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Mini-Review

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The Emerging Role of Glucagon-like Peptide-1 Receptor Agonists for the Management of NAFLD

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CVD, cardiovascular disease; CVOT, cardiovascular outcome trial; FDA, US Food and Drug Administration; FIB-4, fibrosis 4 index; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; LFC, liver fat content; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; RCT, randomized clinical trial; SCALE, Satiety and Clinical Adiposity Liraglutide Evidence; STEP, Semaglutide Treatment Effect in People with Obesity; T2D, type 2 diabetes; WM, weight management.

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Abstract

Context: The burden of cirrhosis from nonalcoholic fatty liver disease (NAFLD) is reaching epidemic proportions in the United States. This calls for greater awareness among endocrinologists, who often see but may miss the diagnosis in adults with obesity or type 2 diabetes mellitus (T2D) who are at the highest risk. At the same time, recent studies suggest that glucagon-like peptide-1 receptor agonists (GLP-1RAs) are beneficial vs nonalcoholic steatohepatitis (NASH) in this population. This minireview aims to assist endocrinologists to recognize the condition and recent work on the role of GLP-1RAs in NAFLD/NASH.

Evidence acquisition: Evidence from observational studies, randomized controlled trials, and meta-analyses.

Evidence synthesis: Endocrinologists should lead multidisciplinary teams to implement recent consensus statements on NAFLD that call for screening and treatment of clinically significant fibrosis to prevent cirrhosis, especially in the high-risk groups (ie, people with obesity, prediabetes, or T2D). With no US Food and Drug Administration (FDA)-approved agents, weight loss is central to successful management, with pharmacological treatment options limited today to vitamin E (in people without T2D) and diabetes medications that reverse steatohepatitis, such as pioglitazone or GLP-1RA. Recently, the benefit of GLP-1RAs in NAFLD, suggested from earlier trials, has been confirmed in adults with biopsy-proven NASH. In 2021, the FDA also approved semaglutide for obesity management.

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Conclusion: A paradigm change is developing between the endocrinologist's greater awareness about their critical role to curve the epidemic of NAFLD and new clinical care pathways that include a broader use of GLP-1RAs in the management of these complex patients.

Key Words: nonalcoholic fatty liver disease (NAFLD), primary care, GLP-1 receptor agonists, obesity, diabetes, metabolic syndrome, liraglutide, semaglutide

Management of patients with chronic metabolic diseases has become increasingly common and a major burden to patients, primary care physicians, and endocrinologists. About two-thirds of the population of the United States is either overweight or obese, with obesity being present in more than 40% of all adults (1). Moreover, a recent study estimates that 1 of 2 adults in the United States will have obesity by 2030 (2). The prevalence of type 2 diabetes (T2D) also continues to increase in the USA (3). Obesity and T2D are associated with metabolic disturbances linked to insulin resistance such as disproportionate visceral adiposity, atherogenic dyslipidemia, hypertension, and cardiovascular disease (CVD). Recently, there has been a growing awareness about their relationship with nonalcoholic fatty liver disease (NAFLD) (4, 5). The term NAFLD is given to the presence of hepatic steatosis, either by imaging or histology, in the absence of secondary factors such as alcohol abuse, medications, or other causes for fatty liver disease (6, 7). It is the most common chronic liver disease in Westernized societies, with about 50% to 60% of adults with obesity having steatosis (8, 9). The presence of obesity, in particular when associated with T2D, increases the risk of developing the more severe form associated with hepatocyte necrosis and predominantly lobular inflammation, and risk of cirrhosis, known as nonalcoholic steatohepatitis (NASH) (5). A recent screening study in 664 middle-aged Americans reported that 38% had NAFLD, and among them, more than one-third had NASH (9). Moreover, when patients with obesity were analyzed, the risk of both NAFLD/NASH doubled and was even higher in those with diabetes. It is also important for endocrinologists to keep in mind that between 44% and 62% of adults with prediabetes have concurrent NAFLD, equivalent to 27 to 38 million patients (10). Patients with NASH are also at a higher risk of hepatocellular carcinoma (6, 7). Finally, the risk of CVD is also much higher and is the leading cause of death (11).

