REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Nonalcoholic Fatty Liver Disease: What Does the Primary Care Physician Need to Know?

Jeffrey Budd, MD,[a] Kenneth Cusi, MD[b,c]

[a]Division of General Internal Medicine; [b]Division of Endocrinology, Diabetes and Metabolism, University of Florida, Gainesville; [c]Malcom Randall VA Medical Center, Gainesville, Fla.

ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the United States and is soon to be the leading cause of liver transplantation. Patients at the greatest risk are those with obesity and type 2 diabetes mellitus. In 2019 the American Diabetes Association guidelines called, for the first time, for clinicians to screen for steatohepatitis and fibrosis all patients with type 2 diabetes and liver steatosis or abnormal plasma aminotransferases. This requires primary care physicians to be aware of key aspects related to the diagnosis and treatment of NAFLD, as well as to when to refer to a specialist. Unfortunately, there is still significant medical inertia as clinicians remain unaware of its high morbidity/mortality. Early diagnosis in the primary care setting is critical to prevent progression to end-stage liver disease. Patients with NAFLD are also at a higher risk of developing type 2 diabetes mellitus and cardiovascular disease. Despite general perception to the contrary, weight loss by lifestyle intervention or bariatric surgery and several pharmacological treatments (eg, vitamin E in nondiabetics, pioglitazone or glucagon-like peptide 1 receptor agonists in patients with or without diabetes) can often be successful to reverse steatohepatitis and prevent disease progression.

 • The American Journal of Medicine (2020) 133:536–543

KEYWORDS: Cirrhosis; Elastography; FIB-4; Glucagon-like peptide 1 receptor agonist; Hepatocellular carcinoma; Insulin resistance; Liver biopsy; Liver fat; NAFLD; NASH; Nonalcoholic steatohepatitis; Pioglitazone; Steatosis; SGLT2 inhibitor; Type 2 diabetes

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is defined as 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. Nonalcoholic steatohepatitis (NASH) is the association of steatosis with hepatocyte injury (hepatocyte ballooning) or with inflammation (hepatitis). In contrast to "simple" steatosis or nonalcoholic fatty liver (NAFL), NASH is often progressive and carries a significant risk of cirrhosis over time. This division is potentially dynamic, because NAFL can progress to NASH if metabolic (or other unknown) factors deteriorate, and NASH can revert with treatment.[1] Figure 1 summarizes the relationship between fatty liver, NAFLD, NAFL, and NASH.

DISEASE BURDEN: PREVALENCE OF NAFLD AND NASH

Obesity, insulin resistance, and diabetes are also common in NAFLD.[2-4] NAFLD is also an independent risk for chronic kidney disease and is associated with the severity of liver disease.[5] The overall prevalence of NAFLD in adults in the United States is ~25%, but >50% in type 2 diabetes mellitus,

Funding: None.

Conflict of Interest: JB has no conflicts of interest to report. KC has received research support as principal investigator for the University of Florida from Cirius, Echosens, Inventiva, Novartis, Novo Nordisk, Poxel and Zydus; and is a consultant for Allergan, Altimmune, Astra-Zeneca, BMS, Boehringer Ingelheim, Coherus, Deuterex, Eli Lilly, Fractyl, Genentech, Gilead, Intercept, Janssen, Pfizer, Poxel, Prosciento, Madrigal, Novo Nordisk, and Sanofi-Aventis.

Authorship: JB contributed with the first draft of the manuscript and editing of the manuscript. KC contributed to its critical revision, writing of subsequent versions, editing and submission of the manuscript. Both authors reviewed and approved the final manuscript.

Requests for reprints should be addressed to Kenneth Cusi, MD, FACP, FACE, Department of Medicine, Endocrinology, Diabetes and Metabolism Division, University of Florida, 1600 SW Archer Road, room H-2, Gainesville, FL 32610.

E-mail address: Kenneth.Cusi@medicine.ufl.edu

0002-9343/
https://doi.org/10.1016/j.amjmed.2020.01.007

and even higher in patients with diabetes in Europe or West and South Asia.[6] Of note, liver ultrasound underestimates the prevalence of NAFLD in mild-to-moderate cases that can still be associated with steatohepatitis.[7] There are about 18.2 million people in the United States living with type 2 diabetes mellitus and NAFLD, of which 6.4 million (37%) are believed to have NASH.[8] Younossi et al[8] estimated that over the next 20 years, NASH in patients with type 2 diabetes mellitus will be responsible for 65,000 transplants, 1.37 million cardiovascular-related deaths, 812,000 liver-related deaths, and will cost about $55.8 billion in the health care system. In the United States and worldwide, NAFLD has become the most common cause of chronic liver disease in adults,[9,10] even in children,[11] and the second leading indication for transplantation behind hepatitis C.[12]

NAFLD is also associated with an overall higher mortality, which increases exponentially with fibrosis stage.[13-15] The leading cause of death is cardiovascular disease, followed by malignancy and liver disease.[13,16-18] Primary care physicians (PCPs) must aggressively treat cardiovascular risk factors in NAFLD, as death from cardiovascular disease is much higher than that from liver disease.[15-21]

