

Controversies in the Diagnosis and Management of NAFLD and NASH

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Abstract: Nonalcoholic fatty liver disease (NAFLD) is recognized as the most common cause of chronic liver disease in the United States. Nonalcoholic steatohepatitis (NASH) occurs in a subset of patients with NAFLD and is characterized by the presence of hepatocellular injury, which is progressive in a substantial proportion of cases and can lead to cirrhosis and all of its complications. Although the diagnosis of NAFLD can be made through imaging studies or liver biopsy, the diagnosis of NASH still requires histologic confirmation. Liver biopsy should be performed in the presence of risk factors for advanced disease. Measures aimed at promoting weight loss, a healthier lifestyle, and optimization of metabolic risk factors remain the cornerstone of management of NAFLD. Therapeutic agents that are presently considered the most promising in NAFLD are effective in less than 50% of patients. Among patients with biopsy-proven NASH, treatment with pharmacologic agents should be considered; however, the role of specific agents in NASH still needs further study. Despite a wealth of research over the past 15 years, many controversies remain with respect to the diagnosis and management of NAFLD and NASH as well as the influence of alcohol on liver disease progression in these patients.

Patients with nonalcoholic fatty liver disease (NAFLD) comprise a dominant proportion of patients with elevated serum aminotransferase levels both in developed and developing countries. A subset of patients with NAFLD have the progressive form of liver disease referred to as nonalcoholic steatohepatitis (NASH), which can lead to the development of cirrhosis and its complications, including hepatocellular cancer and liver failure, often necessitating liver transplantation. Nevertheless, gastroenterologists and hepatologists are left with more questions than answers when it comes to deciding which patients with NAFLD need a biopsy and which patients would benefit from which type of pharmacologic treatment. Additionally, noninvasive diagnostic modalities are rapidly evolving. How to utilize these emerging modalities in routine clinical practice is more of an art than a science at this time. This review is intended to provide advice to the

practicing gastroenterologist on how to navigate through these key clinical conundrums for effective management of a patient with NAFLD.

Which Patients Need a Liver Biopsy and Why

Approximately 80 to 100 million Americans are afflicted with NAFLD.¹ Therefore, it is neither practical nor feasible to subject all patients with NAFLD to a liver biopsy. Liver biopsy remains the gold standard for the diagnosis and staging of NASH. The presence of NASH on initial liver biopsy is the main predictor of development and progression to liver fibrosis. In turn, progression of liver fibrosis is the main determinant of adverse liver-related clinical outcomes. Therefore, diagnosing NASH and advanced fibrosis (bridging fibrosis and cirrhosis) have crucial prognostic and management implications. However, liver biopsy is expensive, subjective, and associated with risks and, thus, limitations.

To develop a rational approach to liver biopsy assessment, physicians need to weigh the risks and benefits of conducting a diagnostic test (liver biopsy in this case), consider alternatives, and perhaps individualize care based on the pretest likelihood of having a disease that warrants early recognition for either the prognostication or institution of treatment.² Although progressive liver disease will not develop in the majority of patients with NAFLD, a subset of these patients may have NASH. NASH is characterized by the presence of ballooned hepatocytes and lobular inflammation with or without perisinusoidal fibrosis in addition to steatosis on liver histology. Cirrhosis may then develop in patients with NASH who are at increased risk for morbidity and mortality due to liver disease.³⁻⁷ Liver biopsy remains the gold standard to confirm NASH and assess fibrosis due to the lack of reliable noninvasive methods.^{8,9}

Recent data are challenging the conventional paradigm that the absence of NASH on index biopsy translates into minimal risk of liver disease progression. It appears that a subset of patients with isolated hepatic steatosis, particularly those with any degree of necroinflammation on index biopsy, or worsening metabolic parameters may progress to advanced NASH on follow-up biopsy.^{10,11} As newer therapies for the treatment of NASH emerge,¹²⁻¹⁴ the identification of patients with NASH who may benefit from treatment becomes important, with the expectation that identification and treatment would lower the risk of death due to liver disease in the long term. Furthermore, a biopsy confirmation or exclusion of NASH enables the practitioner to discuss cardiovascular risk and liver-related prognosis with the patient.

