clinics are seeing referrals from patients in late adolescence and young adulthood with advanced liver disease secondary to NASH.

But the negative consequences of having NAFLD in the setting of prediabetes or T2DM go far beyond those related to the liver. The presence of NAFLD has been associated with a myriad of adverse metabolic alterations in patients with T2DM (17). These patients characteristically show a worse atherogenic dyslipidemia with hypertriglyceridemia, low levels of HDL cholesterol (HDL-C), and smaller and denser LDL particles (18,19). Insulin failure to appropriately suppress hepatic VLDL secretion is at the core of this typical dyslipidemia (20). Although this dyslipidemia appears to be driven by intrahepatic triglyceride accumulation and insulin resistance, it appears to be independent of the presence of obesity or the severity of NASH (18). Other metabolic alterations frequently observed in these patients include higher levels of insulinemia and

hyperglycemia that is more difficult to control. These are probably the result of more severe insulin resistance at the level of the liver (9) and impaired insulin clearance (21). All these metabolic disarrangements translate into worse cardiovascular disease, the main cause of morbidity and mortality in this population (22). In addition, diabetic microvascular complications are also increased in the presence of NAFLD, as suggested by several observational studies (23).

It is clear that the coexistence of NAFLD and prediabetes or T2DM is extremely common and is associated with severe consequences to the health care system. Fortunately, a better understanding of the natural history of the disease, together with access to novel diagnostic tools and recent evidence of safe and effective treatment modalities have set the stage for a major paradigm shift in the management of this disease in patients with prediabetes or T2DM. We are at an important crossroads, and how well we incorporate these new diagnostic and therapeutic advances will likely have a large impact on the quality of life of many patients.

DIAGNOSIS OF NAFLD AND NASH

As can be observed in Fig. 1*A* (24–32), the prevalence of NAFLD depends on the diagnostic tool that is used. Although the prevalence using plasma alanine aminotransferase (ALT) concentration is relatively low (24,33), it actually depends on the cutoff point selected as normal. Although a threshold of 40 IU/L is frequently used in clinical practice and trials, epidemiological studies have suggested lower cutoff points to be considered as normal (i.e., 30 IU/L for males and 19 IU/L for females) in order to improve the sensitivity of the method (34). Nevertheless, there is significant evidence suggesting that plasma aminotransferases are a poor marker of NAFLD even with lower cutoff points. Among patients with T2DM with normal plasma aminotransferase levels, the prevalence of NAFLD was as high as 50% using proton magnetic resonance spectroscopy (^{1}H-MRS), and 56% of these patients had a histologic confirmation of NASH (35). When they are elevated, the level of ALT is usually higher than that of aspartate aminotransferase (AST), unless there is advanced liver disease.

The availability and low cost of liver ultrasound have made it the technique of choice for routine screening (36). Sensitivity ranges from as low as 60% (37) to as high as 94% (38). In a meta-analysis by Hernaez et al. (39), the overall sensitivity (85%) and specificity (94%) were acceptable. However, these good results can be deceiving as they only reflected its performance in distinguishing between moderate-to-severe NAFLD and the absence of disease, excluding an important group of patients with mild hepatic steatosis, where the sensitivity of the test is significantly lower. Although the performance of liver ultrasound for the diagnosis of NAFLD is much better than the determination of plasma aminotransferase concentration, it still underperforms when compared with ^{1}H-MRS or liver biopsy (24–32,40) (Fig. 1*A*). The use of semiquantitative scores based on different echographic parameters may somehow improve the outcome but still has a low performance when the hepatic triglyceride content is $<$12.5% (40).

A noninvasive algorithm based on metabolic and anthropometric data (BMI, waist circumference, plasma triglyceride levels, and γ-glutamyl transferase [GGT] concentration), which is known as fatty liver index (41), has also been endorsed by some associations for the diagnosis of NAFLD because of its simplicity (4). However, it should be taken into account that most of the published evidence comes from comparisons against liver ultrasound findings (i.e., not the gold standard and already a technique with low sensitivity). Therefore, this is likely to overestimate the true performance of this algorithm. When the fatty liver index was compared against more accurate methods, such as liver ^{1}H-MRS, 58% of the patients had an indeterminate classification, and only 77% of the remaining 42% were correctly classified (42). Moreover, the presence of fibrosis has also been shown to affect its performance (43).

More novel techniques, such as controlled attenuation parameter (CAP) and magnetic resonance–based techniques (e.g., ^{1}H-MRS and MRI-proton density fat fraction) have been shown to be more accurate for the diagnosis of NAFLD and have the advantage of being quantifiable, providing a tool to assess changes over time (40,44,45). However, whether changes in steatosis correspond to changes in inflammation or fibrosis remains to be fully elucidated. As techniques for measuring hepatic triglyceride accumulation become more readily available for clinical use, it is likely that they will become the first step for the screening of hepatic steatosis in NAFLD/NASH in high-risk patients. As shown in Fig. 1*A* (24–32), patients with T2DM have a greater than twofold increase in the prevalence of NAFLD regardless of the method used for the diagnosis, suggesting that this population may benefit from routine NAFLD/NASH screening. Of note, the prevalence of NAFLD is ~70% in patients with T2DM when the best available techniques are used (5).

