Nonalcoholic Fatty Liver Disease Screening in Type 2 Diabetes Mellitus Patients in the Primary Care Setting

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Nonalcoholic fatty liver disease (NAFLD) is a major public health problem worldwide and the most common chronic liver disease. NAFLD currently affects approximately one in every four people in the United States, and its global burden is expected to rise in the next decades. Despite being a prevalent disease in the general population, only a minority of patients with NAFLD will develop nonalcoholic steatohepatitis (NASH) with advanced liver fibrosis (stage 3-4 fibrosis) and liver-related complications. Certain populations, such as patients with type 2 diabetes mellitus (T2DM), are recognized to be at the highest risk for developing NASH and advanced fibrosis. Both the American Diabetes Association and the European Association for the Study of Diabetes recommend screening of all T2DM for NAFLD. Incorporating a simple noninvasive algorithm into the existing diabetic care checklists in the primary care practice or diabetologist’s office would efficiently identify patients at high risk who should be referred to specialists. The proposed algorithm involves a first-step annual fibrosis-4 score (FIB-4) followed by vibration-controlled transient elastography (VCTE) for those with indeterminate or high-risk score (FIB-4 ≥1.3). Patients at low-risk (FIB-4 <1.3 or VCTE <8 kPa) can be followed up by primary care providers for lifestyle changes and yearly calculation of FIB-4, while patients at high risk (FIB-4 ≥1.3 and VCTE ≥8 kPa) should be referred to a liver-specialized center. Conclusion: Patients with T2DM or prediabetes should be screened for NASH and advanced fibrosis. The proposed simple algorithm can be easily incorporated into the existing workflow in the primary care or diabetology clinic to identify patients at high risk for NASH and advanced fibrosis who should be referred to liver specialists. (Hepatology Communications 2021;5:158-167).

Over the last decades, the prevalence of nonalcoholic fatty liver disease (NAFLD) has been rising exponentially(1-3) and is currently estimated to affect approximately 80 million, or one in every four, people in the United States,(4) with a projection of more than 100 million individuals affected by 2030.(5) NAFLD can result in cirrhosis, liver failure, and hepatocellular carcinoma (HCC) and has become one of the leading indications for liver transplantation in the United States.(6,7)

NAFLD is defined as the accumulation of hepatic steatosis in ≥5% of hepatocytes in the absence of excessive alcohol consumption (<20 g/day for women and <30 g/day for men). It spans a wide spectrum of liver disease, ranging between two different histologic entities: nonalcoholic fatty liver (NAFL), a relatively benign disease, and nonalcoholic steatohepatitis (NASH), a more serious process. NAFL is defined by hepatic steatosis without evidence of hepatocellular injury, whereas NASH is defined by steatosis...
accompanied by lobular inflammation, hepatocyte ballooning (cell death), with or without fibrosis.\(^{(8,9)}\) NAFLD has a low risk of liver-related complications, whereas NASH has a potentially progressive course that can lead to liver fibrosis, cirrhosis, end-stage liver disease, HCC, and/or liver transplantation as well as extrahepatic complications, notably cardiovascular disease (CVD), extrahepatic malignancy, and chronic kidney disease.\(^{(10)}\)

Out of 80 million Americans currently diagnosed with NAFLD, approximately 25 million (up to 30%) have NASH and 5 million among them (up to 20%) have developed or will develop advanced fibrosis (stage 3-4 fibrosis) from NASH.\(^{(5,11)}\) Once patients develop advanced liver fibrosis, the risk of liver-related morbidity and mortality is largely increased. Therefore, the challenge for primary care providers (PCPs) is to identify early - in their daily practice - patients at high risk of NASH with advanced fibrosis who will need to be referred to liver specialists for monitoring and treatment of liver complications, potential upcoming treatments, and in case of end-stage liver disease, assessment of indications for liver transplantation.