Knowing which patients with suspected or known NAFLD are likely to progress to NASH can be chal-

Table 1. Indications for Liver Biopsy in Patients with NAFLD*

Indications for Biopsy	Strength of Evidence
Clinical:	
1. Metabolic syndrome with elevated ALT/AST	1. Strong
2. Type 2 diabetes mellitus with elevated ALT/AST	2. Strong
3. During bariatric surgery	3. Strong (low risk/high prevalence)
4. During cholecystectomy	4. Low (low risk/high prevalence)
Laboratory tests:	
1. AST>ALT	1. Strong (suggestive of advanced fibrosis)
2. Low platelet count	2. Strong (suggestive of advanced fibrosis)
3. Low albumin	3. Strong (suggestive of advanced fibrosis)
Special clinical considerations:	
1. Older age	1. Emerging
2. Family history of diabetes	2. Emerging

*These recommendations are based on the increased pretest likelihood of the presence of NASH and/or advanced fibrosis on liver biopsy in patients with NAFLD.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

lenging, both due to the vast numbers of patients in question and a lack of clear evidence-based guidelines for liver biopsy in this population. Recommendations are made based on known risk factors for advanced disease, the persistence of abnormal liver chemistry tests, or the exclusion of other diseases. Table 1 provides a list of indications for liver biopsy in patients with elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels who have fatty liver on imaging, assuming that viral hepatitis, autoimmune liver disease, and iron overload, among other causes of abnormal liver tests, have been excluded.

Liver biopsy is also helpful in the identification of other causes of abnormal liver tests that may not be evident on serologic testing, such as marker-negative autoimmune hepatitis, drug-induced liver injury, Wilson disease, and alpha-1-antitrypsin deficiency. We also recommend that patients who are undergoing either bariatric surgery or cholecystectomy provide consent for an intraoperative liver biopsy if they are found to have fatty liver on imaging, especially in the setting of metabolic risk factors and/or elevated ALT and/or AST levels.¹⁵

There are limited data on the optimal assessment of patients who have an incidentally recognized fatty liver on an imaging study. Further studies are needed to better understand the prevalence of NASH and advanced