Unfortunately, PCPs still miss most patients with NASH. And in patients already identified with NAFL, there is often inadequate monitoring for their potential progression to NASH,[1] even in subspecialty gastroenterology practices.[22] Typical reasons why many patients remain unidentified or untreated are: 1) Patients or PCPs are unaware of NAFLD or NASH as a harmful disease; 2) The diagnosis is not considered when risk factors are present; 3) A confirmatory liver biopsy is not done in those at high risk for NASH-fibrosis; and 4) physicians are unaware that several treatment options exist.[3,22,23]

CLINICAL SIGNIFICANCE

- Nonalcoholic fatty liver disease is a common cause of liver disease and carries significant liver and extrahepatic morbidity and mortality. The critical step after a diagnosis of steatosis is to assess for significant liver fibrosis.
- Patients with obesity, type 2 diabetes, or cardiovascular disease are at increased risk.
- The critical step after a diagnosis of steatosis is to assess for significant liver fibrosis.
- Obese patients with type 2 diabetes who have nonalcoholic steatohepatitis have the highest risk of progressive disease and cirrhosis.
- Treatment strategies should target both liver disease (lifestyle intervention, bariatric surgery, pioglitazone, glucagon-like peptide 1 receptor agonists, or vitamin E) and cardiovascular risk factors.

ASSOCIATED COMORBIDITIES

As summarized in Figure 2, NAFLD is linked with several systemic comorbidities and the metabolic syndrome. But, despite common belief, it is not simply synonymous with, or a manifestation of, the metabolic syndrome.[20,23] In fact, NAFLD can be seen in nonobese patients and in many insulin-resistant patients without metabolic syndrome.[23] The prevalence of metabolic syndrome in NAFLD and NASH is 43% and 71%, respectively,[2] and associated with further increased mortality.[15,24]

NAFLD seems to be an additional, independent risk for the development of heart disease.[15-20,25] Risk factors such as insulin resistance, hypertension, and atherogenic dyslipidemia are common and likely the strongest contributors to their increased cardiovascular risk.[26] Dyslipidemia is typically secondary to the insulin resistance associated with steatosis, with decreased high-density lipoprotein cholesterol, elevated triglycerides, smaller low-density lipoprotein cholesterol particle size, and an elevated number of apolipoprotein B particles.[27]

DIAGNOSIS

Establishing the Presence of Hepatic Steatosis

Figure 3 summarizes the process to diagnose NAFLD, NAFL, and NASH. No laboratory test or imaging technique

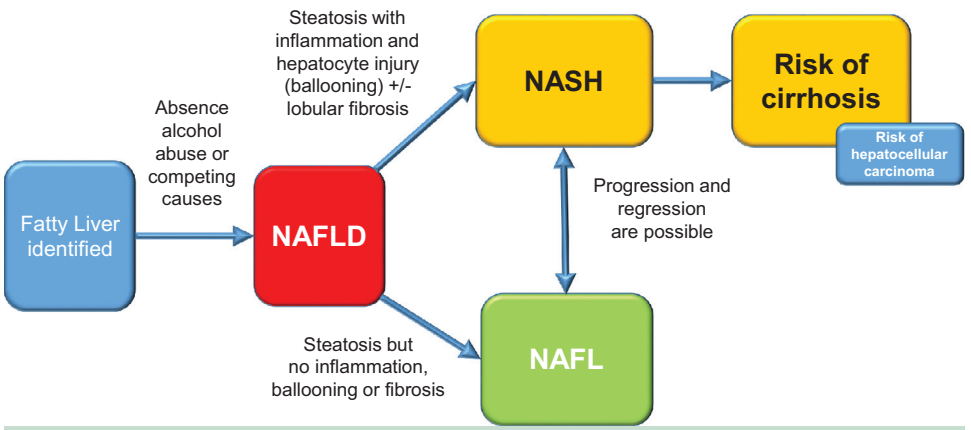

Figure 1 Relationship between fatty liver, NAFLD, NAFL, and NASH. NAFL = nonalcoholic fatty liver; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis.

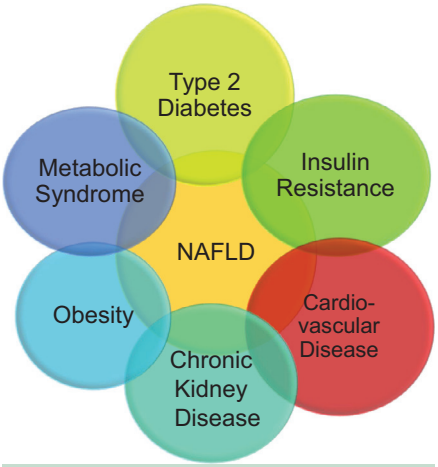

Figure 2 NAFLD comorbidities. NAFLD = nonalcoholic fatty liver disease.

can conclusively diagnose NASH, but they can offer a strong indication of hepatic steatosis or fibrosis ("NASH-fibrosis"), which is the ultimate goal of screening. Ultrasound is an acceptable first-line diagnostic procedure for steatosis, but has low sensitivity (worse in severe obesity) and suffers from operator variability.[7] If available, transient electrography offers improved sensitivity/specificity over conventional ultrasound by translating liver stiffness into stages of fibrosis.[35] The device most widely used by hepatologists is Fibroscan (Echosens North America, Waltham, Mass), assessing both liver fat determined by controlled attenuation parameter and fibrosis by vibration-controlled transient elastography (VCTE).[35] Liver fat is measured most accurately with magnetic resonance imaging (MRI)-based techniques, such as by MR and spectroscopy or by MR proton-density fat fraction.[26,35-37] However, currently, MRI techniques are largely reserved for research given their higher cost and limited access.