Once the diagnosis of NAFLD is made, clinicians should focus their attention on assessing the risk of the patient of having NASH or advanced fibrosis, which are much more common in patients with T2DM. As can be observed in Fig. 1*B* (46–49), cross-sectional studies demonstrate that patients with T2DM have a higher prevalence of advanced fibrosis when compared with the general population, regardless of the diagnostic method used. This is consistent with findings from prospective studies (50,51). Although a liver biopsy remains the gold standard for the diagnosis of NASH and for staging the severity of liver fibrosis, the field is slowly moving toward the use of surrogate noninvasive techniques for the diagnosis of this condition. Several scores have been created based on clinical variables (e.g., levels of plasma ALT, AST, platelets, and albumin, BMI, and the presence of diabetes) and other specific surrogate markers of liver inflammation and/or fibrosis to predict the presence of NASH or advanced fibrosis (46–48,52). Many of these scores have been developed in a small number of patients without including a validation cohort and still await more rigorous testing. We included in Table 1 the most widely used biomarker panels for the prediction of advanced fibrosis. They have been developed in cohorts of approximately ≥250 patients with NAFLD and compared against the results of liver histology tests. These tests include the FibroTest, NAFLD fibrosis score, BARD score, FIB-4 (Fibrosis-4) index, and NAFIC score among others (53). Although this is an available diagnostic option to complement the medical history and/or imaging studies, it should be noted that with most biomarker scores patients frequently fall in a "gray zone" with an intermediate or undetermined risk. For example, in the only score specifically developed for patients with T2DM (52), 44%

Table 1—Biomarker panels for the diagnosis of advanced fibrosis (stages 3 and 4)

	Parameters included	*n*	PPV	NPV	Patients unable to be classified ("gray zone")
FibroTest (115)	Age, sex Total bilirubin GGT α_2-macroglobulin Apolipoprotein A1 Haptoglobin	267	60%	98%	32%
NAFLD fibrosis score (116)	Age, BMI Diabetes AST/ALT ratio Platelet, albumin	733	82%	88%	24%
†BARD score (117)	BMI Diabetes AST/ALT ratio	827	43%	96%	N/A
†FIB-4 index (118)	Age AST and ALT Platelet	541	80%	90%	30%
NAFIC score (119)	Ferritin Type IV collagen Insulin	619	36%	99%	15%
†Hepascore (120)	Age, sex Total bilirubin GGT α_2-macroglobulin Hyaluronic acid	242	57%	92%	11%

N/A, not applicable; NPV, negative predictive value; PPV, positive predictive value. †No independent validation cohort included in the study.

and 87% of the patients fell in the undetermined group for either NASH or advanced fibrosis, respectively. Plasma biomarkers, such as plasma keratin-18 (54), fibroblast growth factor 21, and others, have also been assessed with similar disappointing results. They frequently falter because of low sensitivity for mild-to-moderate NASH or fibrosis and, at the present moment, are of limited discriminatory value in diagnosing or monitoring the disease. The development of new biomarkers using advanced technologies (i.e., metabolomics) (55) and genetic testing (56) is being actively investigated and offers promise in the near future. The most reproducible polymorphism in genome-wide association studies in NAFLD involves the patatin-like phospholipase 3 (PNPLA3; rs738409), which has been shown to be associated with more liver triglyceride accumulation and worse prognosis (57). More recently, a polymorphism of the transmembrane 6 superfamily member 2 (TM6SP2; rs58542926) has also been described of relevance in terms of liver histology. However, although individual genetic predisposition to NAFLD and NASH is likely and genotyping may be considered in selected patients, current genetic tests are not recommended for routine clinical testing given issues related to cost, further validation, and the need for improvement in their diagnostic sensitivity/specificity.