However, NAFLD is frequently underdiagnosed, and patients are often presented to specialty clinics at advanced stages when therapeutic options are limited. In a recent study, cirrhosis was diagnosed incidentally in 2 out of 3 NAFLD patients with cirrhosis.\(^{(12)}\) Furthermore, in a survey conducted among PCPs, 85% underestimated the prevalence of NAFLD\(^{(13)}\) while at the same time, 78% of PCPs did not consider themselves well prepared to manage patients with NAFLD/NASH.\(^{(14)}\)

The paradox of NAFLD as a highly prevalent disease with only a small proportion progressing to severe disease has led to NAFLD currently being one of the most challenging public health problems worldwide. Population-wide policies to effectively identify, refer, and manage those patients are needed.\(^{(15)}\) A successful strategy would include simple cost-effective tools and algorithms for PCPs to screen, diagnose, and refer patients at high risk of developing liver complications to liver specialists for further work-up and management while those at low risk of developing liver complications could be managed by PCPs. Effective risk stratification of patients would both increase the referral of patients at high risk and decrease the referral of those at low risk to liver specialists, thereby improving health care access and resource allocation to those who need it the most.

### Common Risk Factors for NAFLD

NAFLD is closely associated with insulin resistance and is often considered the hepatic manifestation of metabolic syndrome.\(^{(16)}\) In a 2016 meta-analysis on patients with NAFLD, the rates of obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension were 51%, 23%, 69%, and 39%, respectively.\(^{(4)}\)

T2DM is one of the strongest risk factors for the development of NASH, advanced fibrosis/cirrhosis,\(^{(17,18)}\) HCC,\(^{(19)}\) and mortality.\(^{(18,20)}\) Moreover, the underlying association between NAFLD and T2DM is two way, suggesting that NAFLD may precede and/or enhance the development of T2DM and promote diabetes-associated adverse outcomes.\(^{(21)}\) T2DM affects 10.5% of Americans (=34 million), and approximately 1.5 million new cases are diagnosed every year. It is estimated that 40%-70% of patients with T2DM have underlying NAFLD,\(^{(22-24)}\) and among those, 37% have NASH and 17% will develop advanced...
fibrosis. Extrapolated in the United States population, this means that up to 24 million patients with T2DM have NAFLD, while 9 million have NASH and 4 million are at risk for advanced fibrosis (Fig. 1).

Similarly to T2DM, obesity is prevalent in the general population. In the United States, according to the National Health and Nutrition Examination Survey, 42.9% of adults are currently obese and 9.2% are extremely obese (defined by a body mass index ≥40 kg/m²). Obesity is one of the most important risk factors for NAFLD and has been linked with the presence and severity of liver fibrosis. A prospective cohort of 40,700 patients with NAFLD showed that obesity and weight gain were independent predictors of the presence of liver fibrosis.

Genetic and epigenetic determinants have also been found to play a role in the natural history of patients with NAFLD, particularly because family members of patients with NASH are reported to have a more severe disease. Genome-wide association studies have revealed links between specific single nucleotide polymorphisms and the course of the disease, including the patatin-like phospholipase domain-containing 3 (PNPLA3), transmembrane 6 superfamily member 2 (TM6SF2), and more recently 17-beta hydroxysteroid dehydrogenase 13 (HSD17B13), membrane-bound O-acyltransferase domain-containing 7 (MBOAT7), and transmembrane channel-like 4 (TMC4) variants.

**Clinical Disease Progression and Liver-Related Complications**

The natural history and different rates of disease progression and clinical manifestations can be attributed to multiples factors, such as metabolic comorbidities, microbiome, environmental, and genetic/epigenetic factors.

NASH, and most importantly the presence of advanced liver fibrosis, are critical determinants of long-term prognosis and are associated with a higher rate of overall mortality (liver-related mortality, and CVD). Thus, identifying patients at high risk earlier in the disease course is vital to prevent and monitor for the risk of liver-related complications.
such as liver failure and HCC, the most common primary liver cancer.