As NAFLD is a diagnosis of exclusion, heavy alcohol use and competing causes for chronic liver disease must be ruled out (viral, autoimmune, metabolic, hereditary, or drug-induced liver diseases).[38-40] The American Association for the Study of Liver Diseases (AASLD) defines excessive alcohol use as more than 21 drinks per week in men or 14 drinks per week in women.[38] Patient work-up should include serology for hepatitis B and C, ferritin, antinuclear antibody, antismooth muscle antibodies, ceruloplasmin, and alpha-1 antitrypsin deficiency.[40]

Most often, patients with NAFLD have no symptoms.[41] Thus, a high level of suspicion is warranted, especially in patients with obesity or type 2 diabetes.[23,42] Another high-

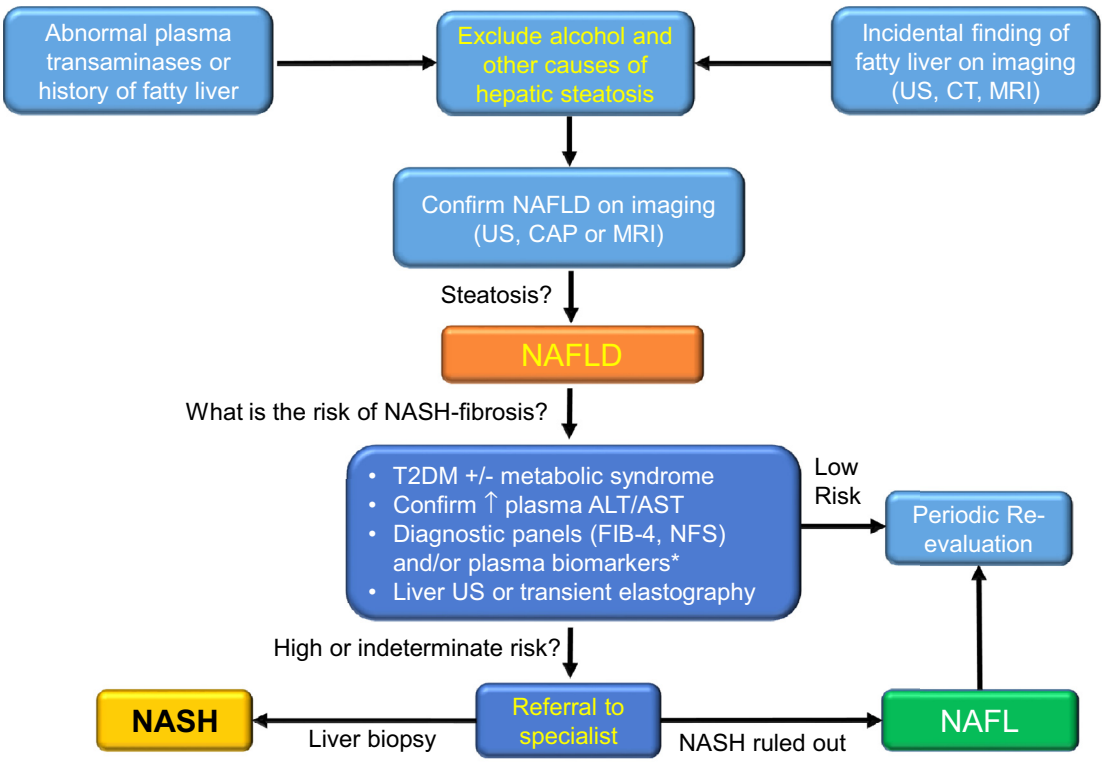

Figure 3 Diagnosis of NAFLD, NAFL, and NASH. ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAP = controlled attenuation parameter; MRI = magnetic resonance imaging; used largely in research settings); NAFL = nonalcoholic fatty liver; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; NFS = NAFLD fibrosis score; T2DM = type 2 diabetes mellitus; US = liver ultrasound.
*Plasma biomarkers: several commercial ones are available and others in development.[24,28-34]

risk group is patients sent to bariatric surgery, where about two-thirds may have steatosis and one-third NASH with fibrosis.[28] Despite the known morbidity/mortality associated with obesity and diabetes, guidelines have been somewhat inconsistent, likely due to the lack of long-term outcome data. The 2018 AASLD screening recommendations are: "Routine screening for NAFLD in high-risk groups attending primary care, diabetes, or obesity clinics is not advised at this time because of uncertainties surrounding diagnostic tests and treatment options, along with lack of knowledge related to long-term benefits and cost-effectiveness of screening."[38] But, they recognize that "There should be a high index of suspicion for NAFLD and NASH in patients with type 2 diabetes. Clinical decision aids such as NAFLD Fibrosis Score (NFS) or fibrosis-4 index (FIB-4), or VCTE, can be used to identify those at low or high risk for advance fibrosis (bridging fibrosis or cirrhosis)."[38] On the other hand, in a somewhat differing recommendation, the combined European Association for the Study of the Liver, European Association for the Study of Diabetes, and the European Association for the Study of Obesity states that "In subjects with obesity or MetS, screening for NAFLD by liver enzymes or ultrasound should be part of routine work-up. In high-risk individuals (age >50 years, type 2 diabetes mellitus, metabolic syndrome), case finding of advanced disease (ie, NASH with fibrosis) is advisable."[42] However, both guidelines are consistent in a recommendation against screening family members for NAFLD.[38,42] The 2019 American Diabetes Association guidelines called, for the first time, for clinicians to screen for steatohepatitis and fibrosis any patient with diabetes having elevated alanine aminotransferase (ALT) or liver steatosis (also included in the 2020 American Diabetes Association guidelines).[29]