If available, vibration-controlled transient elastography (FibroScan) or magnetic resonance elastography (MRE) can also be used to determine the degree of fibrosis (49,58). Both have been shown to correlate well with histologic findings and may avoid the need for a liver biopsy in a significant number of patients. Unlike FibroScan, MRE provides the elasticity of the entire liver and is not affected by elevated BMI values. Although the MRE has shown to perform better than FibroScan (59), it is more expensive and less accessible. Although no study to date has used MRE to screen for advanced fibrosis in the general population, Doycheva et al. (58) applied this technique in an unselected group of T2DM patients (n = 100) and found that 7.1% of patients with T2DM had advanced fibrosis. Unfortunately, many patients cannot be properly classified by noninvasive techniques and may still require a liver biopsy. This is the only reliable way to rule out other chronic liver diseases and to distinguish isolated steatosis from NASH, potentially avoiding unnecessary exposure to pharmacological treatment in patients with mild disease (i.e., isolated steatosis). Current guidelines (3,4) state that a liver biopsy is the only way to diagnose NASH and that noninvasive techniques have not been fully validated for diagnosing this condition. However, as can be observed in Fig. 2, empiric therapy is included as an option for patients unwilling or unable to undergo a liver biopsy. The limitation of this approach is the uncertain diagnosis at baseline, the potential for unnecessary exposure to pharmacological treatment, and the ambiguity in defining treatment response. However, as better noninvasive diagnostic techniques develop and safer and more effective treatments become available, we are likely to see a shift toward a more limited need for liver biopsies prior to treatment initiation for NASH in clinical practice.

In Fig. 2, we have provided a summary of the diagnostic approach that we suggest for most patients with prediabetes or T2DM who are at high risk of NASH. However, each patient should be assessed individually, and a careful evaluation of risks and benefits should be performed on a case-by-case basis.

TREATMENT

Therapy for patients with NASH should be aimed at decreasing disease activity, delaying the progression of fibrosis, and reducing the risk factors associated with their high cardiovascular risk (3,4). Currently, there are no pharmacological treatments approved by regulatory agencies for this condition, so lifestyle intervention remains the standard of care (3,4). In this scenario, it is not infrequent to hear primary care physicians arguing that diagnosing NAFLD and/or NASH is pointless, as lifestyle intervention remains the only therapeutic option available, and all patients with prediabetes or T2DM should receive it regardless of their liver findings. However, this statement overlooks the fact that lifestyle intervention alone rarely achieves complete resolution of NASH, being extremely difficult to accomplish and even more challenging to maintain over time. Moreover, lifestyle intervention plus pharmacological treatment are likely to offer additive benefit. Therefore, although all patients should be counseled and encouraged to adopt lifestyle changes, pharmacological therapy should

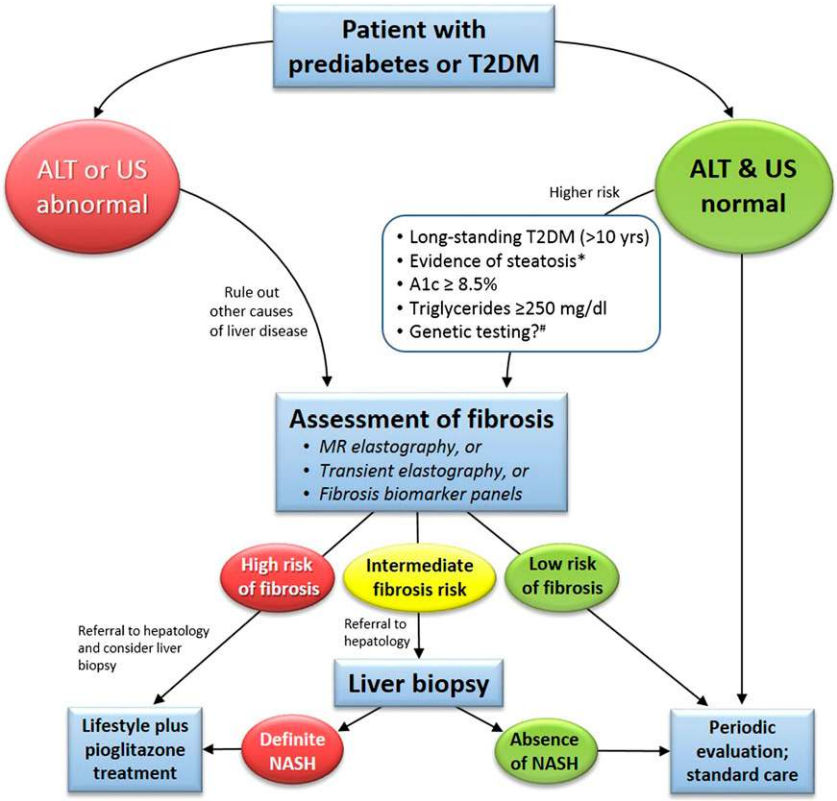

Figure 2—Algorithm for the diagnosis of NAFLD and NASH in patients with prediabetes or T2DM in clinical practice. This suggested algorithm is based on the authors' interpretation of available evidence. MR, magnetic resonance; US, ultrasound. *Based on results from more sensitive tests such as liver ^{1}H-MRS, MRI-proton density fat fraction, or CAP. #Patatin-like phospholipase domain-containing 3 (PNPLA3) I148M and/or transmembrane 6 superfamily member 2 (TM6SF2) E167 K.

be strongly considered early on, especially in patients with advanced disease or those who are at high risk of disease progression. With increasing frequency, U.S. Food and Drug Administration–approved medications for other conditions (e.g., pioglitazone [60] and liraglutide [61] for T2DM; obeticholic acid [62] for primary biliary cholangitis) are proving to be safe and effective in randomized controlled trials for patients with NASH.

