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AGA Clinical Practice Update: Diagnosis and Management of Non-Alcoholic Fatty Liver Disease (NAFLD) in Lean Individuals: Expert Review

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is well-recognized as a leading etiology for chronic liver disease, affecting over 25% of the U.S. and global population. Up to one in four individuals with NAFLD have nonalcoholic steatohepatitis (NASH), which is associated with significant morbidity and mortality due to complications of liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). Although NAFLD is observed predominantly in persons with obesity and/or type 2 diabetes mellitus, an estimated 7–20% of individuals with NAFLD have lean body habitus. Limited guidance is available to clinicians on appropriate clinical evaluation in lean individuals with NAFLD, such as for inherited/genetic disorders, lipodystrophy, drug-induced NAFLD, and inflammatory disorders. Emerging data now provide more robust evidence to define the epidemiology, natural history, prognosis, and mortality of lean individuals with NAFLD. Multiple studies reveal that NAFLD among lean individuals is associated with increased cardiovascular, liver, and all-cause mortality relative to those without NAFLD. This AGA Clinical Practice Update provides Best Practice Advice to assist clinicians in evidence-based approaches to the diagnosis, staging, and management of NAFLD in lean individuals.

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MTL is on the advisory board for Novo Nordisk and receives research grant support from Echosens Corporation and Gilead Sciences. MN has been on the advisory board/consultant for 89BIO, Altimmune, Gilead, cohBar, Cytodyn, Intercept, Pfizer, Novo Nordisk, Blade, EchoSens, Fractyl, Madrigal, NorthSea, Prespectum, Terns, Siemens and Roche diagnostic; MN has received research support from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Madrigal, Novartis, Pfizer, Shire, Viking and Zydus; MN is a shareholder or has stocks in Anaetos, Chronwell, Ciema, Rivus Pharma and Viking. JKL has received research contracts (to Yale University) from Allergan, Celgene, Genfit, Gilead, Intercept, Pfizer, and Viking.

Methods—This expert review was commissioned and approved by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership and underwent internal peer review by the Clinical Practice Updates Committee and external peer review through standard procedures of *Gastroenterology*.

Best Practice Advice Statements—Best Practice Advice #1: Lean NAFLD should be diagnosed in individuals with NAFLD and a BMI < 25 kg/m² (non-Asian race) or a BMI < 23 kg/m² (Asian race).

Best Practice Advice #2: Lean individuals with NAFLD should routinely be evaluated for comorbid conditions, such as type 2 diabetes, dyslipidemia, and hypertension.

Best Practice Advice #3: Lean individuals with NAFLD should be risk stratified for hepatic fibrosis to identify those with advanced fibrosis or cirrhosis.

Best Practice Advice #4: Lean individuals in the general population should not undergo routine screening for NAFLD; however, screening should be considered for individuals over the age of 40 with type 2 Diabetes.

Best Practice Advice #5: NAFLD should be considered in lean individuals with metabolic diseases (such as type 2 diabetes, dyslipidemia, and hypertension), elevated liver biochemical tests, or incidentally noted hepatic steatosis.

Best Practice Advice #6: Clinicians should routinely query patients regarding alcohol consumption patterns in all patients with lean NAFLD.

Best Practice Advice #7: In patients with lean NAFLD, other causes of liver disease should be ruled out, including other causes of fatty liver, such as HIV, lipodystrophy, LAL-D, familial hypobetalipoproteinemia, and medication-induced hepatic steatosis (methotrexate, amiodarone, tamoxifen, and steroids).

Best Practice Advice #8: Current evidence is inadequate to support routine testing for genetic variants in patients with lean NAFLD.

Best Practice Advice #9: Liver biopsy, as the reference standard, should be considered if there is uncertainty regarding contributing causes of liver injury and/or the stage of liver fibrosis.

Best Practice Advice #10: Serum indices (NAFLD fibrosis score and FIB-4) and imaging techniques (transient elastography and MRI elastography) may be used as alternatives to liver biopsy for fibrosis staging and patient follow-up. These tests can be performed at the time of diagnosis and repeated at intervals of 6 months to 2 years, depending on fibrosis stage and the patient's response to intervention.

Best Practice Advice #11: If noninvasive tests (e.g., FIB-4 and NFS) are indeterminate, a second noninvasive test, (e.g., transient elastography or MR elastography) should be performed to confirm the stage and prognosis of NAFLD.

Best Practice Advice #12: In lean patients with NAFLD, lifestyle intervention, including exercise, diet modification, and avoidance of fructose and sugar-sweetened drinks, to target a modest weight loss of 3–5% is suggested.

Best Practice Advice #13: Administration of vitamin E may be considered in lean persons with biopsy-confirmed NASH but without type 2 diabetes or cirrhosis. Pioglitazone 30 mg po mg daily may be considered in lean persons with biopsy-confirmed NASH with or without type 2 diabetes but without cirrhosis.