In the past 2 decades, the prevalence of NAFLD has grown rapidly. It is the leading cause of simultaneous liver-kidney transplantation and the second most common etiology for liver transplantation in the United States, with a trajectory to become soon number 1 (12). For the 18.2 million people in the United States estimated to have T2DM and NAFLD, the 20-year cost of medical care will climb to $55.8 billion and account for about one-third of all liver transplants to be performed, 812 000 liver-related deaths, and 479 000 cases of hepatocellular carcinoma (13). Taken together, it remains puzzling that NAFLD remains overlooked in primary care, as well as in endocrinology and diabetes clinics, and in most outpatient medical care settings. The good news is that recent work suggests that screening and intervention of adults at the highest risk, such as those with T2D and NAFLD (ie, with lifestyle or pioglitazone), is clearly cost-effective (14). Therefore, the grim outlook is preventable if people at risk are identified early in the endocrinology or primary care setting (15).

Overview of the Management of Patients With NAFLD

Because endocrinologists see many patients with insulin resistance, metabolic syndrome, and/or T2D, they should consider themselves as being at the very cornerstone of any comprehensive management plan. There is a growing consensus about the need to develop multidisciplinary teams for the care of patients with NASH (primary care physicians, endocrinologists, nutritionists, gastroenterologists, hepatologists, behavior modification, and other specialists) (16, 17). Of particular value for endocrinologists will be utilization of a recently developed clinical care pathway that stratifies patients based on a diagnostic panel and eventually transient elastography (FibroScan) as having either having a low, intermediate, or high risk of liver fibrosis (18) (a simplified, adapted version is included in Fig. 1). The severity of liver fibrosis is established by a stepwise approach that determines their overall risk based on the metabolic profile of each patient (ie, presence of obesity, T2D, CVD), use of plasma aminotransferases, blood diagnostic panels (such as the fibrosis 4 index [FIB-4] determined from a calculator that includes age, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and platelet count) (19–21), and imaging (ie, liver stiffness measurement [LSM] measured by vibration controlled transient elastography [FibroScan]) (22) or bidimensional-shear wave elastography (19). Eventually, a liver biopsy is needed when the risk of fibrosis is high.

Additional workup with proprietary plasma biomarkers or magnetic resonance imaging techniques, such as proton spectroscopy or proton density fat fraction (19), corrected T1 LiverMultiScan (23) and/or magnetic resonance-elastography (19) are best left to the hepatologist (18).

Patients with T2D are at the highest risk of having clinically significant fibrosis, as suggested by a recent study by Lomonaco et al (24) in 561 middle-aged Americans with T2D. Participants unaware of having NAFLD were invited to be screened for hepatic steatosis and fibrosis by transient elastography (FibroScan) while attending their routine primary care or diabetes clinic visit. The prevalence of NAFLD was 70% and that of moderate-to-advanced fibrosis (stages F2-F4) was 15%. Fewer than one-third of patients with fibrosis had an AST or ALT ≥40 U/L, suggesting that an approach based on plasma aminotransferases alone is insufficient to identify most patients. These findings (high prevalence of disease but plasma AST or ALT <40 U/L in most patients) are consistent with other recent screening studies in patients with T2D from the United States (20, 25), Europe (26), and Southeast Asia (27). This may prompt a change in management toward a broader screening with diagnostic panels such as FIB-4 (that adds no direct cost) for all patients with obesity and T2D that would go beyond today's recommendation of screening only patients with T2D who have steatosis (already present in the vast majority but most times missed) or elevated ALT (normal in the vast majority) (28). The role of the endocrinologist in routinely calculating the FIB-4 (Fig. 1) is central to the success of a NAFLD clinical care pathway recently developed by a multispecialty task force (18) for the timely referral of patients to the hepatologist. Of note, the aim of screening is to stage the severity of fibrosis in patients with NASH and treat it early on because its presence is closely associated with future liver-specific and overall mortality (16, 18, 29, 30).