Given this rapidly growing arsenal of therapeutic options, clinicians will be increasingly faced with the dilemma of choosing the right option. In this section, we will provide clinicians with practical recommendations for the treatment of these complex patients. Management should be focused on the following five aspects (Fig. 3):

1. Lifestyle intervention
2. Pharmacological treatment of liver disease
3. Treatment of hyperglycemia
4. Treatment of dyslipidemia
5. Control of other cardiovascular risk factors

Lifestyle Intervention

Lifestyle intervention is beneficial for patients with NAFLD, improving not only liver disease but also hyperglycemia, atherogenic dyslipidemia, and blood pressure levels (3,4,63). However, less is known about the long-term effects of lifestyle intervention on liver histology (i.e., beyond 1 year of intervention), on the least amount of weight loss needed to achieve such histological benefit, and on the best strategy to maintain it over time.

In imaging studies using the gold standard ^{1}H-MRS technique, the relative reduction in hepatic steatosis by lifestyle intervention has been usually in the range of ~40–50%, although absolute changes (perhaps the most important factor for histological improvement) usually have been small and on the order of ~5% (3,10,63). Among the few well-controlled studies with paired liver biopsies, Promrat et al. (64) reported an improvement in hepatic steatosis and necroinflammation in patients losing ≥7% of total body weight over 48 weeks with a moderate-intensity hypocaloric diet plus an exercise program (200 min/week). Overall, this study showed that improvement on histology was proportional to the magnitude of the weight loss. Using a similar approach (a hypocaloric diet combined with walking 200 min/week), a recent uncontrolled study (65) in 261 patients with paired biopsies after 12 months reported similar benefits from lifestyle intervention. Together, it appears that a weight reduction in the magnitude range of ~5–7% may clearly decrease steatosis but that more weight loss is needed (~8–10% reduction) to reverse steatohepatitis. Weight reductions of ≥10% may also cause a significant regression of fibrosis (65). In line with these findings, large weight reductions obtained after bariatric surgery showed that most patients experience a decrease in steatosis (~90%), in steatohepatitis (~80%), and even in fibrosis (~65%) (66). These results were confirmed in a recent prospective study (67) where ~50% of patients had improvement in fibrosis scores. Of note, the magnitude of fibrosis reduction depends on the baseline severity of liver disease, with no improvement in fibrosis observed 5 years after bariatric surgery in a large cohort of patients (n = 381) with overall mild liver disease (68). However, most bariatric surgery studies have several limitations. These studies are usually small (<100 patients) and lack standardization of the preoperative very-low calorie diet intervention and the postoperative dietary intervention or details about how the intraoperative liver biopsy sample is obtained (which may alter the baseline histological reading). In addition, the repeat postbypass liver biopsies are usually performed at varying intervals over time. Finally, most studies have not been prospective or controlled, and therefore they were potentially at risk for patient selection bias. Indeed, there are no randomized controlled trials evaluating a given bariatric surgery procedure versus lifestyle intervention, placebo (sham procedure), a given pharmacological intervention, or across surgical approaches in patients with NASH. It is also unclear whether changes in liver disease are merely the result of weight reduction or whether bariatric surgery has an intrinsic metabolic effect on the liver.

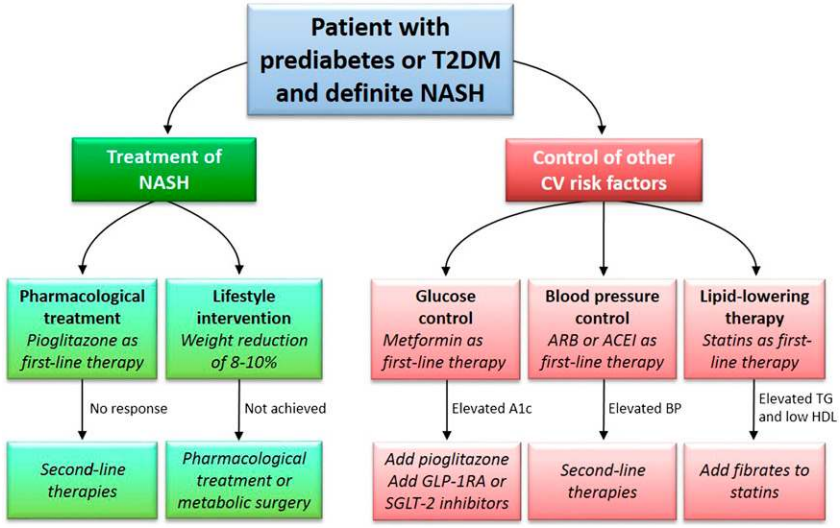

Figure 3—Algorithm for the management of patients with prediabetes or T2DM and definite NASH. This suggested therapeutic algorithm is based on the safety and efficacy of interventions assessed in randomized controlled trials. BP, blood pressure; CV, cardiovascular; TG, triglyceride.