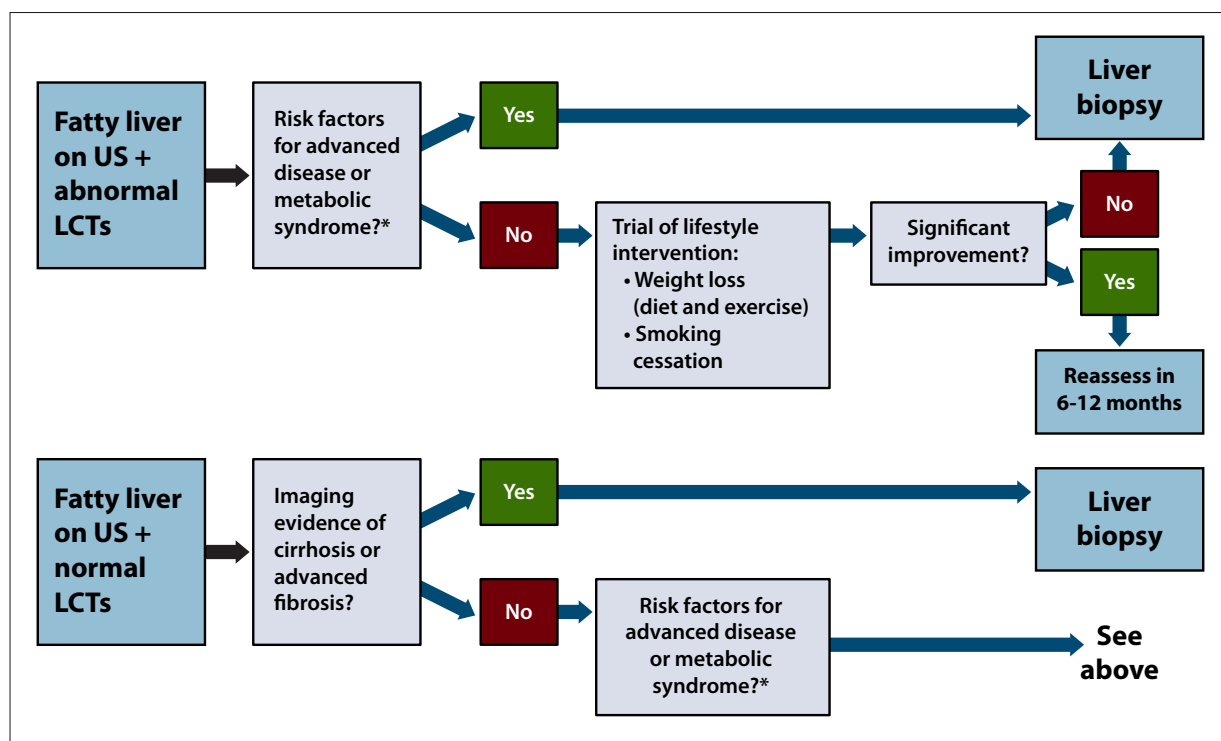


Figure. A proposed algorithm for the decision to obtain a liver biopsy in patients with presumed NAFLD after negative serologic evaluation and exclusion of alcohol as a contributing factor. Although the data are not as strong, serologically calculated fibrosis indices can be used in addition to or in lieu of imaging.

*Diabetes/glucose intolerance, age greater than 65 years, hypertension, body mass index greater than 30 kg/m², high triglycerides/low high-density lipoprotein, family history of diabetes, and aspartate aminotransferase level greater than alanine aminotransferase level.

LCTs, liver chemistry tests; NAFLD, nonalcoholic fatty liver disease; US, ultrasound.

fibrosis in such a population, especially when serum ALT and AST levels are within the normal limits. Until further evidence is available, we think that it is reasonable to consider a liver biopsy in patients with incidental hepatic steatosis on imaging who also have metabolic syndrome or severe dyslipidemia in the setting of moderate to severe fatty infiltration in the liver. In patients who have mild steatosis on imaging, it is important to look for imaging features of advanced fibrosis or cirrhosis because cirrhosis is associated with reduced liver fat content.¹⁶ In these cases, serologic measures of fibrosis or noninvasive imaging assessment of fibrosis could be used as an adjunct to select patients for biopsy (Figure).

In summary, patients with NAFLD who have coexisting metabolic syndrome and diabetes, especially those older than 65 years, are at increased risk for NASH and advanced fibrosis as well as increased risk for liver-related morbidity and mortality. Therefore, a liver biopsy assessment should be considered in these patients with NAFLD.^{2,17} Until the discovery of the next generation of noninvasive biomarkers, liver biopsy should be considered in patients with NAFLD who have increased risk of NASH and advanced fibrosis or when the diagnosis is uncertain.

Histology Interpretation: Making the Diagnosis

Few controversies are as central as one addressing specific histologic criteria to make a diagnosis. In the early years following recognition of fatty liver disease, it was observed that there were 2 broad categories of NAFLD, one that was stable (usually referred to as simple steatosis or non-NASH fatty liver) and one that carried a risk of progression (which is now commonly called NASH).³ This broad dichotomy has been largely borne out by subsequent reports on the natural histories of these conditions.^{7,18} However, substantial challenges remain in the histologic classification of NAFLD. Four parameters are used to histologically grade and stage NAFLD, including steatosis, inflammation, cellular ballooning, and fibrosis. Among these, hepatocellular ballooning remains particularly problematic, with weak interobserver agreement even among experienced observers.^{8,19-21}

The impact of hepatocellular ballooning and interobserver variability can lead to significant differences in data interpretation, as most patients with definite NASH have evidence of classic hepatocellular ballooning. For example, this may have been a factor in the number

of subjects not meeting entry criteria in the PIVENS (Pioglitazone vs Vitamin E vs Placebo for Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis) trial, although this was ultimately attributed to sampling variation in that study.¹² Keratin 8/18 immunostaining may alleviate this problem but has not yet been widely applied as a measurable endpoint.²²

Reconciling these issues can be facilitated by directly reviewing histologic samples with the attending pathologist and sometimes by referring questionable samples for second opinions. However, until more definitive studies are completed, this issue is likely to persist.