Elevated plasma aminotransferases should prompt a consideration for NAFLD. Although not diagnostic, ALT is usually higher than aspartate aminotransferase (AST).[23] In most patients, an ALT ≥40 IU/L is usually an indicator of active steatohepatitis, while increased AST (≥26 IU/L, and definitively if ≥40 IU/L) is more an indicator of advanced fibrosis, although plasma aminotransferases have just a modest correlation with the severity of steatohepatitis or fibrosis.[30-32,43-45] Of note, normal ALT is ≤19 IU/L for women and ≤30 IU/L in men.[44] Still, most commercial laboratories report "abnormal plasma aminotransferases" as >40 IU/L. This cut-off lacks sensitivity to reliably rule out NAFLD/NASH, as shown by Portillo-Sanchez et al,[46] where 56% of obese patients with type 2 diabetes mellitus had NAFLD even as ALT was ≤40 IU/L. Because patients with diabetes are at such high risk of disease progression, it has been suggested that work-up for NAFLD should be done even with normal plasma aminotransferases.[42]

Determining the Presence of Steatohepatitis (NASH) and of Liver Fibrosis (Disease Stage)

Once the diagnosis of NAFLD is established, a referral to a specialist may be necessary to establish the diagnosis of NASH and need for a liver biopsy. Biopsy is the gold standard to rule out other causes of chronic liver disease, establish the diagnosis of steatohepatitis and stage the disease (severity of fibrosis), and help establish the best treatment strategy.[33,38,47] Its drawbacks are cost, sampling error, and complications.[38] Serious adverse events occur in ~1% of biopsies in advanced liver disease, although they are minimized in expert hands.[34]

Noninvasive methods usually determine the likelihood of liver fibrosis and the need for a liver biopsy.[48,36] Several scoring systems are available combining patient demographics with routine chemistries or varying plasma biomarkers.[23,30-32,36,38,42,43,45,48] Of these, the FIB-4, or alternatively, NFS, should be considered first because both are free and best validated.[38,42] In Figure 4 we summarize the parameters and interpretations for these 2 scores. In our personal experience, caution should be exerted when using NFS because this panel may overestimate the prevalence of liver fibrosis in patients with type 2 diabetes mellitus, as diabetes is already embedded in its formula. Referral to a specialist should be considered for patients with indeterminate or high estimated risk for severe fibrosis, as suggested in Figure 3.

Imaging by VCTE or MR elastography are 2 noninvasive methods to detect advanced fibrosis.[36,49,50] In both cases, the propagation of a shear wave through liver tissue is measured. Resistance to these shear waves reflects liver stiffness and degree of fibrosis. VCTE uses ultrasound to

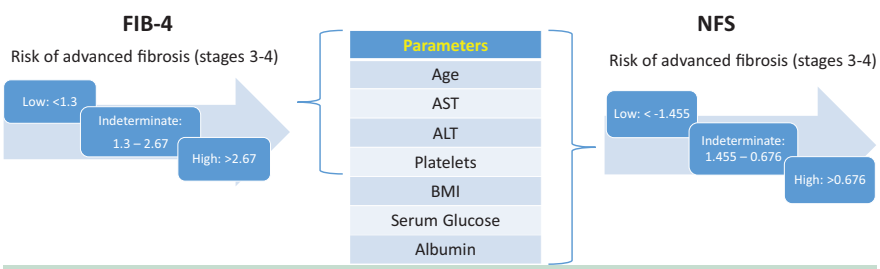

Figure 4 Parameters and interpretatio of FIB-4 and NFS for establishing the risk of advanced fibrosis (stages 3-4). ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; FIB-4 = fibrosis-4 score; NFS = NAFLD fibrosis score.

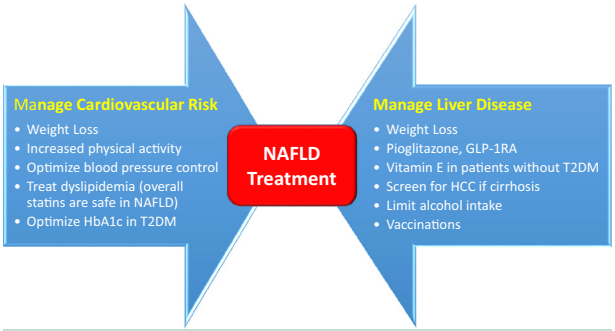

Figure 5 Integrated management of NAFLD.
HCC = hepatocellular carcinoma; NAFLD = nonalcoholic fatty liver disease; T2DM = type 2 diabetes mellitus.

measure this wave propagation, instead of magnetic resonance for MR elastography.[37,51] Acoustic radiation force imaging and shear wave elastography are other less commonly used imaging techniques to assess liver fibrosis in NAFLD.[36]

MANAGEMENT

NAFLD is a treatable disease. The target of therapy is not steatosis per se but rather steatohepatitis and fibrosis. Treatment should focus on patients with steatohepatitis with moderate-to-severe fibrosis (stage F2 and greater) because they are at the highest risk of cirrhosis. Management strategies are summarized in Figure 5.