Best Practice Advice #14: The therapeutic role of glucagon peptide 1 (GLP-1) agonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors in the management of lean NAFLD is not fully defined and requires further investigation.

Best Practice Advice #15: Hepatocellular carcinoma surveillance with abdominal ultrasound with or without serum AFP twice per year is suggested in patients with lean NAFLD and clinical markers compatible with liver cirrhosis.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is well-recognized as a leading etiology for chronic liver disease with a global public health impact, affecting over 25% of the United States (U.S.) and global population.¹ Up to one in four patients with NAFLD may have non-alcoholic steatohepatitis (NASH), which is associated with significant morbidity and mortality due to complications of liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC).¹ In the context of rising incidence and prevalence of NAFLD in tandem with obesity and the metabolic syndrome, NAFLD-associated cirrhosis and HCC now represent a leading indication for liver transplantation in the U.S.^{2, 3}

Although NAFLD is observed predominantly in persons with obesity and/or type 2 diabetes mellitus (T2DM), an estimated 7–20% of individuals with NAFLD have lean body habitus.^{1, 4–7} Although similar NASH pathogenesis may be observed in lean patients with NAFLD, rates of disease progression, associated conditions, and the diagnostic and management approach differs for lean vs non-lean patients with NAFLD. There is a major unmet need to provide clear guidance to clinicians regarding the evaluation and management of NAFLD among lean patients.

This review is designed to provide best practice advice on several key clinical issues pertaining to the diagnosis, risk stratification, and treatment of NAFLD in lean individuals. We developed 15 Best Practice Advice statements to address key issues with high clinical relevance.

Best Practice Advice #1: Lean NAFLD should be diagnosed in individuals with NAFLD and a BMI < 25 kg/m² (non-Asian race) or a BMI <23 kg/m² (Asian race).

Lean NAFLD is generally defined by the presence of NAFLD in an individual who does not have an overweight or obese body mass index (BMI). For adults, the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) define a normal range BMI to be between 18.5 – 24.9 kg/m², whereas a BMI of 25 – 29.9 kg/m² is considered overweight and a BMI of 30 – 34.9 kg/m² is grade 1 obesity.⁸ The WHO recommends a lower BMI cut-off for overweight and obesity (BMI of 23 – 27.5 kg/m² to define overweight and BMI > 27.5 kg/m² for obesity) for those of Asian ancestry, recognizing that different populations may experience metabolic risk at a lower BMI.^{8, 9}

We suggest using the term ‘lean NAFLD’ when discussing NAFLD in the setting of a normal range BMI, while considering race-based cut-offs. Although the terms ‘non-obese’ NAFLD and ‘lean’ NAFLD are sometimes used interchangeably, this review will focus on lean patients as defined by normal BMI. Recent findings from the Global NAFLD/NASH Registry revealed that approximately 6.8% of patients with confirmed NASH have lean body habitus and, relative to overweight/obese patients, this cohort appeared to be older, more often Asian, and had fewer components of the metabolic syndrome, while retaining similar risk for advanced liver fibrosis.¹⁰ Data from NHANES III epidemiology survey revealed that 10.8% of lean individuals had evidence of NAFLD, and were characterized as more likely to be older and more frequently men.¹¹

Best Practice Advice #2: Lean individuals with NAFLD should routinely be evaluated for comorbid conditions, such as T2DM, dyslipidemia, and hypertension.

Lean patients with NAFLD have been observed to have alterations in bile salt metabolism which may contribute to pathologic changes in cholesterol metabolism and liver fat.¹² Various studies have also reported differences in genetic variants, including the *TM6SF2* rs58542926 (T) allele, which protect against diet-associated obesity compared to those with non-lean NAFLD.¹²

An individual’s risk for cardiometabolic disease may differ in those with lean NAFLD compared to non-lean NAFLD. In several observational studies, patients with lean NAFLD had a lower proportion of cardiometabolic disease risk factors, including hypertension, T2DM, and metabolic syndrome, and less atherosclerotic disease compared to those with non-lean NAFLD.^{6, 13} Other studies have shown that compared to lean subjects without NAFLD, lean individuals with NAFLD have a similar or higher prevalence of multiple cardiometabolic risk factors, riskscores,¹⁴ and cardiovascular events as overweight and obese persons with NAFLD.^{13, 15–17} We suggest that lean persons with NAFLD be evaluated and treated for modifiable cardiovascular disease risk factors, including diabetes, dyslipidemia, and hypertension.

Best Practice Advice #3: Lean individuals with NAFLD should be risk stratified for hepatic fibrosis to identify those with advanced fibrosis or cirrhosis.