Noninvasive Tests: Are We There Yet?

Recently, concerns have been raised regarding the risk of NAFLD underdiagnosis, due in great part to overreliance on aminotransferases.^{23,24} In addition to suspecting NAFLD in patients with ultrasound findings compatible with fatty liver and in those with elevated aminotransferases, underlying NAFLD should be suspected in all patients with metabolic risk factors.²⁴

Steatosis

Liver ultrasound is the most common initial imaging technique for the diagnosis of NAFLD. Compared with other imaging studies, it is widely available, convenient, safe, and relatively inexpensive. However, it has limited sensitivity when steatosis is less than 30% on liver biopsy.²⁵ Ultrasound is inaccurate, operator-dependent, and insensitive, and it lacks precision. It also has a high failure rate in patients with NAFLD.²⁵ Therefore, it is not reliable for assessment of NAFLD. Computed tomography (CT) also has limited sensitivity if steatosis is mild, is costly, and involves radiation exposure.²⁵ Due to these limitations, ultrasound and CT are not favored for accurate diagnosis of NAFLD and are unable to accurately quantify liver fat content. Magnetic resonance imaging including spectroscopy (MRS) has higher sensitivity and specificity in quantifying steatosis and is also safe; however, it is expensive and, in the case of MRS, not widely available.²⁶ Recent data suggest that magnetic resonance imaging and MRS may be better than histology in assessing longitudinal changes in liver fat content.^{27,28}

Hepatocellular Injury and Fibrosis

The main limitation of imaging studies is their inability to differentiate NASH from isolated hepatic steatosis. Noninvasive assessment of liver fibrosis is developing rapidly and is fairly reliable in distinguishing mild/no fibrosis from very advanced fibrosis but lacks sensitivity and specificity in the diagnosis of more moderate degrees of injury. Transient elastography is a promising technol-

ogy, among others, undergoing evaluation in the assessment of liver fibrosis in patients with NAFLD; however, further studies are needed to address limitations of test performance related to high body mass indices or higher degrees of hepatic steatosis.²⁹

Several individual parameters and combinations of clinical and laboratory parameters have been studied in an attempt to noninvasively diagnose NASH. Among these, measurement of cytokeratin 18 levels has shown good correlation with the presence of NASH, although it provides limited information compared with liver biopsy.³⁰ It is fairly specific but lacks the sensitivity needed for it to be an adequate screening test to stage NASH.³¹ Future studies of cytokeratin 18, other markers, and combinations of markers are needed, including assessment of performance characteristics in different populations, longitudinal evaluation, and evaluation in the setting of interventional studies.

The ability to predict advanced fibrosis in patients with NASH also has been extensively studied. Several panels have been studied and reviewed elsewhere.³² Among these, the NAFLD fibrosis score³³ and FIB-4 are derived from readily available clinical parameters for the cross-sectional assessment of advanced fibrosis that have area-under-the-receiver-operating-characteristic curves greater than 0.8 and very good negative predictive values (92% to 95%).³⁴ The Enhanced Liver Fibrosis panel, commercially available in Europe, is an extracellular matrix marker set consisting of tissue inhibitor of metalloproteinase 1, amino-terminal propeptide of type III procollagen, and hyaluronic acid, which correlate well with fibrosis stage in chronic liver disease.³⁵ However, its relevance in NASH specifically is less well studied. Although noninvasive methods to predict advanced fibrosis in patients with NASH are not widely used in clinical practice, in the future, they may facilitate the identification of a majority of patients with severe fibrosis without the need for a liver biopsy. Therefore, we believe that the accurate, noninvasive diagnosis of NAFLD, NASH, and advanced fibrosis is one of the most important unmet needs in the evaluation of a patient with suspected NAFLD.

Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis: A Heterogeneous Diagnosis

Another important area of uncertainty and/or controversy includes the possibility that NASH is more heterogeneous than has been commonly appreciated. Although the majority of patients with NASH fall into the classic pattern associated with features of the metabolic syndrome (defined by central obesity, impaired glucose

tolerance, high triglycerides, and low high-density lipoprotein [HDL]), some patients do not fall into this paradigm. Mounting data suggest that many patients with NAFLD have a lipid profile characterized by not only high triglycerides and low HDL but also higher low-density lipoprotein (LDL) particle concentration and lower LDL particle size.³⁶ However, no consistent lipoprotein pattern has been established, raising the possibility that disordered lipoprotein metabolism may be more or less important in different persons.^{37,38} There may be certain subpopulations of patients with NASH in whom more aggressive disease develops, such as those with certain endocrine signatures. Similarly, fatty liver disease can be part of other uncommon genetic disorders, such as Alstrom syndrome, lipodystrophies, and some mitochondrial disorders.³⁹

The influence of ethnicity and genetic factors in the development of more severe disease is important and continues to evolve. Occasionally, advanced NASH develops in the absence of metabolic comorbidities, including obesity. This group of patients remains poorly defined and requires further study. In this setting, non-invasive measures of steatosis and fibrosis can help guide the need for liver biopsy (Figure). Treatment in this population is less well defined; however, leaner patients with NASH have generally been included in current clinical trials. As in all patients with NASH, care should be taken to exclude the role of alcohol and regular marijuana use, both of which can lead to steatohepatitis. In addition, the exclusion of other causes or contributors to steatohepatitis is very important given that NASH remains a diagnosis of exclusion. A thorough discussion of alternate pathways leading to NASH was recently published.⁴⁰ Taken in aggregate, carriage or forme frustes of these entities could introduce significant variability into treatment studies.

Alcohol Use: How Much Takes the “Non” Out of Nonalcoholic Fatty Liver Disease?

The concept of “non” alcoholic disease is incorporated in the definition of NAFLD. However, the precise effects of mild-to-moderate alcohol intake in the setting of NAFLD remain unknown. Furthermore, the exact cutoffs have varied among studies, with the most recent studies allowing modest ethanol use. By convention, this now generally is set at less than 30 g/day for men and less than 20 g/day for women. Individual differences in genetic susceptibility or other risk factors make any absolute threshold of alcohol for a given patient unreliable.

Higher levels of alcohol intake increase the risk of ethanol-related liver disease (>60 g/day for men and >40 g/day for women), particularly in the pattern of

Table 2. Pharmacologic Treatment Options in Patients with NASH for Which There Is the Most Evidence

Vitamin E
<ul style="list-style-type: none"> • NASH without diabetes • Insufficient evidence to treat diabetics or cirrhotics
Pioglitazone
<ul style="list-style-type: none"> • NASH with or without diabetes • Limited data in cirrhotics
Pentoxifylline
<ul style="list-style-type: none"> • Needs further study to determine ideal subpopulation

NASH, nonalcoholic steatohepatitis.

binge drinking.⁴¹ Some have referred to this gray area as “BASH” (ie, both alcoholic steatohepatitis and NASH) to indicate intermediate levels of ethanol use plus the presence of metabolic risks such as obesity and type 2 diabetes.⁴² More patients with NASH die from cardiovascular causes than liver disease. Alcohol has demonstrable benefit in the reduction of cardiovascular morbidity and mortality.⁴³ Interestingly, several studies, including a recent meta-analysis, suggest that modest alcohol use may reduce not only the prevalence of fatty liver but also the development of NASH among those with NAFLD.⁴⁴

Although these data are provocative, other studies suggest the contrary.⁴⁴⁻⁴⁶ Recent data derived from large prospective cohort studies suggest that the joint effects of alcohol and obesity may synergistically increase the risk of liver injury and may also increase the risk of liver-related death and incident hepatocellular carcinoma.⁴⁵⁻⁴⁷ This is an area in need of further clinical research.