Well-designed prospective studies are needed to determine the ideal patient, type of surgery, and long-term efficacy and safety of bariatric surgery in NAFLD/NASH. Consistent with these limitations, a Cochrane review (69) concluded that it is too early for a definitive assessment of benefits versus harms of bariatric surgery in NASH, and current recommendations consider it premature to indicate bariatric surgery specifically to treat NASH, although it is not contraindicated in otherwise eligible obese individuals with NAFLD or NASH (unless they have established cirrhosis) (3).

The above evidence suggests that lifestyle interventions are as good as the magnitude of weight reduction they produce. Further supporting this concept, studies with weight loss medications such as orlistat (70) or liraglutide (61) have reported a histological improvement proportional to the amount of weight loss. This is the reason why pharmacological agents that induce weight loss should always be considered, especially if lifestyle intervention is unsuccessful (Fig. 3). This probably implies that there may not be a lifestyle intervention strategy that is better than the rest, and that weight reduction per se should be the primary aim. For example, resistance training and aerobic exercise interventions achieving similar weight reduction were equally effective in reducing liver triglyceride content by ~30% among patients with diabetes and NAFLD (71). Comparable effects have been observed with equally hypocaloric low-carbohydrate versus high-carbohydrate diets (72) and low-fat versus low-carbohydrate diets (73). However, some studies report steatosis reduction even with minimal weight loss, indicating that other factors may also play a (minor) role in NASH improvement (3,4). For example, several small (n = 18–45) and short-term (4–24 weeks) studies reported a modest reduction in intrahepatic triglyceride accumulation by ^{1}H-MRS (~15%) after aerobic or resistance exercise without any significant weight loss (74). Moreover, 2- to 4-week isocaloric low-fat diets significantly reduced intrahepatic triglyceride accumulation as determined by ^{1}H-MRS without producing any weight loss when compared with isocaloric high-fat diets (74). Diet supplements, such as vitamin D or n-3 fatty acids, have also been suggested for treatment in patients with NAFLD, but treatment with both supplements has failed to show any consistent associations with liver triglyceride accumulation or NASH (75,76). Clearly, more studies are needed to completely understand the role of lifestyle intervention in the treatment of NASH and to establish the best strategy to treat patients with T2DM and NASH.

Pharmacological Treatment of Liver Disease

As more drugs prove their safety and efficacy in randomized controlled trials in patients with NASH, and both physicians and patients continue to struggle with the challenge of achieving and maintaining a significant weight reduction, we envision a paradigm shift in the near future toward more frequent combination of pharmacological treatment with lifestyle intervention in patients with NASH.

In Fig. 4 (60–62,77–79), we have summarized the histologic effects of several drugs included in randomized controlled trials that have reported on resolution of NASH. Only with treatment with pioglitazone (either 30 or 45 mg daily) (60,78,79), vitamin E (78), and liraglutide (61) did a significant proportion of patients achieve resolution of NASH when compared with placebo (Fig. 4*A*). The treatment effects were ~30% for pioglitazone and liraglutide and ~15% for vitamin E. However, cross-comparisons between studies should be avoided because of differences in the populations studied and other factors, such as differences in the proportion of patients with T2DM (60,79). It should also be taken into account that the definition of resolution of NASH varied somewhat across the studies.

Regarding individual histologic parameters, as can be observed in Fig. 4 (60–62,77–79), pioglitazone (either 30 or 45 mg daily) (60,78,79), vitamin E (78), and obeticholic acid (62) showed the most consistent results, with significant improvements in steatosis (Fig. 4*C*), inflammation (Fig. 4*D*), and ballooning (Fig. 4*E*). Pioglitazone 45 mg had the highest reduction in steatosis and inflammation grades. Vitamin E and obeticholic acid were also beneficial but with an improvement of a somewhat lesser magnitude (~25% and ~50%, respectively, of that reported for pioglitazone). The overall reduction in ballooning grades was rather small but significant for most medications, except for low-dose elafibranor (77) and liraglutide (61). Discrepancies in the liraglutide study (relatively high rates of resolution of NASH with nonsignificant changes in individual histological scores) may be a result of the small size of the study, with only 45 patients having paired biopsies. Certainly, larger studies with liraglutide and other glucagon-like peptide 1 receptor agonists are needed in order to establish their future role in the treatment of NASH. Comparison of results expressed as a percentage of patients with improvement for