Several cross-sectional studies have observed that lean participants with NAFLD have a lower prevalence of advanced fibrosis and cirrhosis compared to those that were overweight or obese with NAFLD.^{6, 13} In a small longitudinal study, lean participants with biopsy-confirmed NAFLD followed for a median of 8.4 years had a higher risk of liver-related death compared to overweight or obese participants with NAFLD, though those with lean NAFLD had a higher prevalence of advanced fibrosis at baseline in this study.¹⁸ A larger longitudinal study of over 1300 subjects with biopsy-confirmed NAFLD from Europe and Australia showed that those with lean NAFLD had less severe histologic disease compared to non-lean NAFLD.¹⁹ Despite these differences, over about 7.5 years of follow-up, nearly 5% of those with lean NAFLD reported liver-related events even though the vast majority maintained a lean BMI.¹⁹ Similarly, in a population-based Swedish registry study with nearly 20 years of follow-up, patients with lean NAFLD had lower stages of fibrosis at baseline, but a higher risk for developing severe liver disease compared to non-lean patients

with NAFLD.¹⁵ These findings highlight that individuals with lean NAFLD are at risk for progressive liver disease, independent of weight gain, and should not be classified as having a benign NAFLD phenotype. All patients with lean NAFLD should undergo risk stratification with non-invasive tests (NITs) to identify those at highest risk for progression (see BPA #10).

Best Practice Advice #4 Lean individuals in the general population should not undergo routine screening for NAFLD; however, screening should be considered for individuals over the age of 40 with T2DM.

If approximately 10–20% of individuals with NAFLD are lean, this translates to 8–10 million adults in the US with lean NAFLD.²⁰ There is a lack of consensus on who should be screened for NAFLD, regardless of BMI. The European Association for the Study of Liver (EASL) and the European Diabetes and Obesity societies recommend screening for NAFLD in all patients with obesity or metabolic syndrome.²¹ The American Diabetes Association recommends evaluation for NASH and hepatic fibrosis in persons with T2DM and elevated liver biochemical tests or fatty liver on ultrasound.²² The American Association for the Study of Liver Disease (AASLD) does not endorse NAFLD screening,²³ and cites limited cost-effectiveness for screening for NAFLD in patients with T2DM.²⁴ However, emerging data suggest that screening and risk stratification pathways are cost-effective when applied to those with T2DM.^{25–27} This led to the recent adoption for screening in high risk individuals by the AGA²⁸. Since the prevalence of NAFLD among lean individuals is relatively low, general screening for NAFLD among lean individuals is not advised. However, screening for NAFLD and subsequent risk stratification for advanced fibrosis should be performed in lean persons with T2DM.

Best Practice Advice #5: NAFLD should be considered in lean individuals with metabolic diseases (such as T2DM, dyslipidemia, and hypertension), elevated liver biochemical tests, or incidentally noted hepatic steatosis.

In individuals with multiple cardiometabolic disease risk factors, elevations in liver biochemical tests, or incidentally noted hepatic steatosis, NAFLD should be considered in the differential diagnosis across the BMI range.²⁹ We suggest that the initial diagnostic approach should be the same for lean or non-lean individuals with suspected NAFLD. In the case of elevated liver biochemical tests, patients should undergo standard evaluation including for drug induced liver injury and chronic liver diseases.³⁰

Best Practice Advice #6: Clinicians should routinely query patients regarding alcohol consumption patterns in all patients with lean NAFLD.

When distinguishing between NAFLD and alcohol-related liver disease, many consider an average alcohol consumption over 14 drinks/week for women or 21 drinks/week for men to be consistent with alcohol-related liver disease rather than NAFLD.²³ However, alcohol use below this threshold likely contributes to liver fat. In a recent cohort study of participants who consumed alcohol within thresholds consistent with NAFLD, higher average weekly alcohol use associated with a higher prevalence of computed tomography-defined NAFLD.³¹ Moreover, alcohol use patterns, including the number of drinking days per week, the maximum number of drinks consumed in 24 hours, and binge drinking

behavior, all associated with an increased odds of NAFLD.³¹ We suggest that health care providers query patients on alcohol use and alcohol consumption patterns when considering possible contributions of alcohol to hepatic steatosis. Additionally, under-reported alcohol use likely contributes to the misdiagnosis of NAFLD in lean individuals. Sensitive biomarkers of alcohol use including urine ethyl glucuronide (detection within 3–5 days) and blood phosphatidylethanol (detection within 1–2 weeks) can be considered to exclude alcohol overuse.

Best Practice Advice #7. In patients with lean NAFLD, other causes of liver disease should be ruled out, including other causes of fatty liver, such as HIV, lipodystrophy, LAL-D, familial hypobetalipoproteinemia, and medication-induced hepatic steatosis..