Who Should Be Treated and with Which Agent?

Any approach to the treatment of NASH must include lifestyle modification (diet and regular exercise). The vast majority of patients benefit from weight loss and attention to limiting caloric content as well as the macronutrient content of their diet. Weight loss of at least 5% to 9% of body weight appears to correlate with histologic improvement in patients with NASH.^{48,49} Exercise alone, independent of weight loss, may have histologic benefits as well.^{50,51} Table 2 outlines pharmacologic treatment options in subpopulations of patients with NASH for which there is the most evidence.

Until more reliable biomarkers are available, patients being considered for drug treatment must have biopsy-confirmed NASH if the intention is to improve NASH. It is rare that a patient has isolated NASH without metabolic comorbidities. Not surprisingly, the main cause of mortality in patients with NASH is cardiovascular disease. Care of patients with metabolic risk factors, including diabetes,

obesity, dyslipidemia, and hypertension, should be optimized irrespective of a biopsy diagnosis of NASH.

Pioglitazone

Thiazolidinediones (TZDs) are selective peroxisome proliferator-activated receptor- γ agonists. Among other effects, TZDs promote adipocyte maturation and regulate hepatic lipid metabolism to improve insulin sensitivity at the level of adipose tissue and liver, as well as in muscle. They stimulate maturation of visceral fat and, hence, change the adipocytokine profile secreted by adipose tissue. TZDs lead to an increase in adiponectin levels, which counteracts proinflammatory cytokines, such as tumor necrosis factor α , and promotes beta-oxidation of fatty acids.^{52,53}

Compared with placebo, pioglitazone, a TZD, has been associated with histologic improvement in patients with NASH.^{54,55} Belfort and colleagues showed that pioglitazone is better than placebo in improving steatosis, lobular inflammation, and ballooning degeneration and that it demonstrated significant improvement in liver histology.⁵⁴ In a more recent study, 247 nondiabetic subjects with biopsy-proven NASH were randomized to receive pioglitazone 30 mg, vitamin E 800 IU, or placebo for 96 weeks.¹² The primary outcome was an improvement in histologic features of NASH, as assessed by the NAFLD Activity Score, which specifically required an improvement in hepatocellular ballooning.

Primary comparisons were made only between pioglitazone and placebo or vitamin E and placebo. Although the primary outcome in the pioglitazone group did not reach the prespecified $P < .025$ level of significance, pioglitazone was associated with significant improvements in individual components of histology and insulin resistance and with a reduction in liver enzymes. The inability to reach the primary outcome was considered to be due to a disproportionate misclassification of the presence of ballooning in the pioglitazone group compared with the placebo and vitamin E group. Importantly, a greater proportion of subjects receiving pioglitazone (47%) vs placebo (21%) had complete resolution of steatohepatitis at end-of-treatment biopsy ($P = .001$). Overall, the PIVENS trial offers useful insight into the role of TZDs, specifically pioglitazone, in the treatment of NASH.

Although only 1 randomized controlled trial was able to show statistically significant improvement in fibrosis,⁵⁵ 2 meta-analyses of randomized controlled trials suggested that pioglitazone may improve liver fibrosis in patients with biopsy-proven NASH.^{56,57}

Adverse effects related to pioglitazone are common and range from undesirable to life-threatening. The most common is weight gain (mean, 3-5 kg), which occurs in

Table 3. Potential Adverse Events to Consider in Discussion with Patients

Pioglitazone
<ul style="list-style-type: none"> • Weight gain: most patients⁵⁸ • Contraindicated in patients with symptomatic CHF⁷⁵ • Bone loss^{64,65} • Bladder cancer: RR, 1.15-1.22⁷⁶
Vitamin E
<ul style="list-style-type: none"> • Bleeding/hemorrhagic stroke⁷⁷ • Prostate cancer⁷⁸ • Increased mortality⁷⁹