In addition to lifestyle changes, such as adoption of a Mediterranean diet and regular exercise to promote weight loss in obesity (31), management includes becoming familiar with treatment options already included in recent consensus statements (16, 18) and several guidelines (6, 7). Although many drugs are in development for the treatment of NASH, currently no treatment is US Food and Drug Administration (FDA)-approved. However, vitamin E has been shown in randomized controlled trials (RCTs) to induce liver histological benefit in adults with NASH without diabetes (32) with results that were more mixed in patients with T2D (33). Pioglitazone improves steatohepatitis, and to a lesser extent fibrosis (34), both in patients with (33, 35, 36) and without (32, 37) diabetes. However, as discussed next, this review hopes to increase the awareness among endocrinologists about the role of glucagon-like peptide-1 receptor agonists (GLP-1RAs) not only as a valuable asset to manage diabetes and obesity, but also as effective for the management of NASH (38, 39).

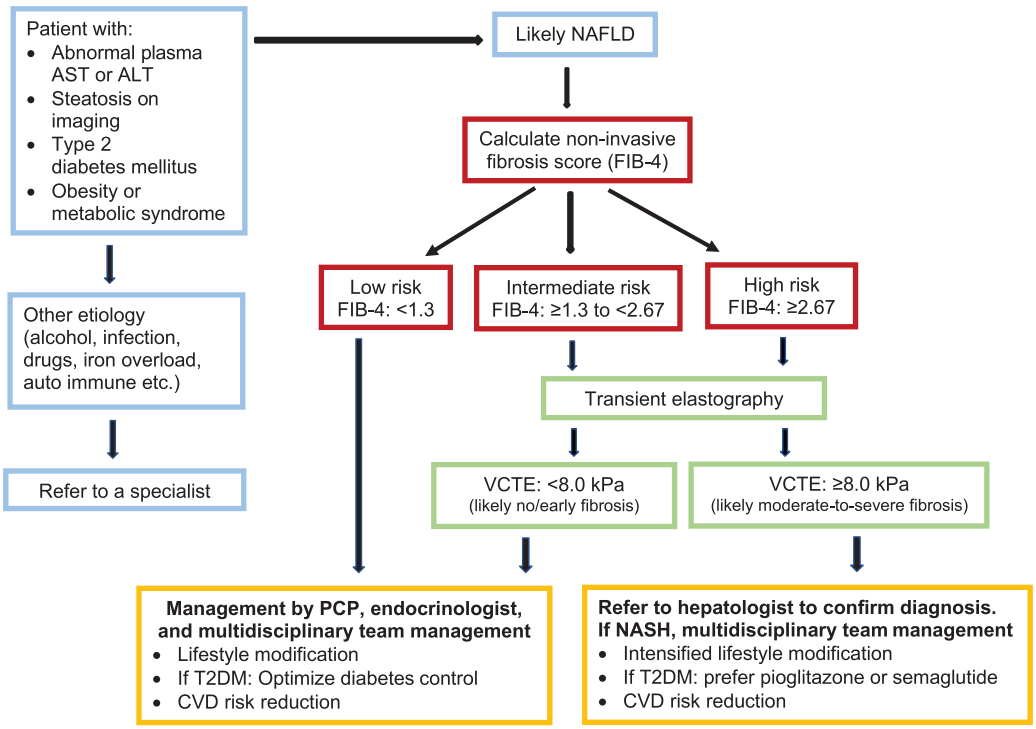

Figure 1. Approach to patients at risk of clinically significant liver fibrosis.