Treatment of Steatohepatitis (NASH)

Weight loss is the cornerstone of treatment. Many nutritional approaches combined with lifestyle efforts have been tried, but the most important factor for reversal of NASH is the amount of weight loss achieved.[38,42] Possibly the approach with the greatest evidence of long-term cardiometabolic benefit is the Mediterranean diet centered on consumption of vegetables and fresh fruit, unprocessed cereals, nuts, fish or white meat, and olive oil, while avoiding simple sugars and red (or processed) meats.[20] Usually, weight loss of >5% is associated with a decrease in steatosis, but greater loss is needed for resolution of steatohepatitis and improvement in fibrosis.[42,52,53]

Weight loss medications or bariatric surgery should be considered. Of note, there are no US Food and Drug Administration (FDA)-approved drugs for NASH, but agents that induce weight loss or reverse insulin resistance improve steatohepatitis. In proof-of-concept studies, antiobesity medications approved by the FDA have shown to improve liver function tests and steatosis, even steatohepatitis, in proportion to the weight loss achieved.[54] Bariatric surgery is also cost effective for obese patients with NASH regardless of fibrosis stage.[55,56] The AASLD recommends considering bariatric surgery for patients with NASH who would be eligible otherwise.[38]

A treatment approach aimed at treating both diabetes and NASH appears to be the most practical and cost-effective strategy. Among FDA-approved pharmacological agents for the treatment of diabetes, neither sulfonylureas, dipeptidyl peptidase-4 inhibitors, acarbose, metformin, or insulin are believed to significantly improve steatohepatitis or liver fibrosis, although decreases in AST/ALT or liver fat have been reported in small uncontrolled studies.[3,20] Treatment of patients with NAFLD with the glucagon-like peptide 1 receptor agonist (GLP-1RA) liraglutide has led in most studies to a reduction in plasma aminotransferases and steatosis.[57] Similar outcomes have been reported with other GLP-1RAs, with results heavily influenced by treatment duration and the magnitude of weight loss.[20,57] Armstrong et al[58] reported improvement in liver histology in 52 patients with NASH treated with liraglutide for 48 weeks. An ongoing randomized controlled trial (RCT) of semaglutide in patients with NASH will report results in late 2020 (Clinical.Trials.gov NCT02970942). Finally, recent studies suggest a role for sodium-glucose co-transporter-2 (SGLT2) inhibitors for the treatment of NAFLD. They may induce modest (2%-4%) weight loss, and in small studies, reported decreases in ALT and of hepatic steatosis.[59]

The best evidence for pharmacological treatment of NASH is from 5 RCTs including a total of 498 patients where pioglitazone (30 or 45 mg/d) vs placebo consistently improved steatohepatitis.[30,60-64] Improvement occurs in ≥50% of patients, depending on the specific primary outcome of each trial. The placebo-subtracted difference in resolution of NASH ranges from 30% to 40%. Liver fibrosis improved in 2 of these trials.[61,62] Pioglitazone is a dual peroxisome proliferator-activated receptor-γ/α agonist that reverses insulin resistance and improves mitochondrial function in hepatocytes, among several postulated mechanisms of action.[65-67] Pioglitazone has been included in current guidelines for patients with or without type 2 diabetes mellitus and biopsy-proven NASH.[29,38,42]

Vitamin E at a dose of 800 units/d improves liver histology in nondiabetic adults with NASH,[63] although benefit has been modest in patients with diabetes.[64] In children, ALT decreases but changes in steatohepatitis on histology are insignificant compared with placebo.[68] How vitamin E works is unclear, but is believed to be related to its antioxidant properties.[69] Controversy persists about the relationship between vitamin E treatment at doses >400 units/d and all-cause mortality in the general population.[70] Recent meta-analyses suggest no harm.[71,72] The AASLD limits the vitamin E recommendation to adults without diabetes and with biopsy-proven NASH.[38]

Other aspects of liver disease deserve attention. Heavy drinking should be discouraged.[38] Vaccinations recommended for all chronic liver disease should also be considered for NAFLD (influenza, pneumococcal, hepatitis A and B).[73] NASH cirrhosis carries a significant risk for hepatocellular carcinoma and calls for regular screening by a specialist.[38,42]

Management of Cardiovascular Risk Factors

Cardiovascular disease is the leading cause of mortality in patients with NAFLD.[15-20,38,42] Management should include careful glucose, lipid, and blood pressure control.[20,23] Several medications for the treatment of diabetes, such as pioglitazone, GLP-1RAs, and SGLT2 inhibitors, also reduce cardiovascular disease.[3,65]

Attention to glycemic control in patients with diabetes may delay progression of microvascular complications, but it has not been tested in an RCT in terms of slowing the progression of NASH.[23] Statin therapy for dyslipidemia is safe in patients with NAFLD/NASH.[38,74,75] Despite this evidence, patients with NAFLD are less likely to receive appropriate statin therapy.[21,75] Control of hypertension reduces cardiovascular risk. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers (also statins) have been associated with a reduced risk of liver fibrosis.[76] However, the evidence from RCTs is weak.[74,75]