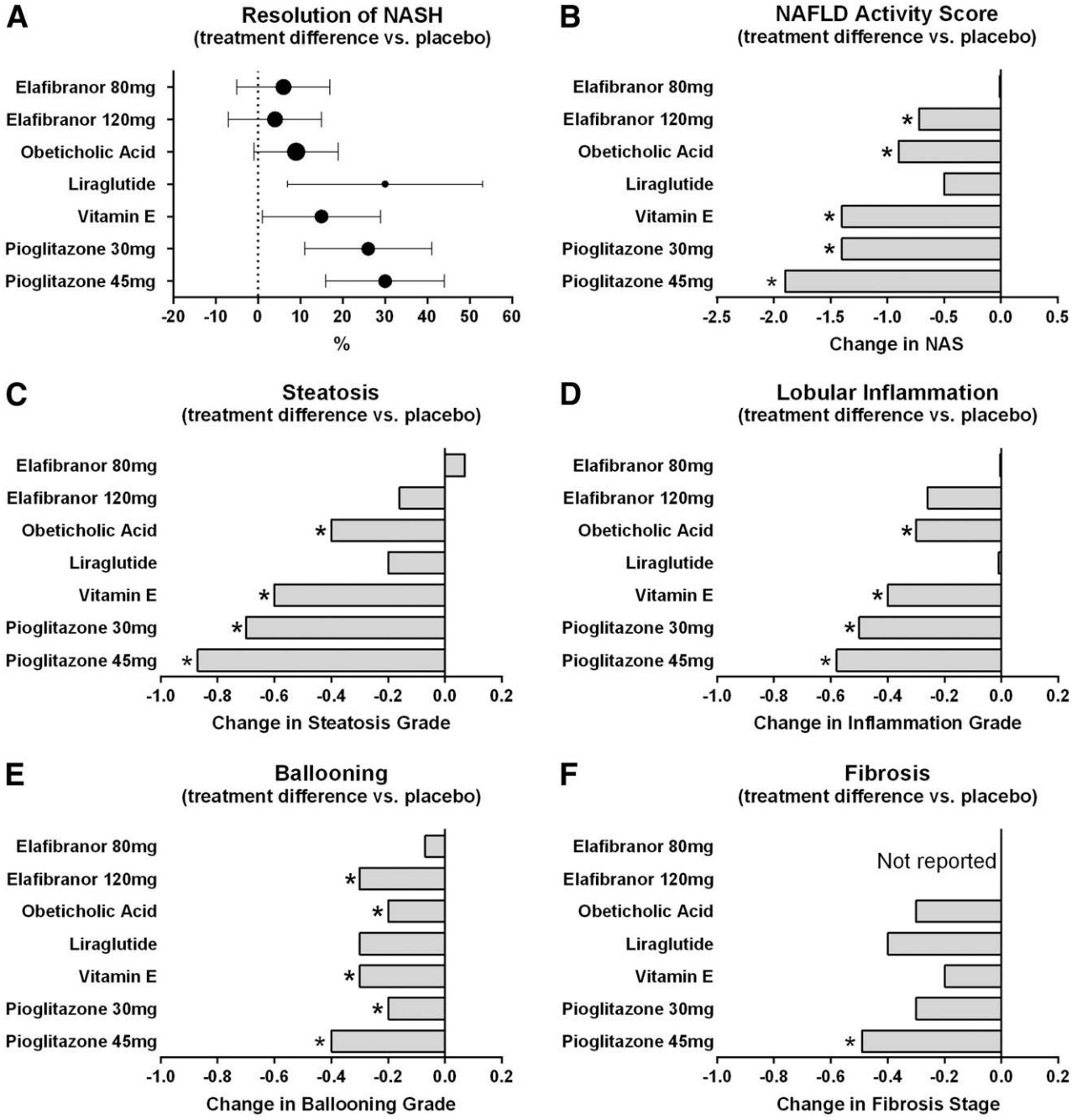

Figure 4—Treatment effect vs. placebo for different histological outcomes for pharmacological agents assessed in randomized controlled trials reporting resolution of NASH as one of the outcomes. *Implies statistical significance (panels *B*–*F*). NAS, NAFLD activity score.

each histological parameter can be found in Supplementary Fig. 1.

There has been increasing interest in finding medications that could prevent fibrosis progression in NASH or that could even reverse established fibrosis. A mean reduction in fibrosis stage was significant only for pioglitazone 45 mg (60) (Fig. 4*F*), but other studies have also suggested a benefit. Belfort et al. (79) reported significant changes in fibrosis compared with baseline, and Aithal et al. (80) also reported a reduction in fibrosis in patients without diabetes treated with pioglitazone 30 mg/day. Thus, it is possible that pioglitazone may alter the natural history of the disease and its progression to cirrhosis in some patients with NASH, encouraging early diagnosis and treatment. Other medications with a potential for liver antifibrotic properties require confirmation in larger studies. For instance, after obeticholic acid therapy more patients showed improvement in liver fibrosis compared with treatment with placebo (35% vs. 19%, $P = 0.004$), although the mean fibrosis score did not change significantly. Other agents include pentoxyfilline (mean treatment effect on fibrosis [$n = 46$] −0.6, $P = 0.038$) (81) and liraglutide (treatment effect [$n = 45$] −0.4, $P = 0.11$) (61). A preliminary report (82) has also indicated some beneficial effect from cenicriviroc therapy on fibrosis but not on resolution of NASH or

individual histological parameters after 12 months of therapy.