In parallel with the observed rise in prevalence of NAFLD, the burden of NAFLD-related HCC is also increasing.\(^{(38)}\) Cirrhosis from all etiologies is a risk factor for HCC. NASH is one of the leading etiologies of HCC, with projection models showing the NASH contribution to HCC overtaking chronic hepatitis C by 2025.\(^{(39)}\) In general, the 5-year survival rate for HCC from all etiologies is low (approximately 15%) due to diagnosis at a late stage.\(^{(40)}\) Patients with cirrhosis should be screened every 6 months with liver imaging so that they can be diagnosed early at a curable stage. In particular, patients with NASH cirrhosis are less likely to be screened for HCC than patients with cirrhosis from other etiologies, leading to diagnosis at more advanced stages when curative therapies are no longer possible and hence an even poorer prognosis,\(^{(41-43)}\) with an overall survival of approximately 11 months (vs. 15.5 months for patients with non-NASH HCC).\(^{(44)}\)

Liver transplantation is the only curative treatment for HCC and liver failure. Due to the rising incidence of liver failure and HCC from NAFLD, NALFD has become one of the leading indications for liver transplantation in the United States. Data from the Scientific Registry of Transplant Recipients between 2002 and 2016 show that the proportion of patients with NASH and HCC increased almost 8-fold (2.1% to 16.2%, \(P < 0.001\)) while the proportion of patients with NASH on the liver transplant waiting list increased more than 10-fold.\(^{(45)}\) Unfortunately, despite the increased need, available organs remain a limited resource.

**Risk Stratification by PCP**

NAFLD is an increasing global entity, and PCPs have a crucial role in the screening, stratification, management, and referral of these patients. However, a large number of high-risk cases remain undiagnosed, and low risk patients are unnecessarily referred to specialists.\(^{(51,52)}\)

Despite NAFLD being a prevalent disease in the general population (and thus in the primary care clinic), only a minority of patients with NAFLD have NASH and advanced liver fibrosis and are at high risk of developing liver-related complications. It is this significant minority who need to be evaluated and managed by specialists to prevent and monitor for liver-related complications while the remaining patients need primary care management of their cardiovascular risk as well as their metabolic syndrome. Risk stratification is therefore crucial for the appropriate referral of the high-risk minority to specialists.

For such a prevalent disease with a minority of high risk patients, universal screening would not be efficient or cost effective.\(^{(53)}\) Further, triggers for evaluation, such as increased liver tests or abdominal ultrasound findings, are insensitive for detecting advanced fibrosis.\(^{(54)}\) Therefore, a targeted approach to screen the population with the highest risk for advanced fibrosis, such as those with T2DM and obesity, would be most efficient and effective at identifying that significant minority of patients with advanced fibrosis.

**Extrahepatic Complications**

As NAFLD is considered a hepatic manifestation of the metabolic syndrome, patients with NAFLD are at increased risk for complications associated with the metabolic syndrome, such as CVD, cancer, and chronic kidney disease.\(^{(46)}\) CVD is the most common cause of mortality in patients with NAFLD. The same risk factors for more severe NASH are also risk factors for CVD, including male sex, age, insulin resistance and T2DM, abdominal obesity, hypertension, dyslipidemia, and increased carotid-artery intimal medial thickness.\(^{(47)}\) A 2016 meta-analysis\(^{(48)}\) of 16 cohort studies over a median follow-up of 7 years showed that NAFLD is associated with a higher risk of fatal and nonfatal cardiovascular events, including myocardial infarction, stroke, unstable angina, and coronary revascularization.

A strong association between NAFLD and chronic kidney disease has been largely described in the literature.\(^{(49)}\) NASH is associated with a 2-fold increase risk of chronic kidney disease, and patients with advanced liver fibrosis are at a 5-fold higher risk of chronic kidney disease compared to patients without fibrosis, independently of the presence of diabetes.\(^{(50)}\)

Finally, NAFLD as well as metabolic syndrome are also linked to other extrahepatic diseases, such as colorectal cancers, osteoporosis, psoriasis, and various endocrinopathies (e.g., polycystic ovary syndrome, thyroid dysfunction).\(^{(9)}\)
from NASH. In this manuscript, we focus on patients with T2DM.