GLP-1RAs: Rationale for Their Use in Patients With NASH

There are many mechanisms by which GLP-1RAs promote metabolic improvement and weight loss, as reviewed elsewhere (5, 40). We focus on recent studies that support their use among endocrinologists for the management of adults with NAFLD/NASH.

Effects of GLP-1RAs in Patients With T2DM

Current guidelines recommend GLP-1RAs for patients with T2D in need of weight loss or with CVD (41). Glycated hemoglobin (Hba1c) decreases in a dose-dependent manner (usually between 1% and 2%) linked to a number of patient-related determinants (ie, baseline Hba1c, pretreatment body weight, duration of diabetes) and factors specific to each GLP-1RA (ie, short [exenatide twice daily and lixisenatide] vs long-acting [all others available in clinical practice], relative potency, weight-loss induction) (42–44). Although there has been variability in the results from GLP-1RAs in cardiovascular outcome trials (CVOTs) in patients with T2DM, the direction of the change has been usually favorable, even if not all reached the primary efficacy endpoint of improvement in major cardiovascular events, such as with lixisenatide (The Evaluation of Lixisenatide in Acute Coronary Syndrome [ELIXA]) (45) or later with exenatide (Exenatide Study of Cardiovascular Event Lowering [EXSCEL]) (46). Clear positive results have been reported with liraglutide (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [LEADER]) (47) or weekly injectables such as semaglutide (A Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes [SUSTAIN-6]) (48) or dulaglutide (Dulaglutide and cardiovascular outcomes in type 2 diabetes [REWIND]) (49). Treatment with oral semaglutide (A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes [PIONEER 6]) (50) also showed a similar positive trend as the injectable semaglutide formulation in SUSTAIN-6, but short of statistical significance ($P = 0.17$) as not powered as a CVOT. A systematic review of CVOT including 56 004 participants, concluded that treatment with glucagon-like peptide-1 receptor agonists (GLP-RAs) reduce death from cardiovascular causes by 12% ($P < 0.003$), fatal or nonfatal stroke by 16% ($P = 0.0001$), fatal or nonfatal myocardial infarction by 9% ($P = 0.043$), all-cause mortality by 12% ($P = 0.001$), hospital admission for heart failure by 9% ($P = 0.028$), and a composite of kidney outcomes by 17% ($P < 0.0001$) (51). Of interest, cardiovascular benefits of GLP-RA extend to patients age >65 and even ≥75 (52).

At least in part, cardiovascular risk reduction is attributed to their ability to decrease systolic blood pressure between 1.8 mmHg to 4.6 mmHg (42). Another beneficial effect is an improvement in total and low-density lipoprotein cholesterol and triglyceride levels (43). Hypertension and dyslipidemia are common in patients with NAFLD. In terms of safety, the most common adverse events are mild-to-moderate gastrointestinal side effects (nausea, diarrhea, dyspepsia, and vomiting) (51). They are dose-dependent and usually transient. In the CVOTs, severe hypoglycemia, pancreatitis, or pancreatic cancer were not observed (51). A similar conclusion was reached in a meta-analysis that included 100 trials, although there was an increased risk of cholelithiasis (odds ratio 1.30; 95% CI, 1.01-1.68; $P = 0.041$) (53).

In summary, the American Diabetes Association recommendation (41) for using GLP-1RAs to improve glycemic control and reduce CVD in patients with T2DM comes as a valuable reassurance for their use in patients with NAFLD/NASH because cardiovascular disease is also the number 1 cause of death in this population (10, 11).