In patients with NASH and prediabetes or T2DM, the evidence appears to show that pioglitazone has the greatest treatment effect. It targets not only liver histology, but also the underlying metabolic disturbances, in particular insulin resistance (83). Of note, histological improvement after pioglitazone therapy is closely correlated with the reversal of adipose tissue insulin resistance (84) and an increase in plasma adiponectin levels (85). In the long term, its metabolic and histologic benefits appear to persist over time (60), but they wane after treatment discontinuation (86).

Before consideration, benefits must be balanced against potential adverse events of pioglitazone therapy (83). In a meta-analysis of 16,390 patients (87), although congestive heart failure was slightly more frequent with pioglitazone therapy compared with other treatments (hazard ratio 1.41 [95% CI 1.14–1.76], $P = 0.002$), there was a significant reduction in the combined outcome of death, myocardial infarction, or stroke. This finding is consistent with the antiatherogenic effect of pioglitazone reported in other randomized controlled trials (88–90). Moreover, in a recent study (91) in patients without T2DM, pioglitazone therapy decreased stroke and myocardial infarction (fatal and nonfatal) by 24% in patients with a previous ischemic stroke or transient ischemic attack. Pioglitazone therapy also reduced the progression from prediabetes to T2DM by ~50% (82) to ~70% (92). Thus, it may offer a liver-specific and comprehensive metabolic treatment to patients with NASH in whom the presence of insulin resistance and prediabetes are already common (17). Pioglitazone may cause weight gain, but it is usually less than commonly believed (~2–3 kg in long-term studies of 2–4 years duration in patients with T2DM) and recently has been reported (60) to be 3.1 kg after 36 months of treatment in patients with prediabetes or T2DM and NASH. An additional concern has been about whether pioglitazone may increase the risk of bladder cancer in males. Evidence is conflicting, with some studies showing association (i.e., one extra case per 3,408 patients treated with extended treatment) (93), although a larger 10-year prospective study failed to find any association (94).

In summary, pioglitazone may change the natural history of the disease in patients with T2DM and NASH. Early addition of this drug to the antidiabetic regimens of such patients should be considered after metformin therapy. Whether histological outcomes can be improved in patients with T2DM and NASH by combining treatment with vitamin E and pioglitazone is being actively explored by our group in a long-term three-arm study of vitamin E/pioglitazone versus vitamin E/placebo versus placebo/placebo (Clinical trial reg. no. NCT01002547, clinicaltrials.gov).

Treatment of Hyperglycemia

Treatment of hyperglycemia is important because NASH in patients with prediabetes/diabetes carries a worse prognosis (5). Paradoxically, most studies in patients with NASH have been carried out in patients without diabetes, so the role of controlling hyperglycemia per se in patients with steatohepatitis and T2DM, independent of changes in insulin sensitivity, remains largely unknown. A common observation in clinical practice is that patients with uncontrolled diabetes and elevated plasma aminotransferase levels usually normalize (or significantly improve) their aminotransferase levels once their diabetes has been better controlled. In the same way, the development of uncontrolled hyperglycemia has been observed to be associated with an increase in plasma aminotransferase levels. Moreover, in a small proof-of-concept study with paired biopsies, patients with the greatest histological improvement after 2.4 years of follow-up were the ones with the largest A1C reduction. However, interpretation must be performed carefully because the same group also showed the greatest weight loss and the largest improvement in insulin sensitivity (95).

Overall, these findings suggest that any diabetes treatment may be of benefit for patients with NASH if they have uncontrolled hyperglycemia. Proof of this comes from studies that have shown a reduction of steatosis after treatment with insulin (96) or an improvement of plasma aminotransferase levels after sodium–glucose cotransporter 2 inhibitor therapy (97). However, future studies are needed to assess the effect of glycemic control on steatohepatitis in T2DM.

Whether the above observations show a direct response to changes in plasma glucose levels (decreasing glucotoxicity) or to the alleviation of insulin resistance remains unclear. Regardless of the mechanism, physicians should pay close attention to diabetes control in patients with NASH as this is likely, but unproven, to delay the progression of liver disease. In addition, because NAFLD has been associated with worse progression of retinopathy (98) and nephropathy (23), the presence of NAFLD may identify a group of patients who could potentially benefit from stricter glycemic control.