Causes of primary or secondary steatosis in lean persons should be considered. The causes of “lean NAFLD” include those related to diet (e.g., high fructose or high fat intake); changes in fat distribution of the body (e.g., visceral obesity); changes in body composition (e.g., lipodystrophy in HIV and non-HIV persons); medications (methotrexate, amiodarone, tamoxifen, and corticosteroids); and rare congenital abnormalities, such as lysosomal acid lipase deficiency (LAL-D), familial hypobetalipoprotein B, and abetalipoproteinemia.^{32, 33} Other conditions that should be considered are viruses (e.g., hepatitis C genotype 3), nutritional and gastrointestinal tract related factors (e.g., total parental nutrition), endocrine disorders (e.g., hypothyroidism), and toxin exposures (e.g. vinyl chloride) (Table 1).³³

We suggest a step-wise approach to ruling out alternative diagnoses for lean individuals with suspected NAFLD, particularly if cardiometabolic risk factors are absent and should be guided by clinical context as outlined in Table 2.

Best Practice Advice #8. Current evidence is inadequate to support routine testing for genetic variants in patients with lean NAFLD.

NAFLD pathophysiology is complex and is likely the result of interactions between many factors, including the interplay between genetic variants and environmental factors. In up to 75% of cases,³⁴ variable hepatic fat accumulation has been found related to inherited factors. Genetic variants in *PNPLA3 I148M*, *TM6SF2 E167K*, *MBOAT7*, *GCKR*, *HSD17B13* are the most common variants related to NAFLD and its severity.³⁵ These variants, especially the *PNPLA3* and *TM6SF2* variants,^{36,37,38} have been associated with the severity of steatosis, steatohepatitis, fibrosis, cirrhosis, and the risk of hepatocellular carcinoma and mortality.³⁹ On the other hand, *HSD17B13* has been linked to robust protection against liver inflammation, cirrhosis, HCC, and even to mortality.^{40, 41} Measurement of polygenic risk scores has evolved as a potential method to balance the genetic variants and achieve higher accuracy in correlating the disease and its severity. The risk scores are a weighted sum of disease-risk alleles that a person carries.^{34, 42, 43, 44} The polygenic or genetic risk scores are in early stages of investigation and are not advised for clinical use. Furthermore, given the paucity of data on genetic variants in lean NAFLD, routine genotyping in lean NAFLD patients is not advised.^{45–48} Additional studies are needed to inform an evidence-based approach to the selection of patients for genetic testing, appropriate assays, test interpretation, and clinical management.

Best Practice Advice #9. Liver biopsy, as the reference standard, should be considered if there is uncertainty regarding contributing causes of liver injury and/or the stage of liver fibrosis.

Liver biopsy is considered the reference standard for identifying NASH and staging hepatic fibrosis.^{23, 49} However, liver biopsy is invasive, and is associated with sampling errors and both intra-observer and inter-observer variability.²³ Despite its drawbacks, liver biopsy is the definitive method for diagnosing NAFLD/NASH, especially in the lean NAFLD population, and to exclude alternative etiologies (see Table 1). Liver biopsy should therefore be considered in lean patients with NAFLD if other causes cannot be excluded through routine testing. Additionally, liver biopsy, along with other specific tests (see Table 2) may be helpful in the considerations of more rare causes of lean NAFLD. As a standard practice, a tissue sample of 2-cm length or greater is preferred to allow an accurate reading.⁵⁰ The Brunt criteria and Kleiner score can be used to assess those patients who have NASH to provide categorical assessment of disease activity and fibrosis.^{51, 52}

Best Practice Advice #10. Serum indices (NAFLD fibrosis score and FIB-4) and imaging techniques (transient elastography and MRI elastography) may be used as alternatives to liver biopsy for fibrosis staging and patient follow-up. These tests can be performed at the time of diagnosis and repeated at intervals of 6 months to 2 years, depending on fibrosis stage and the patient's response to intervention.

Given the limitations of liver biopsy, numerous noninvasive tests (NITs) have been developed and have shown accuracy in the assessment of NAFLD-related fibrosis in lean individuals (Supplementary Table).⁵³ NITs can be categorized into: 1) those that use routinely performed laboratory and clinical tests to calculate a risk score, such as the Fibrosis-4 score (FIB-4) and NAFLD Fibrosis score (NFS); 2) imaging tools that quantify liver stiffness, the most frequently used method being transient elastography (TE), but two-dimensional shear wave elastography (2D-SWE) and magnetic resonance elastography (MRE) are also used; and 3) blood-based biomarkers of liver fibrosis, such as the enhanced liver fibrosis (ELF) test.^{53–59} Since fibrosis is the histologic feature most associated with poor outcomes, many NITs are focused on identifying NAFLD-related fibrosis and/or fibrotic NASH. Few studies have specifically evaluated NITs in lean individuals with NAFLD. In a multi-center study of 709 participants with NAFLD of whom 11% were lean, the AUROC curves for identifying advanced fibrosis were generally higher for most NITs among lean compared to obese participants.⁶⁰ In a study in patients with lean NAFLD, FIB-4 and NFS performed similarly in lean and obese patients, which is important as BMI is a part of the NFS calculation.⁶⁰ Importantly, NITs had high negative predictive values, which demonstrates the usefulness at ruling out advanced fibrosis. Finally, this study has also shown that vibration-controlled transient elastography (VCTE or TE) has similar performance in lean and obese patients.