GLP-1RAs for the Treatment of Obesity

Lifestyle modification that leads to weight loss improves steatohepatitis but is accepted to be difficult to sustain in the long term (6, 18, 31). Treatment with GLP-1RAs promote weight loss by reducing appetite/food craving and enhancing satiety, delaying gastric emptying, and increasing brown adipose tissue thermogenesis and by mechanisms modulating gut-to-brain communication (5, 40). Many RCTs have compared the efficacy for weight loss between GLP-1RAs in patients with T2D (42). These studies demonstrate a dose-dependent weight loss that is greater with higher potency GLP-1RAs, such as semaglutide. Programs specifically developed for weight management have only tested liraglutide 3.0 mg/daily (Satiety and Clinical Adiposity Liraglutide Evidence [SCALE]) (54–57) and semaglutide 2.4 mg/weekly (Semaglutide Treatment Effect in People with Obesity [STEP]) (58–62). The phase 3 SCALE program was based on 4 RCTs of liraglutide 3.0 mg/daily of 32- to 56-week duration, involving 5358 people: SCALE Obesity and Prediabetes (54), SCALE Diabetes (55), SCALE Maintenance (56), and SCALE Sleep Apnea (57). Taken together, there was a significantly larger number of patients achieving a decrease in body weight of ≥5% and ≥10% with liraglutide, with a mean weight loss from baseline ranging from 5.7% to 8.0% (6.0-8.4 kg) compared with 0.1% to 2.6% (0.1-2.8 kg) with placebo. In a 3-year follow-up of the SCALE Obesity and Prediabetes, the greater weight loss with liraglutide translated into a >50% reduction in the risk of progression from prediabetes to T2D (63). This

is important to clinicians in primary care as progression from prediabetes to T2D is 2.2-fold higher in patients with NAFLD (64).

Because greater weight loss was observed in early head-to-head trials of semaglutide compared with liraglutide (65), the STEP program involved several RCTs (n = 4988) (58) developed to assess the efficacy and safety for weight management of higher dose semaglutide (2.4 mg/weekly). Results of the 68-week-duration STEP 1 to STEP 4 trials have been recently reported (STEP 1: weight management [WM] (58, 59); STEP 2: WM in T2D (60); STEP 3: intensive behavioral therapy (61); STEP 4: sustained WM (62); STEP-5 is an ongoing 102-week treatment trial). As anticipated, weight loss was greater than in the SCALE trials. The most impressive is perhaps STEP 4 (62), in which patients with overweight/obesity without T2D, all initially treated with semaglutide 2.4 mg/weekly for 20 weeks, were randomized to receive either continued semaglutide or placebo for another 48 weeks. The mean weight loss of volunteers that continued on semaglutide was 7.9% in contrast to a weight regain of 6.9% on placebo. Pooling the STEP 1 to 4 studies together, semaglutide 2.4 mg/weekly led to a mean weight loss ranging from -7.9% to -16% (-7.1 to -16.8 kg), whereas with placebo it ranged from +6.9% to -5.7% (+6.1 to -6.2 kg). These results led to the approval on June 4, 2021 of semaglutide 2.4 mg/weekly (as Wegovy) for the treatment of obesity (https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014). Such results clearly make semaglutide a strong candidate for the use in patients with NAFLD.

Treatment of NAFLD With GLP-1RAs

Effect of GLP-1RAs on Hepatic Steatosis

The hepatic effects of GLP-1RA involve multiple indirect pathways including an adaptation of portal and peripheral plasma insulin and glucagon concentrations, improvement in hepatocyte mitochondrial function and in hepatic insulin sensitivity (66), abatement of adipose tissue lipotoxicity from weight loss as well as weight-independent mechanisms (5, 40). However, it does not appear to be from a direct effect on hepatocytes because the most recent evidence suggests that hepatocytes lack GLP-1 receptors (67, 68).

Liraglutide has been the GLP-1RA most broadly studied in NAFLD (69). An early study by Okhi et al (70) observed a decrease in weight and plasma aminotransferases in 82 Japanese patients with T2DM and NAFLD divided into 3 treatment groups (liraglutide, sitagliptin, or pioglitazone). Small uncontrolled studies followed with comparable results, many reporting a reduction in liver fat content (LFC) with magnetic resonance-based imaging techniques (69). Table 1 includes only the larger, longer duration studies (≥50 people and ≥24-week duration) where one can appreciate that treatment with liraglutide consistently leads to weight loss (from 2.2% to 6.4%) and is associated with lower LFC (from 19% to 32%). For instance, in the study by Feng et al (71), liraglutide was clearly superior compared with metformin or gliclazide, whereas Petit et al (72) observed a close correlation between reduction in LFC and the degree of weight loss ($P < 0.0001$).