PCPs and diabetologists represent the most important link in the chain of management of these patients because they are the first medical point of contact for this population. A simple, noninvasive, stepwise algorithm that is incorporated in the existing workflow and care systems of providers would ensure a higher screening rate.

**WHO TO SCREEN? T2DM AND PREDIABETES PATIENTS**

Selective screening on high-risk populations, such as patients with T2DM, will increase the yield as these patients have a high pretest probability and therefore a higher positive predictive value. Because patients with T2DM and prediabetes are at the highest risk for advanced fibrosis, we advocate for widespread screening of these patients in the primary care setting.

While there is variability in society guidelines on how and who to screen, there is universal recognition that patients with T2DM are at high risk for NAFLD, NASH, and advanced fibrosis. Although the European Association for the Study of the Liver (EASL) 2016 guidelines and the 2020 American Diabetes Association (ADA) guidelines both propose screening of all patients with T2DM, the American Association for the Study of Liver Diseases (AASLD) 2018 guidelines are more nuanced. The 2016 EASL guidelines\(^9\) proposed screening by means of liver enzymes and/or ultrasound assessment. All patients with steatosis, independently of liver enzymes, or individuals with persistently elevated liver enzymes should be further evaluated. The most recent 2020 guidelines published by the ADA\(^{55}\) also recommend that all patients with T2DM and prediabetes be evaluated for NAFLD. They recommend evaluation for NAFLD by measuring baseline and yearly liver enzymes and referral to a specialized center for persistently elevated or worsening transaminases. The AASLD guidelines\(^8\) state that “there should be a high index of suspicion for NAFLD and NASH in patients with T2DM,” but did not recommend systematic screening for NAFLD. They recommend the use of noninvasive measures of fibrosis, such as the NAFLD fibrosis score, fibrosis-4 index (FIB-4), or vibration controlled transient elastography (VCTE) to identify those at low or high risk for advanced fibrosis.

However, there is no clear consensus about how to implement screening and which patients should be referred to specialized centers. Moreover, these guidelines add one more task to PCPs and diabetologists to have to evaluate and consider. A recent article published by the U.S. Members of the Global NASH Council recommends risk stratifying patients according to metabolic risk factors, including T2DM, using FIB-4 as the first initial assessment. Patients with a FIB-4 score ≥1.3 should undergo further evaluation by a liver specialist.\(^{56}\)

**WHAT TO SCREEN FOR? NASH WITH ADVANCED FIBROSIS**

NASH, and most importantly liver fibrosis, are critical determinants of long-term prognosis of patients with NAFLD. Liver biopsy is the gold standard for the assessment of NASH and fibrosis; however, its invasive nature, high cost, sampling variability, and interobserver and intraobserver variability make it less suitable for screening and disease monitoring in clinical practice and unattractive to clinicians and patients.\(^{57}\) Many biomarkers have been investigated for the diagnosis of NASH and fibrosis. While we do not yet have a sufficiently accurate test to diagnose NASH available to be used in clinical practice, we do have a variety of biomarkers to estimate the stage of liver fibrosis.\(^{58,59}\) These biomarkers include clinical scoring systems (NAFLD fibrosis score, FIB-4, aspartate aminotransferase/platelet ratio index, BARD score), commercially available assays (enhanced liver fibrosis panel, Fibro Test [FibroSURE], HepatoScore, and FibroMeter), and physical measurements, such as liver stiffness (measured by VCTE, acoustic radiation force impulse, shear wave elastography, and magnetic resonance elastography). These noninvasive tools do not completely eliminate the need for liver biopsy but they drastically reduce the number of patients who need a liver biopsy.

As recently published by Armstrong and Marchesini,\(^{60}\) the use of a noninvasive scoring system, such as FIB-4 or NAFLD fibrosis score, is the simplest and most accurate strategy to identify patients at high risk of advanced fibrosis. It is widely known that serum transaminases, which were extensively used in the past, are not a good indicator of the
presence or severity of disease because many patients with NAFLD have normal serum transaminases, even in the presence of cirrhosis. In a recent study, the use of VCTE in a high-risk population (hazardous alcohol and/or T2DM) in primary care resulted in the diagnosis of cirrhosis in 3% of this population. Interestingly, 60% of these patients were obese or presented with T2DM.