Treatment of Dyslipidemia

Patients with NAFLD, independent of obesity or the histologic severity, have worse atherogenic dyslipidemia (18,19). As mentioned earlier, it is usually characterized by hypertriglyceridemia, low HDL-C levels, and smaller and denser LDL particles. In clinical practice, patients with NAFLD are frequently denied a statin for a combination of reasons, the most important being the fear of hepatotoxicity in patients with already elevated plasma aminotransferase levels (99). A recent study (100) showed that only 42.6% of patients with NAFLD received an appropriate statin therapy, despite their significantly elevated cardiovascular risk.

Evidence from retrospective (101) and cross-sectional (102) studies has shown that statins are safe in these patients, and that they may even contribute to decreased plasma aminotransferase levels and improve hepatic steatosis and histology (99). However, a randomized controlled trial (103) with simvastatin failed to show any effect on hepatic steatosis, and the only small randomized controlled trial (104) in patients with NASH did not show any effect of simvastatin on liver histology. Although prospective studies assessing the safety and efficacy of statins are much needed for confirmation, the current dogma is that patients with NAFLD should be treated with a statin because of their elevated cardiovascular risk (Fig. 3) (99). Moreover, because these patients frequently exhibit hypertriglyceridemia even after starting statin therapy, they may even benefit from the addition of fenofibrate in combination with the statin. This has been shown to be useful in post hoc analyses of large randomized controlled trials, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) (105) and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) (106) trials, where the subgroup of patients with high triglyceride and low HDL-C levels (typical dyslipidemia in NAFLD)

had a reduction in cardiovascular outcomes after the addition of fenofibrate to treatment.

Whether the addition of ezetimibe could further contribute to a reduction in cardiovascular risk or to the progression of liver disease in this population has been a matter of extensive debate. In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), the addition of ezetimibe to a statin after an acute coronary syndrome event showed a significant reduction in the composite primary outcome (107), and ezetimibe is, therefore, likely to be of benefit for high-risk patients. However, current guidelines still do not recommend its routine use for the prevention of cardiovascular disease (99). Studies assessing its effects on surrogate markers of liver disease in NAFLD have shown negative findings (108,109).

Control of Other Cardiovascular Risks

All other traditional cardiovascular risk factors should also be actively addressed in patients with NASH because of their elevated cardiovascular risk. Current data on the association of smoking and the progression of NAFLD is scarce. In a large multicenter cohort from the Nonalcoholic Steatohepatitis Clinical Research Network (110), smoking was associated with advanced fibrosis, at least in part through mechanisms associated with insulin resistance. Regardless of the direct effects of smoking on the liver, smoking cessation should be strongly encouraged in order to reduce cardiovascular risk in this already high-risk population. In a similar way, optimal blood pressure control should also be encouraged (Fig. 3). Although at this time no formal recommendation can be given regarding the best agent to manage hypertension in NASH, small uncontrolled clinical studies have suggested that ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may be able to play a role in improving insulin signaling and preventing fibrosis in the liver (111). An open-label, uncontrolled study (112) in humans with NASH has shown histologic improvement after 20 months of therapy with telmisartan or valsartan. With telmisartan therapy, the improvements were more important, which may be accounted for by the activity of peroxisome proliferator–activated receptor γ. However, in the most comprehensive study to date with ARBs, negative results were reported (113). Regardless of whether these medications contribute to the treatment of NASH or not, either ACEIs or ARBs should be prescribed early on to patients with NAFLD and T2DM (in the presence of microalbuminuria and/or hypertension) in order to delay the progression of nephropathy, which may progress more rapidly in the setting of NAFLD.

CONCLUSIONS

Much progress has been made in our understanding of the pathogenesis, diagnosis, and treatment of NAFLD. For the first time, pharmacological treatments offer hope (i.e., pioglitazone, vitamin E, liraglutide, obeticholic acid, and elafibranor) of altering the progressive nature of the disease in many patients. However, at the present time, patients are often missed as practitioners are limited to screening with low-sensitivity tools, such as measurement of plasma aminotransferase concentration and liver ultrasound. Until recently, the field lacked noninvasive, cost-effective tests and was at a stage equivalent to diabetic nephropathy before the use of microalbuminuria or osteoporosis before the availability of DEXA imaging. Both of these are indolent chronic conditions (like NASH), and today diabetic nephropathy and osteoporosis are actively pursued and treated early on with a marked reduction in morbidity and health care costs. The availability of simple diagnostic tests that can be widely used by practitioners, in combination with access to low-cost, safe, and more effective medications in the near future (114), will radically change disease management in the near future. We predict that, invigorated by these recent diagnostic (e.g., improved imaging and plasma biomarkers/genetic tests) and therapeutic (e.g., pioglitazone) developments, screening and early intervention for NASH will become a standard of care for all patients with T2DM. Until then, much work remains to be done.

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