In controlled trials, Vanderheiden et al (73) reported an improvement in HbA1c, insulin secretion, plasma aminotransferases, and LFC in 71 patients with longstanding T2D on high-dose insulin therapy (>1.5 units/kg/day). Frossing et al (74) treated women with polycystic ovarian syndrome with resolution of hepatic steatosis in about two-thirds of them. Dulaglutide 1.5 mg/week also may lower plasma aminotransferases in people with T2D in a pattern consistent with steatosis reduction (75), as confirmed recently by Kuchay et al (76). Of interest, the recent FDA approval (2020) of the higher doses of dulaglutide (3.0 mg or 4.5 mg/weekly) may provide an opportunity for greater dose-related reductions in body weight and overall efficacy in NAFLD, as suggested from a recent trial in patients with T2D inadequately controlled with metformin (77).

Effect of GLP-1RAs on Steatohepatitis and Hepatic Fibrosis

Two RCTs have examined the effect of GLP-1RAs on liver histology. Armstrong et al (38) randomized 52 overweight patients with biopsy-proven NASH to either liraglutide 1.8 mg/daily or placebo for 48 weeks. Resolution of NASH (primary endpoint) occurred in 39% of patients with liraglutide compared with 9% on placebo ($P = 0.019$). Progression of fibrosis was also less with liraglutide (9% vs 36%, respectively; $P = 0.04$). The study was limited by its small sample size, few patients with T2D, and lack of change in the composite NAFLD activity score, but provocative enough to inspire additional interest in the drug class.

The role of semaglutide in patients with NASH (39) generated significant anticipation given its greater potency compared to liraglutide in head-to-head studies (65, 78) and reported reductions in plasma ALT (79). The study randomized 320 patients with biopsy-proven NASH and fibrosis to receive either injectable semaglutide once daily at 3 different doses (0.1 mg, 0.2 mg, 0.4 mg) or placebo for 72 weeks. Daily doses aimed to deliver more drug while

Table 1. Summary of studies on the effect of GLP-1RA on hepatic steatosis by imaging or liver histology in patients with NAFLD

Primary outcome: relative reduction in liver fat on imaging[a]					
Author	GLP1-RA	n	Study design	Weight change[b]	Reduction in liver fat content
Vanderheiden et al, 2016	Liraglutide	71	RCT	↓ 2.2%	↓ 31%
Feng et al, 2017	Liraglutide	87	Open label	↓ 6.4%	↓ 19%
Petit et al, 2017	Liraglutide	68	Open label	↓ 4.4%	↓ 19%
Frossing et al, 2018	Liraglutide	72	RCT	↓ 5.7%	↓ 32%
Kuchay et al, 2020	Dulaglutide	52	Open label	↓ 2.6%	↓ 20%
Primary outcome: percentage of patients with resolution of NASH (by liver histology)[c]					
Author	GLP1-RA	n	Study design	Weight change[b]	NASH resolution
Armstrong et al, 2016	Liraglutide	52	RCT	↓ 4.8%	30%
Newsome et al, 2020	Semaglutide	320	RCT	↓ 4%-12%	19%-42%

Studies with a minimal treatment period of ≥24 weeks and ≥50 patients. Arrows indicate statistically significant changes vs comparator.
Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; NAFLD, nonalcoholic fatty liver disease; RCT, randomized controlled trial.
[a] Placebo or comparator subtracted change in hepatic steatosis.
[b] Placebo or comparator subtracted weight loss.
[c] Placebo-subtracted change in number of patients with resolution of NASH.