Hence, risk assessment of NAFLD may be performed in primary care clinics using noninvasive testing in order to avoid unnecessary referrals. We recommend the use of FIB-4 and/or VCTE according to local resources, availability, and clinical context. The use of the FIB-4 score is attractive in the primary care setting because it is based on common clinical parameters (age, aspartate aminotransferase, alanine aminotransferase, and platelets) that are widely available and can be easily calculated during routine visits. Moreover, when compared to other noninvasive tests, the FIB-4 score has been shown to have the best diagnostic accuracy and a high negative predictive value (>90%) for advanced fibrosis when using the lower cutoff (1.3). Noninvasive scores, such as FIB-4, are best used to rule out rather than to rule in advanced fibrosis due to their higher specificity and negative predictive value, which argues in favor of our strategy to screen all patients with prediabetes and T2DM.

Liver stiffness as measured by VCTE is the best evaluated point-of-care technique, with a high negative predictive value and low operative cost. A recent study using data from 261 patients biopsy-proven from the European NAFLD registry showed that VCTE had better diagnostic performance than a general clinical score in assessing fibrosis. However, VCTE requires availability of the machine, a trained technician, and interpretation of the results and therefore is usually less accessible to PCPs.

**HOW TO SCREEN? INTEGRATION OF SCREENING FOR NASH WITH ADVANCED FIBROSIS INTO AN EXISTING CARE MODEL FOR PRIMARY CARE OR DIABETOLOGY CLINICS**

The optimal screening program needs to be a simple algorithm that can be seamlessly integrated into an existing workflow. Patients with T2DM are complex, with multiple comorbidities that can be rapidly time consuming in primary care clinics that are already overburdened. The average length of visits in a primary care office is estimated to be 17 minutes, which can be very limiting when multiple medical problems need to be managed and lifestyle measures should be explained and adapted to each patient’s reality. Interestingly, a study showed that if PCPs do the screening, counseling, immunization, drug prescription, routine chronic care, and treatment of acute conditions, they could in reality accommodate care for less than half of their practice. Strategies employed currently by physicians to meet the recommended standard of care issued by the ADA include a checklist system that mirrors the guidelines as well as patient navigators.

Most physicians have a checklist system that mirrors the guidelines. The most recent guidelines recommend screening patients with prediabetes or T2DM for NAFLD. A simple approach is to incorporate the calculation of FIB-4 into the existing checklists used in the diabetic population in primary care clinics. The 2020 guidelines published by the ADA include a checklist that includes baseline and yearly transaminases. The addition of platelet count to this checklist would easily allow for the calculation of the FIB-4 score to identify patients at high risk of advanced fibrosis. An indeterminate or high-risk score would then prompt additional evaluation with VCTE. This kind of approach would benefit from the introduction of a patient navigator that could manage the checklist and collaborate directly with PCPs and would allow integrating the screening of patients with advanced liver fibrosis into an already well-validated model of care. A recent study showed that FIB-4 followed by VCTE is likely the most cost-effective strategy for screening or detecting cirrhosis among patients with NAFLD in primary care clinics when compared to FIB-4 followed by magnetic resonance elastography or liver biopsy, proving that a sequential strategy with FIB-4 and VCTE may be a valid option to risk stratify these patients.