MRE, with two-dimensional magnetic resonance elastography (2D-MRE), has been accurate in assessing fibrosis in patients with NAFLD.⁶¹ Although studies with MRE in lean NAFLD have not been conducted, MRE is thought to be less affected by BMI or body habitus.⁶¹ MRE should be considered, when available, as a confirmatory test for fibrosis assessment (Fig 1). The ELF test consists of measurements of N-terminal propeptide of type III

procollagen, hyaluronic acid, and tissue inhibitor of metalloproteinase-1. ELF has been used to assess hepatic fibrosis in addition to predicting liver outcomes. A systematic review and meta-analysis showed that an ELF low cut-off value of 7.7 has a sensitivity of 0.93 (95% CI 0.82–0.98) for excluding fibrosis and ELF at a high cutoff at 9.80 had a high specificity of 0.86 (95% CI 0.77–0.92) for diagnosing fibrosis⁵⁶. ELF has not been tested in patients with lean NAFLD, and further studies are needed. We conclude that ELF may be used as a confirmatory prognostic test in patients with lean NAFLD until further data are available.

We have proposed an algorithm for assessing and staging lean NAFLD patients. (Fig 1). Longitudinal NIT assessment of fibrosis should be considered every 6 months to 1 year in patients who have $\geq$ F2 and every 1–2 years in those who have F0 or F1 fibrosis.

Best Practice Advice #11. The results of some noninvasive tests (e.g., FIB-4 and NFS) may fall within the indeterminate zone. In this circumstance, a second noninvasive test, (e.g., transient elastography or MR elastography), if available, should be performed to confirm the stage and prognosis of the NAFLD.

Sequential testing, with two serologic tests or a serologic test combined with an imaging test, is likely to minimize the frequency of indeterminate cases and improve diagnostic accuracy. A study from primary care clinics in England assessed sequential testing of FIB-4 followed by TE among patients with T2DM.⁶² That strategy led to a nearly 7-fold increased diagnostic rate for identifying advanced fibrosis, and the data were supported by a meta-analysis that assessed > 5700 patients in whom sequential testing with FIB-4 and TE improved the sensitivity and specificity to rule in or rule out advanced fibrosis.⁶³ Data from the UK demonstrated that a FIB4+ELF care pathway reduced the referral of patients with mild disease.⁶⁴ Limited data specific to lean patients with NAFLD are available. However, sequential testing with serum tests and elastography may increase the accuracy of NITs in fibrosis staging in this population (Fig 1).

Finally, given that patients with NASH and $\geq$ F2 fibrosis are the targeted population for clinical therapy trials and future NASH-directed pharmacotherapy, recent studies have focused on combining biomarkers to identify NASH and $\geq$ F2 fibrosis or “at risk NASH” more accurately. The MRE Elastography Fibrosis-4 (MEFIB-4) scores combine MRE with FIB-4 in diagnosing $\geq$ F2 fibrosis with high accuracy and excellent PPV⁶⁵. The FibroScan-AST (FAST) score combines the steatosis values measured via controlled attenuation parameter (CAP) on TE, LSM on TE, and AST values to diagnose at risk NASH, with an AUROC between 0.8 and 0.85.⁶⁶ The MRI-AST (MAST) score combines the steatosis values measured via MRI proton density fat fraction (PDFF), LSM on MRE, and AST to diagnose patients with at risk NASH; MAST had an AUROC of 0.93 in the derivation cohort and an AUROC of 0.86 in the validation cohort.⁶⁷ Finally, NIS-4 is a blood-based biomarker panel that consists of miR-34a-5p, alpha-2 macroglobulin, YKL-40, and glycated hemoglobin.⁶⁸ The NIS-4 test assesses at risk NASH⁶⁸ and it had an AUROC of 0.80 (95% CI 0.73–0.85) in the discovery cohort. These tests have not been evaluated in lean NAFLD, but they may be used in identifying patients with at risk NASH (Fig 1). The advantage of these tests is that they measure steatohepatitis combined with fibrosis, thus examining the entire spectrum of the disease pathobiology.

Best Practice Advice #12. In lean patients with NAFLD, lifestyle intervention, including exercise, diet modification, and avoidance of fructose and sugar-sweetened drinks, to target a modest weight loss of 3–5% is suggested.