minimizing gastrointestinal side effects, although it resulted in similar gastrointestinal tolerability to weekly formulations. Of note, there was a good representation of patients with T2D (62%). Treatment led to a dose-dependent metabolic improvement and reduction in liver enzymes, with a mean weight loss of 13% in the 0.4-mg semaglutide group compared with 1% in the placebo group. The primary histological endpoint of resolution of steatohepatitis without worsening of fibrosis, an established FDA endpoint in NASH RCTs, was significantly greater with semaglutide vs placebo, with a significant difference at all doses but largest with 0.4 mg/daily compared with placebo (59% vs 17%, $P < 0.001$). Despite these positive findings, the proportion of patients with fibrosis stage improvement fell short of statistical significance, ranging from 32% to 49% compared with 33% on placebo. The reasons for the unexpected lack of fibrosis improvement (although observed with weight loss ≥10% during lifestyle interventions studies) (6, 31, 40) is unknown. The reasons for the lack of fibrosis improvement likely reflects the short duration of the trial, relatively small study population, disease heterogeneity (genetic and environmental factors), and the imperfections related to the suboptimal "gold standard" of a liver biopsy with its challenges related to sample variability and reading across pathologists. Finally, from the limited information currently available, the response from these GLP-1RA trials has been similar in patients with or without diabetes, as well as whether patients are overweight or have severe obesity (38, 39, 80). Still, the results have hinted at the potential role of GLP-1RAs for the treatment of NASH and a larger phase 3 trial is under development.

Summary: Future Directions

NAFLD remains overlooked likely because of many factors that include patient and physician unawareness, lack of a highly sensitive and simple test to identify patients, constrained office visits with competing demands to address multiple comorbidities of obesity and T2D, and the lack of FDA-approved treatments to bring attention to the disease state. The recent development of a clinical care pathway (18) to identify early patients at the highest risk of fibrosis from NASH (ie, with T2D or ≥2 metabolic risk factors, with elevated ALT or steatosis, or family history of cirrhosis from NASH) may assist endocrinologists and clinicians in primary care settings to manage these complex patients, a management pathway consistent with existing guidelines (6, 7, 28). The FIB-4 is the most practical initial approach for staging liver fibrosis, with a score <1.3 indicating a low-risk of advanced fibrosis compared with a score ≥2.67 indicating a high probability and the need for referral to the specialist (18).

Promotion of a healthy lifestyle, and weight loss if needed, are cornerstones of management. However, adherence remains a challenge and alone may not be sufficient for severe disease activity or advanced fibrosis. In addition to vitamin E or pioglitazone, including GLP-1RAs in the pharmacological management of NASH is a promising option. Endocrinologists should prefer pioglitazone or GLP-1RAs for the management of T2D when steatohepatitis is present (18). Future studies should examine the role of oral GLP-1RA (ie, oral semaglutide), the role of SGLT2 inhibitors, and of the combination of diabetes medications with proven efficacy in the management of NASH. Also,

examine the role of genetics (81, 82) and other predictors to identify "treatment responders" to GLP-1RAs. Finally, recent results from the SURPASS trials with tirzepatide, a dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist, have promising implications for the management of obesity, diabetes and NAFLD (83–85). These studies show that tirzepatide at weekly doses ranging from 5 to 15 mg induce a significant dose-dependent reduction in body weight, ranging from ~8% to ~13%, together with a marked improvement in glucose metabolism and cardiometabolic risk factors. In these trials, benefits exceed those of semaglutide at 1mg/week (ie, currently the maximal dose approved for the treatment of T2D) (83, 84), although studies did not compare tirzepatide against the higher 2.4 mg/weekly dose of semaglutide approved for the management of obesity. Taken together, it is likely that in the near future GLP-1RA will play a greater role among clinicians to treat patients with NAFLD (86).

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Additional Information

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Data Availability: Data sharing is not applicable to this manuscript as no datasets were generated or analyzed during the current study.

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