The introduction of a patient navigator into the care system of patients with chronic liver diseases or patients with diabetes has shown an improvement in care and glycemic control and better patient engagement. We believe that the integration of a patient navigator who comanages the checklist with the PCP would also greatly improve the screening rates as well as the rates of patients.
following up with subsequent testing and liver specialist services if needed. In the absence of a patient navigator, the use of electronic medical record reminders/flags could also be used. This strategy has been shown to improve the management of patients with diabetes and could be extended to the NAFLD population.\(^\text{76,77}\)

In summary, we propose the following stepwise approach for screening and management of patients with NAFLD (Fig. 2):

**A. Incorporation of the FIB-4 score into the care checklist and care pathway to identify patients at high risk of NASH with advanced fibrosis.**

1. Addition of a platelet count and FIB-4 calculator to the care checklist of the patient with diabetes or prediabetes.\(^\text{55}\) The formula for FIB-4 is readily available online.
2. Involvement of a patient navigator to (i) flag patients who need laboratory measurements for the calculation of FIB-4; (ii) identify patients with indeterminate or high-risk FIB-4 scores who need referral to a specialized liver center and/or referral for VCTE; (iii) follow-up to ensure that the patient underwent VCTE or the specialist appointment.

**B. Referral for VCTE**

1. **FIB-4 <1.3:** Low risk patients (patients are unlikely to have advanced fibrosis). Follow-up with PCPs for appropriate preventive interventions of lifestyle changes and a yearly calculation of FIB-4.
2. **FIB-4 ≥1.3:** Refer the patient for VCTE (i) if liver stiffness measure is <8 kPa: follow up with PCP and repeat FIB-4 and VCTE in 1 year; (ii) if liver stiffness measure is ≥8 kPa: Refer the patient to a liver specialist.

(Note, in case of VCTE failure, an alternative, such as shear wave elastography/acoustic radiation...)

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**FIG. 2.** Stepwise approach for screening, risk stratification, and referral of patients with NAFLD between primary care and diabetic clinics and liver specialists. A pragmatic risk stratification algorithm is crucial to identify patients at high risk of advanced liver fibrosis. In this algorithm, we propose screening all patients with T2DM or prediabetes for advanced liver fibrosis by using FIB-4. The proposed algorithm involves a first-step annual FIB-4 score followed by VCTE for those with indeterminate or a high-risk score (FIB-4 ≥1.3). Patients at low risk (FIB-4 ≤1.3 or VCTE <8 kPa) can be followed up by PCPs for lifestyle changes and yearly calculation of FIB-4, while patients at high risk (FIB-4 ≥1.3 and VCTE ≥8 kPa) should be referred to liver-specialized clinics for further assessment and evaluation.
force imaging, magnetic resonance elastography [particularly when body mass index is >35 kg/m²] may be considered according to local availability).

C. Referral to specialized liver centers for further assessment of all patients with FIB-4 ≥1.3 and VCTE ≥8 kPa.

Regarding extrahepatic complications, patients with NAFLD have a significantly increased risk of cardiovascular mortality, which is independent of the stage of liver disease. We propose that all patients with NAFLD would benefit from a careful assessment of their 10-year cardiovascular risk using the atherosclerotic CVD risk calculator. Moreover, according to ADA 2020 guidelines[78] and in the absence of contraindications, T2DM patients should benefit from statin therapy in primary prevention in the following cases: (1) all patients between 40 and 75 years without atherosclerotic CVD; (2) all patients between 20 and 39 years with additional atherosclerotic CVD risk factors; (3) all patients with a 10-year atherosclerotic CVD risk ≥20%. Regarding the increased risk of chronic kidney disease, we propose a close surveillance of serum creatinine, estimated glomerular filtration rate, and albumin-to-creatinine ratio on urinary spot.

Conclusion

NALFD is now the leading cause of chronic liver disease in the United States and Europe, and its global burden is expected to rise in the next decades, carrying clinical, economic, and social implications. Despite affecting approximately one quarter of the worldwide population, only a minority of these patients will develop liver-related morbidity and mortality. There is growing recognition that certain populations, such as patients with T2DM, are at particularly high risk. More specific guidelines are needed in order to help physicians identify patients with NASH at high risk of liver-related complications. A successful strategy would include incorporation of a simple cost-effective algorithm into an existing diabetes care system, such as the use of checklists and patient navigators. This algorithm would allow the PCPs to screen, stratify, and refer patients with high risk of NASH and advanced fibrosis to liver specialists for further work-up and management. Utility studies have already shown that the use of noninvasive screening strategies, particularly in patients at high risk, can be cost effective.

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