Lifestyle modification and medical weight loss through hypocaloric diet and exercise is recommended advised as a first-line intervention for treatment of NAFLD. However, specific guidance on how best to operationalize recommendations in obese and lean individuals are currently limited, and do not address variability in clinical phenotype based on host and liver disease factors. Current 2017 guidelines of the AASLD address the role of lifestyle modification as follows: “Weight loss generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity.”²³ In a large longitudinal study which included over 2000 lean adults with NAFLD, weight reduction over a median follow-up of 3 years was associated with NAFLD resolution in a dose dependent manner.⁶⁹ A randomized controlled trial from Asia investigated the effects of a 12 month lifestyle intervention on weight reduction and MR-spectroscopy liver fat fraction in non-obese and obese patients.^{70, 71} As expected, more patients in the intervention group had improvement in MR-liver fat, regardless of their obesity-status. Interestingly, almost half of non-obese individuals achieved NAFLD remission with 3–5% weight loss, while the same was reached in obese individuals with 7–10% weight loss. After up to 6 years of follow-up, non-obese patients in the lifestyle intervention group were more likely to maintain weight loss and ALT normalization compared to the reference group.

Other studies have shown that physical activity, aerobic and anerobic exercise were associated with reduction in liver fat and other metabolic benefits independent of weight loss.^{72–74} Finally, high fructose consumption is a well-known risk factor for NAFLD/NASH, especially in children and adolescents. In a study of young nonobese individuals without metabolic risk factors, the single independent factor for the detection of NAFLD was higher juice and soft drink intake contributing up to a four-fold increase risk of NAFLD compared with individuals consuming less sugar-sweetened beverages.⁷⁵ Therefore, limiting fructose intake is suggested in particular in younger lean patients with NAFLD.

Based on these data, we recommend modest weight loss of 3–5% in lean persons with NAFLD as it has been found to be beneficial. Although, the type of diet in lean NAFLD should be studied further, patients may benefit from limiting fructose and sugar-sweetened beverages. Exercise, increasing physical activity, and decreasing visceral fat are beneficial as well.

Best Practice Advice #13. Administration of vitamin E may be considered in lean persons with biopsy-confirmed NASH but without T2DM or cirrhosis. Pioglitazone 30 mg po mg daily may be considered in lean persons with biopsy-confirmed NASH without cirrhosis.

The current drug development efforts are predominantly focused on patients with NASH who are overweight and obese; indeed, many trials exclude lean patients. Therefore, evidence on effective pharmacotherapy in lean patients with NASH remains inadequate. Treatment options for individuals with NASH include vitamin E (limited to patients without T2DM) or pioglitazone, both endorsed as first-line treatment options by the AASLD and EASL.²³ The Pioglitazone vs Vitamin E vs Placebo for Treatment of Non-Diabetic Patients

with Nonalcoholic Steatohepatitis (PIVENS) trial that compared pioglitazone, vitamin E, and placebo in patients with NASH but without T2DM reported improvement in liver biochemistry, inflammation, and fibrosis in the vitamin E and pioglitazone treatment arms.⁷⁶ Subsequent studies have confirmed the role of pioglitazone in improving NASH histology in persons with or without T2DM.^{77, 78} Vitamin E, at its recommended dose of 800 IU daily, has shown potent antioxidant properties and improved histology in NASH patients.^{79, 80} However, some concerns have been raised about its potential increase in all-cause mortality, haemorrhagic shock, and prostate cancer.^{79, 80} Pioglitazone has been associated with adverse reactions, including weight gain, peripheral edema, heart failure and fractures; therefore the use of PPAR- γ agonists requires individualized assessment in patients with NASH.^{79, 80} The use of either vitamin E or pioglitazone should be restricted to patients with biopsy-confirmed NASH.

Best Practice Advice #14. The therapeutic role of glucagon peptide 1 (GLP-1) agonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors in the management of lean NAFLD is not fully defined and requires further investigation.

Glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose transport protein 2 (SGLT2) inhibitors are promising agents for the treatment of NASH.^{81–83 84, 85} Ongoing trials with GLP-1 receptor agonists in NASH patients are mostly enriched with overweight and obese patients. Until further data are available, the use of GLP-1 receptor agonists or SGLT2 inhibitors is premature for the treatment of lean NASH but may be considered in the management of comorbid metabolic conditions such as T2DM.

Best Practice Advice #15: Hepatocellular carcinoma surveillance with abdominal ultrasound with or without serum AFP twice per year is suggested in patients with lean NAFLD and clinical markers compatible with liver cirrhosis.