MONITORING AND FOLLOW-UP

In the absence of steatosis, but when risk factors for NAFLD exist, repeating plasma aminotransferases or an ultrasound every 3-5 years should be considered.[42] Because simple steatosis (NAFL) can be progressive, monitoring for change in status is also needed, but the most cost-effective way remains uncertain. As discussed, establishing the overall risk of fibrosis when steatosis is present is best done by combining patient demographics, plasma AST/ALT with liver panels (ie, FIB-4), and by imaging, such as ordering elastography testing. Patients identified with a high risk of advanced NASH-fibrosis should be referred to a hepatologist. If confirmed on a liver biopsy, the patient should be treated and monitored by a multidisciplinary team that involves the PCP, nutritionist for weight reduction, endocrinologist if diabetes is present, and a hepatologist. Of note, NAFLD in diabetes may not only be associated with a greater risk of cardiovascular disease, but also of microvascular diabetic complications.[5,23,26] Because of this, PCPs and endocrinologists should routinely consider if NASH may be present in patients with type 2 diabetes mellitus, as they do for diabetic retinopathy or nephropathy.

CONCLUSION

PCPs need to be aware of several key points about NAFLD. First, NAFLD is not as believed in the past simply an irrelevant diagnosis of "fatty liver" but carries a risk of significant morbidity and mortality. Second, the diagnosis should always be considered when working up liver disease, especially in patients with obesity and prediabetes/type 2 diabetes mellitus. Screening guidelines today are more centered on case finding, although rapidly evolving. The risk of NASH-fibrosis/cirrhosis should be a consideration in any patient with elevated plasma transaminases or steatosis on imaging (Figure 3). Third, once NAFLD is diagnosed, the next critical step is estimating the risk of fibrosis to prevent disease progression. A referral to a specialist should be considered if risk falls in the indeterminate or high-risk categories (Figure 4). Finally, NAFLD is treatable and should encompass a strategy targeting liver disease and cardiovascular risk management (Figure 5). Weight loss of 5%-10% is essential and is best achieved as part of a structured program. Pioglitazone has proven to be safe and effective in patients with NASH with or without diabetes and is recommended in current guidelines. GLP-1RAs and SGLT2 inhibitors will likely play a greater role in NASH treatment, alone or combined with pioglitazone or newer agents, given their impact on cardiovascular disease. Many new agents are being tested for the treatment of NASH.[77] It is time for PCPs to raise awareness among patients and peers to routinely include NASH in the management of patients with obesity or type 2 diabetes mellitus.

References

1. Pais R, Charlotte F, Fedchuk L, et al. A systematic review of follow-up biopsies reveals disease progression in patients with non-alcoholic fatty liver. *J Hepatol* 2013;59(3):550–6.
2. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016;64(1):73–84.
3. Khan RS, Bril F, Cusi K, Newsome PN. Modulation of insulin resistance in nonalcoholic fatty liver disease. *Hepatology* 2019;70(2):711–24.
4. Marchesini G, Moscatiello S, Di Domizio S, Forlani G. Obesity-associated liver disease. *J Clin Endocrinol Metab* 2008;93(11 suppl 1):S74–80.
5. Musso G, Gambino R, Tabibian JH, et al. Association of non-alcoholic fatty liver disease with chronic kidney disease: a systematic review and meta-analysis. *PLoS Med* 2014;11(7):e1001680.
6. Younossi Z, Tacke F, Arrese M, et al. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Hepatology* 2019;69(6):2672–82.
7. Bril F, Ortiz-Lopez C, Lomonaco R, et al. Clinical value of liver ultrasound for the diagnosis of nonalcoholic fatty liver disease in overweight and obese patients. *Liver Int* 2015;35(9):2139–46.
8. Younossi ZM, Tampi RP, Racila A, et al. Economic and clinical burden of nonalcoholic steatohepatitis in patients with type 2 diabetes in the U.S. *Diabetes Care* 2020;43(2):283–9.
9. Calzadilla Bertot L, Adams LA. The natural course of non-alcoholic fatty liver disease. *Int J Mol Sci* 2016;17(5). https://doi.org/10.3390/ijms17050774.
10. Noureddin M, Loomba R. Nonalcoholic fatty liver disease: indications for liver biopsy and noninvasive biomarkers. *Clin Liver Dis* 2012;1(4):104–7.
11. Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. *Pediatrics* 2006;118(4):1388–93.
12. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the united states. *Gastroenterology* 2015;148(3):547–55.
13. Ong JP, Pitts A, Younossi ZM. Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease. *J Hepatol* 2008;49(4):608–12.
14. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. *Hepatology* 2017;65(5):1557–65.
15. Allen AM, Terry TM, Larson JJ, Coward A, Somers VK, Kamath PS. Nonalcoholic fatty liver disease incidence and impact on metabolic