CHF, congestive heart failure; RR, relative risk.

approximately 60% to 70% of patients.⁵⁸ Pioglitazone carries a black box warning from the US Food and Drug Administration in relation to increased risk of congestive heart failure. However, TZDs have not been shown to increase mortality due to heart failure. Furthermore, pioglitazone has been shown to decrease mortality from ischemic cardiovascular events, the leading cause of death in patients with NASH.^{59,60} Additionally, less common but important risks include postmenopausal bone loss and a small potential risk of bladder cancer (although this has not been clearly established)⁶¹⁻⁶⁷ (Table 3). Overall, the safety and tolerability of pioglitazone are predictable, and adverse events do not appear to be treatment-limiting. Despite potential adverse effects, pioglitazone is an option for the treatment of NASH; however, it is perhaps best suited for those with impaired glucose tolerance or diabetes.

Vitamin E

Vitamin E supplementation suppresses lipid peroxidation and oxidative stress, which may improve inflammation and fibrosis in patients with NASH.⁶⁸ In a large, double-blind, randomized, placebo-controlled trial, 800 IU/day of vitamin E was superior to placebo in improving NASH histology and ALT in nondiabetic adults with NASH.¹² In a study of similar design in a pediatric population, vitamin E was not more effective than placebo in achieving the primary endpoint of a sustained reduction in ALT. Although it did result in more resolution of NASH histologically, it did not improve individual histologic components more than placebo.¹⁴

Vitamin E is considered to be fairly benign; however, it is a fat-soluble vitamin that could have ill effects if taken in excess. In a meta-analysis, vitamin E supplementation increased all-cause mortality, possibly related to unfavorable changes in plasma lipoproteins.⁶⁹ Although these data have been challenged, it is important to keep in mind that therapy with high-dose vitamin E may not be without adverse effects⁷⁰ (Table 2).

The available evidence suggests that vitamin E improves liver enzymes, steatosis, and liver injury in NASH. Importantly, there is no evidence that pioglitazone or vitamin E improves fibrosis, which may be the most relevant histologic endpoint. There are insufficient data to recommend vitamin E for patients with NASH and concomitant diabetes or cirrhosis.

Pentoxifylline

Interestingly, pentoxifylline also has been associated with histologic improvement, including improvement in fibrosis, in small randomized trials of patients with NASH.⁷¹⁻⁷³ It appears that these beneficial effects are at least partly mediated through decreasing oxidative stress.⁷⁴ However, future studies in larger groups of patients are needed to substantiate these results.

Future Directions

Although there is evidence supporting a beneficial effect of some pharmacologic agents, to date, there is no formally approved medical therapy for NASH, and the magnitude of these improvements is small. Ongoing and future trials will hopefully offer additional and more effective therapies for the growing numbers of patients with liver disease due to NASH.

A major limitation of the current data is that only a fraction of patients respond to therapy, and no agent has been convincingly shown to decrease fibrosis, arguably the most relevant therapeutic endpoint. Furthermore, the placebo response in NASH trials is approximately 19% and probably related to the effect of lifestyle interventions in the control arms. As a result, there is a major unmet need for therapeutic options for the growing numbers of patients with NASH-associated cirrhosis. Therefore, studies are needed to identify predictors of response that highlight which patients may benefit from intensive lifestyle changes or the use of specific pharmacologic agents.

Studies of longer duration will help to assess long-term safety, durability, and benefits of various interventions on not just liver-related but cardiovascular and metabolic outcomes, which strongly contribute to the disease burden of NASH. Management of NASH, like that of other complex metabolic diseases, will likely necessitate a multifaceted approach. Trials exploring the potential additive effects of insulin sensitizers with cytoprotective agents or other modalities are eagerly awaited.

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