Cirrhosis, whether secondary to NAFLD or other causes, is a well-established risk factor for incident hepatocellular carcinoma (HCC).^{86, 87} The AASLD guidelines, along with most experts, recommend considering screening for HCC in all patients with cirrhosis.⁸⁸ Health care providers should consider patient age, overall health status and comorbidities, functional status, and personal preferences for screening and willingness to undergo treatment should HCC be diagnosed during screening. Abdominal ultrasound with or without serum alpha-feto protein (AFP) should be offered to all patients with cirrhosis, including lean patients with NAFLD-related cirrhosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
HCC	hepatocellular carcinoma
US	United States
AGA	American Gastroenterological Association
BMI	body mass index
CDC	Centers for Disease Control and Prevention
WHO	World Health Organization
NHANES	National Health and Nutrition Epidemiology Survey
EASL	European Association for the Study of the Liver
AASLD	American Association for the Study of Liver Diseases
LAL-D	lysosomal acid lipase deficiency
LIPA	lipase A
LDL	low density lipoprotein
HDL	high density lipoprotein
MTTP	microsomal triglyceride transfer protein
OTC	(ornithine transcarbamylase) deficiency
CPSI	carbamoylphosphate synthetase
HAART	highly active antiretroviral therapy
CETP	cholesterol ester transfer protein
NIT	non-invasive test
FIB-4	fibrosis-4
NFS	NAFLD fibrosis score
TE	transient elastography
2D-SWE	two-dimensional shear wave elastography
MRE	magnetic resonance elastography
ELF	enhanced liver fibrosis
NPV	negative predictive value

PPV	positive predictive value
AUROC	area under receiver operating characteristics
IFG	impaired fasting glucose
LSM	liver stiffness measurement
APRI	AST-to-platelet-ratio-index
VCTE	vibration-controlled transient elastography
2-D MRE	two-dimensional magnetic resonance elastography
T2DM	type 2 diabetes mellitus
MEFIB-4	magnetic resonance elastography fibrosis-4
FAST	FibroScan-AST
MAST	MRI-AST
PDFF	proton density fat fraction
PIVENS	Pioglitazone vs Vitamin E vs Placebo for Treatment of Non-Diabetic Patients with Nonalcoholic Steatohepatitis
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
GLP-1	glucagon-like peptide-1
SGLT2	sodium-glucose transport protein-1

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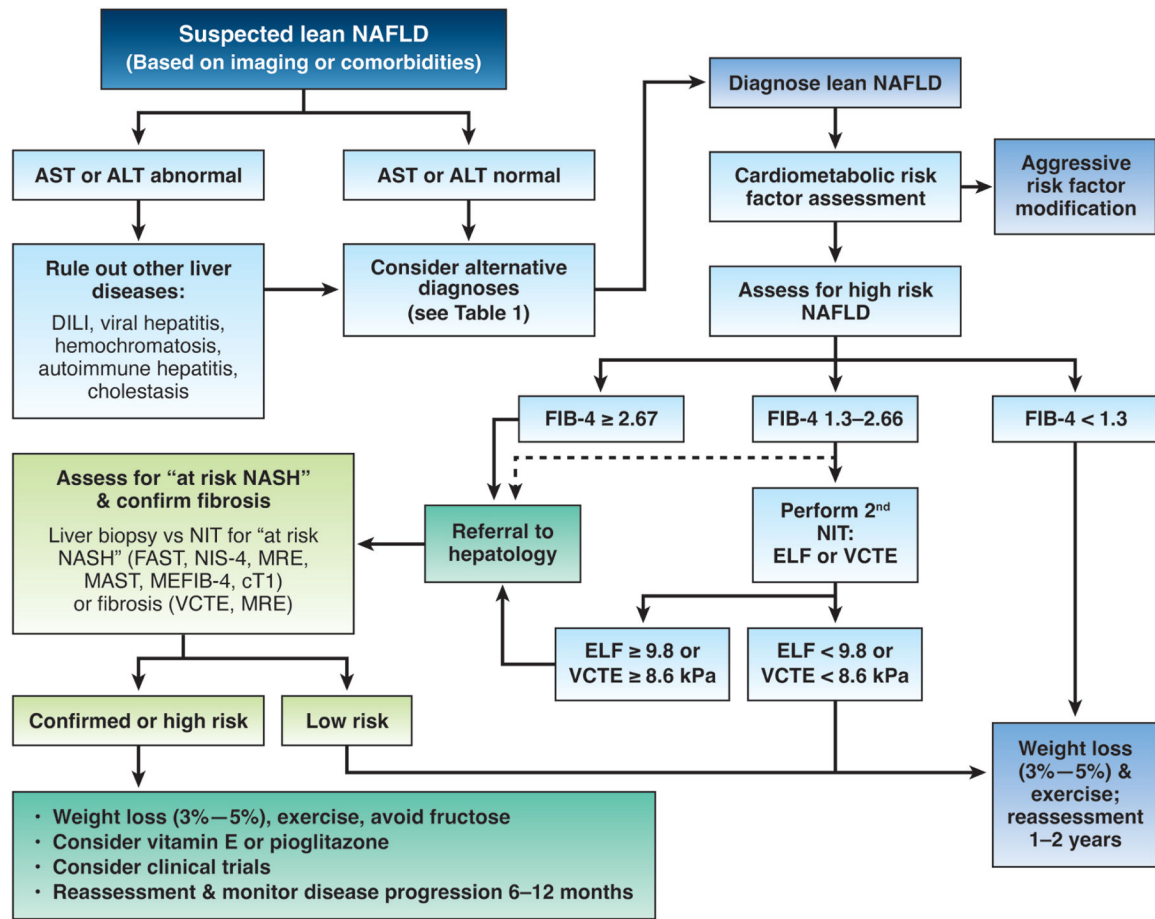