burden and death: a 20 year-community study. *Hepatology* 2018;67(5):1726–36.
16. Mathews SE, Kumar RB, Shukla AP. Nonalcoholic steatohepatitis, obesity, and cardiac dysfunction. *Curr Opin Endocrinol Diabetes Obes* 2018;25(5):315–20.
17. Francque SM, van der Graaff D, Kwanten WJ. Non-alcoholic fatty liver disease and cardiovascular risk: pathophysiological mechanisms and implications. *J Hepatol* 2016;65(2):425–43.
18. Erlinger S. Do patients with nonalcoholic fatty liver disease die from their heart? *Clin Res Hepatol Gastroenterol* 2011;35(3):163–5.
19. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med* 2010;363(14):1341–50.
20. Stefan N, Haring HU, Cusi K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. *Lancet Diabetes Endocrinol* 2019;7(4):313–24.
21. Blais P, Lin M, Kramer JR, El-Serag HB, Kanwal F. Statins are underutilized in patients with nonalcoholic fatty liver disease and dyslipidemia. *Dig Dis Sci* 2016;61(6):1714–20.
22. Rinella ME, Lominadze Z, Loomba R, et al. Practice patterns in NAFLD and NASH: real life differs from published guidelines. *Therap Adv Gastroenterol* 2016;9(1):4–12.
23. Bril F, Cusi K. Management of nonalcoholic fatty liver disease in patients with type 2 diabetes: a call to action. *Diabetes Care* 2017;40(3):419–30.
24. Younossi ZM, Otgonsuren M, Venkatesan C, Mishra A. In patients with non-alcoholic fatty liver disease, metabolically abnormal individuals are at a higher risk for mortality while metabolically normal individuals are not. *Metabolism* 2013;62(3):352–60.
25. Erlinger S. Do patients with nonalcoholic fatty liver disease die from their heart? *Clin Res Hepatol Gastroenterol* 2011;35(3):163–5.
26. Bril F, Cusi K. Nonalcoholic fatty liver disease: the new complication of type 2 diabetes mellitus. *Endocrinol Metab Clin North Am* 2016;45(4):765–81.
27. Bril F, Sninsky JJ, Baca AM, et al. Hepatic steatosis and insulin resistance, but not steatohepatitis, promote atherogenic dyslipidemia in NAFLD. *J Clin Endocrinol Metab* 2016;101(2):644–52.
28. Udelsman BV, Corey KE, Lindvall C, et al. Risk factors and prevalence of liver disease in review of 2557 routine liver biopsies performed during bariatric surgery. *Surg Obes Relat Dis* 2019;15(6):843–9.
29. American Diabetes Association. Comprehensive medical evaluation and assessment of comorbidities. *Standards of medical care in Diabetes−2020. Diabetes Care*. 2020;43(suppl 1):S37–47.
30. Bril F, McPhaul MJ, Caulfield MP, et al. Performance of plasma biomarkers and diagnostic panels for nonalcoholic steatohepatitis and advanced fibrosis in patients with type 2 diabetes. *Diabetes Care* 2020;43(2):290–7.
31. Siddiqui MS, Yamada G, Vuppalanchi R, et al. Diagnostic accuracy of noninvasive fibrosis models to detect change in fibrosis stage. *Clin Gastroenterol Hepatol* 2019;17(9):1877–1885.e5.
32. Bril F, McPhaul MJ, Caulfield MP, et al. Performance of the SteatoTest, ActiTest, NashTest and FibroTest in a multiethnic cohort of patients with type 2 diabetes mellitus. *J Investig Med* 2019;67(2):303–11.
33. Nalbantoglu IL, Brunt EM. Role of liver biopsy in nonalcoholic fatty liver disease. *World J Gastroenterol* 2014;20(27):9026–37.
34. Seeff LB, Everson GT, Morgan TR, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. *Clin Gastroenterol Hepatol* 2010;8(10):877–83.
35. Li Q, Dhyani M, Grajo JR, Sirlin C, Samir AE. Current status of imaging in nonalcoholic fatty liver disease. *World J Hepatol* 2018;10(8):530–42.
36. Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. *Gastroenterology* 2019;156:1264–81.
37. Mariappan YK, Glaser KJ, Ehman RL. Magnetic resonance elastography: a review. *Clin Anat* 2010;23(5):497–511.
38. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018;67(1):328–57.
39. Hashimoto E, Taniai M, Tokushige K. Characteristics and diagnosis of NAFLD/NASH. *J Gastroenterol Hepatol* 2013;28(suppl 4):64–70.
40. Adams LA, Talwalkar JA. Diagnostic evaluation of nonalcoholic fatty liver disease. *J Clin Gastroenterol* 2006;40(suppl 1):S34–8.
41. Bhatt HB, Smith RJ. Fatty liver disease in diabetes mellitus. *Hepatobiliary Surg Nutr* 2015;4(2):101–8.
42. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016;64(6):1388–402.
43. Bazick J, Donithan M, Neuschwander-Tetri BA, et al. Clinical model for NASH and advanced fibrosis in adult patients with diabetes and NAFLD: guidelines for referral in NAFLD. *Diabetes Care* 2015;38(7):1347–55.
44. Neuschwander-Tetri BA, Unalp A, Creer MH, Network Nonalcoholic Steatohepatitis Clinical Research. Influence of local reference populations on upper limits of normal for serum alanine aminotransferase levels. *Arch Intern Med* 2008;168(6):663–6.
45. Verma S, Jensen D, Hart J, Mohanty SR. Predictive value of ALT levels for non-alcoholic steatohepatitis (NASH) and advanced fibrosis in non-alcoholic fatty liver disease (NAFLD). *Liver Int* 2013;33(9):1398–405.
46. Portillo-Sanchez P, Bril F, Maximos M, et al. High prevalence of non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus and normal plasma aminotransferase levels. *J Clin Endocrinol Metab* 2015;100(6):2231–8.
47. Gaidos JK, Hillner BE, Sanyal AJ. A decision analysis study of the value of a liver biopsy in nonalcoholic steatohepatitis. *Liver Int* 2008;28(5):650–8.
48. Xiao G, Zhu S, Xiao X, Yan L, Yang J, Wu G. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: a meta-analysis. *Hepatology* 2017;66(5):1486–501.
49. Tapper EB, Challies T, Nasser I, Afdhal NH, Lai M. The performance of vibration controlled transient elastography in a US cohort of patients with nonalcoholic fatty liver disease. *Am J Gastroenterol* 2016;111(5):677–84.
50. Costa-Silva L, Ferolla SM, Lima AS, Vidigal PVT, Ferrari TCA. MR elastography is effective for the non-invasive evaluation of fibrosis and necroinflammatory activity in patients with nonalcoholic fatty liver disease. *Eur J Radiol* 2018;98:82–9.
51. Tapper EB, Castera L, Afdhal NH. FibroScan (vibration-controlled transient elastography): where does it stand in the united states practice. *Clin Gastroenterol Hepatol* 2015;13(1):27–36.
52. Musso G, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. *Diabetologia* 2012;55(4):885–904.
53. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology* 2015;149(2):367-78.e5;quiz e14-5.
54. Yoo ER, Sallam S, Perumpail BJ, et al. When to initiate weight loss medications in the NAFLD population. *Diseases* 2018;6(4). https://doi.org/10.3390/diseases6040091.
55. Klebanoff MJ, Corey KE, Chhatwal J, Kaplan LM, Chung RT, Hur C. Bariatric surgery for nonalcoholic steatohepatitis: a clinical and cost-effectiveness analysis. *Hepatology* 2017;65(4):1156–64.
56. Bower G, Toma T, Harling L, et al. Bariatric surgery and non-alcoholic fatty liver disease: a systematic review of liver biochemistry and histology. *Obes Surg* 2015;25(12):2280–9.
57. Cusi K. Incretin-based therapies for the management of nonalcoholic fatty liver disease in patients with type 2 diabetes. *Hepatology* 2019;69(6):2318–22.
58. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a

multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* 2016;387(10019):679–90.
59. Cusi K. Time to include nonalcoholic steatohepatitis (NASH) in the management of patients with type 2 diabetes. *Diabetes Care* 2020;69 (6):2318–22.
60. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006;355(22):2297–307.
61. Cusi K, Orsak B, Bril F, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. *Ann Intern Med* 2016;165 (5):305–15.
62. Aithal GP, Thomas JA, Kaye PV, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. *Gastroenterology* 2008;135(4):1176–84.
63. Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010;362 (18):1675–85.
64. Bril F, Biernacki DM, Kalavalapalli S, et al. Role of vitamin E for nonalcoholic steatohepatitis in patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care* 2019;42(8):1481–8.
65. Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: mechanisms and treatment options.. *JHEP Rep* 2019;1 (4):312–28.
66. Bril F, Kalavalapalli S, Clark VC, et al. Response to pioglitazone in patients with nonalcoholic steatohepatitis with vs without type 2 diabetes. *Clin Gastroenterol Hepatol* 2018;16(4):558–566.e2.
67. Kalavalapalli S, Bril F, Koemel JP, et al. Pioglitazone improves hepatis mitochondrial function in a mouse model of nonalcoholic steatohepatitis. *Am J Physiol Endocrinol Metab* 2018;315(2): E163–73.
68. Amanullah I, Khan YH, Anwar I, Gulzar A, Mallhi TH, Raja AA. Effect of vitamin E in non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomised controlled trials. *Postgrad Med J* 2019;95(1129):601–11.
69. Harrison SA, Torgerson S, Hayashi P, Ward J, Schenker S. Vitamin E and vitamin C treatment improves fibrosis in patients with nonalcoholic steatohepatitis. *Am J Gastroenterol* 2003;98 (11):2485–90.
70. Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 2005;142(1):37–46.
71. Curtis AJ, Bullen M, Piccenna L, McNeil JJ. Vitamin E supplementation and mortality in healthy people: a meta-analysis of randomised controlled trials. *Cardiovasc Drugs Ther* 2014;28(6):563–73.
72. Aune D, Keum N, Giovannucci E, et al. Dietary intake and blood concentrations of antioxidants and the risk of cardiovascular disease, total cancer, and all-cause mortality: a systematic review and dose-response meta-analysis of prospective studies. *Am J Clin Nutr* 2018;108(5):1069–91.
73. Leise MD, Talwalkar JA. Immunizations in chronic liver disease: what should be done and what is the evidence. *Curr Gastroenterol Rep* 2013;15(1):300.
74. Chatrath H, Vuppalanchi R, Chalasani N. Dyslipidemia in patients with nonalcoholic fatty liver disease. *Semin Liver Dis* 2012;32(1):22–9.
75. Bril F, Portillo Sanchez P, Lomonaco R, et al. Liver safety of statins in prediabetes or T2DM and nonalcoholic steatohepatitis: post hoc analysis of a randomized trial. *J Clin Endocrinol Metab* 2017;102(8):2950–61.
76. Goh GB, Pagadala MR, Dasarathy J, et al. Renin-angiotensin system and fibrosis in non-alcoholic fatty liver disease. *Liver Int* 2015;35(3):979–85.
77. Younossi ZM, Loomba R, Rinella ME, et al. Current and future therapeutic regimens for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Hepatology* 2018;68(1):361–71.