Figure 1:
Management and Treatment algorithm in patients with suspected lean NAFLD

Table 1:

Potential Secondary Causes of Fatty Liver in Lean Individuals

Liver Related	Systemic
Specific liver conditions: Chronic Hepatitis C (especially genotype 3) Wilson's disease A1 antitrypsin	Endocrine: Hypothyroidism Hypopituitarism Polycystic ovary syndrome Growth hormone insufficiency
Liver diseases of pregnancy: Acute fatty liver of pregnancy HELLP syndrome	Other genetic disorders: - Lysosomal acid lipase deficiency (LAL-D) - Familial hypobetalipoprotein B - Abetalipoproteinaemia - Urea cycle disorders - Hereditary fructose intolerance - Glycogen storage disease - Fatty acid oxidation disorders - Autosomal recessive carbamoylphosphate synthetase I (CPSI) deficiency
Drug induced liver injury: - Methotrexate, amiodarone, corticosteroids, valproic acid, tetracycline and amphetamines - HIV medications (cART: didanosine, stavudine and zidovudine)	Environmental Toxins: Metal: Arsenic, cadmium, mercury, lead Chloroalkenes: (vinyl chloride, trichloroethylene, perchlorethylene) Herbicides, pesticide
	Nutritional Effects: - Total parenteral nutrition - Malnutrition/ Kwashiorkor disease - Acute weight loss (e.g., bariatric surgery, prolonged fasting) - Short bowel syndrome - Celiac disease

Table 2:

Stepwise approach for ruling out alternative causes of lean NAFLD

Consider more common alternative diagnoses in most lean patients with suspected NAFLD:			
Diagnosis	Diagnostic tool	Clinical Management	
Covert alcohol use	- AUDIT questionnaire - Carbohydrate-deficient transferrin - Phosphatidylethanol	Alcohol cessation counseling	
Hepatitis C	Hepatitis C Ab/RNA	Direct Acting Antiviral therapy	
Celiac Disease	Tissue Transglutaminase/IgA level	Gluten-free diet	
Hypothyroidism	Thyroid stimulating hormone level	Levothyroxine	
Drug Induced Liver Injury	Review medications: Methotrexate, amiodarone, corticosteroids, valproic acid, tetracycline and amphetamines HIV medications (cART: didanosine, stavudine and zidovudine)	Consider alternative medications if possible	

Consider additional alternative diagnoses depending on clinical suspicion:			
Clinical Scenario	Diagnosis(es)	Diagnostic tool	Clinical Management
- Muscle weakness and/or neurologic symptoms - Low Alkaline phosphatase level	Wilson's disease	- Ceruloplasmin (low) 24-hr urinary copper level	Copper chelation therapy
- Chronic obstructive pulmonary disease - Family history	Alpha-1 antitrypsin deficiency	Genetic testing	ATT infusions Lung/liver transplant
Pregnancy	- Acute fatty liver of pregnancy - HELLP syndrome	- Liver biochemical tests - Hepatic ultrasound - Platelet count	Delivery
- Irregular menses - Hirsutism - Acne - Male-pattern baldness - infertility	Polycystic ovary syndrome	- Testosterone - LH - FSH	Hormonal birth control
- Reduced muscle strength - Short stature - dyslipidemia	Hypopituitarism/growth hormone deficiency	Low growth hormone	Referral to endocrinologist
Lipid abnormalities	Hypobetalipoproteinemia	- Low triglycerides, apoB, LDL levels - Genetic testing	Vitamin E supplementation

Consider additional alternative diagnoses depending on clinical suspicion:			
Clinical Scenario	Diagnosis(es)	Diagnostic tool	Clinical Management
Lipid abnormalities	<i>ABHD5</i> insufficiency	Elevated triglycerides and LDL levels	Family counseling
- Hepatomegaly - Microvesicular steatosis - Splenomegaly - Malabsorption - Steatorrhea - Lipid abnormalities	Lysosomal acid lipase deficiency	- High LDL - Low HDL level - Lysosomal acid lipase enzyme activity	Sebelipase alpha treatment
Lipodystrophy	- Familial partial lipodystrophy syndromes - Secondary lipodystrophy from HIV	Low leptin	Leptin replacement therapy
Muscle weakness and fatigue	Mitochondrial disorders	Elevated lactate	Dietary restriction/supplementation
Mental status changes	Urea cycle disorders (e.g., ornithine transcarbamylase deficiency or carbamoylphosphate synthetase I deficiency)	High blood ammonia	Prevent excess ammonia formation