Nonalcoholic Fatty Liver Disease

Tyler Thrasher, Manal F. Abdelmalek

Nonalcoholic fatty liver disease (NAFLD), the hepatic manifestation of the metabolic syndrome, is the leading cause of chronic liver disease. Treatments target lifestyle modification and improvement of underlying risk factors. Noninvasive biomarkers for diagnosis and staging of NAFLD and safe, cost-effective treatments for patients with nonalcoholic steatohepatitis (NASH) and/or NASH-related cirrhosis are currently under investigation.

Nonalcoholic fatty liver disease (NAFLD) refers to the presence of hepatic steatosis, as demonstrated by imaging or histology, in the absence of significant alcohol consumption or other known secondary causes [1]. NAFLD is strongly associated with obesity and metabolic disturbances such as insulin resistance, type 2 diabetes mellitus, and dyslipidemia. In the past few decades, obesity and type 2 diabetes have become epidemic health problems; as a consequence, an increase in the prevalence of NAFLD has been observed in all age groups. NAFLD has become the most frequent cause of chronic liver disease in both Western and developing countries [2]. NAFLD comprises a spectrum of disease ranging from simple steatosis (fatty liver), through nonalcoholic steatohepatitis (NASH) and liver scarring (fibrosis), to cirrhosis and hepatocellular carcinoma (see Figure 1) [3].

Clinical Presentation

NAFLD is largely asymptomatic. Many patients show minimal or no clinical symptoms, although fatigue can be a significant problem [4]. Most patients are diagnosed after discovery of abnormal liver enzyme levels on routine blood tests. When taking the patient's history, physicians should concentrate on determining the presence of conditions associated with NAFLD and excluding alternative causes of steatosis, such as excessive alcohol intake, alternative causes for elevated liver enzyme levels (eg, viral hepatitis, celiac sprue, autoimmune liver disease, and hemochromatosis), and/or concomitant medications known to cause increased chronic hepatitis or hepatic steatosis (eg, glucocorticoids, tamoxifen, amiodarone, and methotrexate). Liver aminotransferase levels are insensitive for diagnosing NAFLD versus NASH, as levels of aminotransferases may fluctuate or can be normal in patients with histologic features of NASH [5]. NAFLD is associated with higher overall and liver-related mortality in the general US population. Cardiovascular disease, cirrhosis, and cancer are the 3 leading causes of death among persons with NAFLD [6, 7].

Natural History

Retrospective studies have shown that fibrosis progresses in 25%–38% of patients with NAFLD, with ballooned hepatocytes (swollen liver cells) and inflammation on index biopsy being the strongest predictor for hepatic fibrosis [8]. End-stage NASH accounts for 30%–75% of all cases of cirrhosis for which the cause is unknown. About 7% of patients with compensated NASH-related cirrhosis develop hepatocellular carcinoma within 10 years, and 50% will require a transplant or will die from a liver-related cause [9]. The overall and liver-related mortality of patients with NAFLD is higher than for age- and sex-matched populations, principally due to increased liver- and cardiovascular-related mortality [10].

Diagnostic Evaluation

In the absence of overt signs or symptoms of advanced liver disease (eg, splenomegaly, ascites, thrombocytopenia, muscle wasting, or hepatic encephalopathy), patients with NAFLD typically have blood test results that are normal or show mild elevations of aminotransaminases, alkaline phosphatase, and gamma glutamyltranspeptidase. Ultrasound, computed tomography, and routine magnetic resonance imaging are all excellent at detecting steatosis, but none can reliably detect NASH or fibrosis.

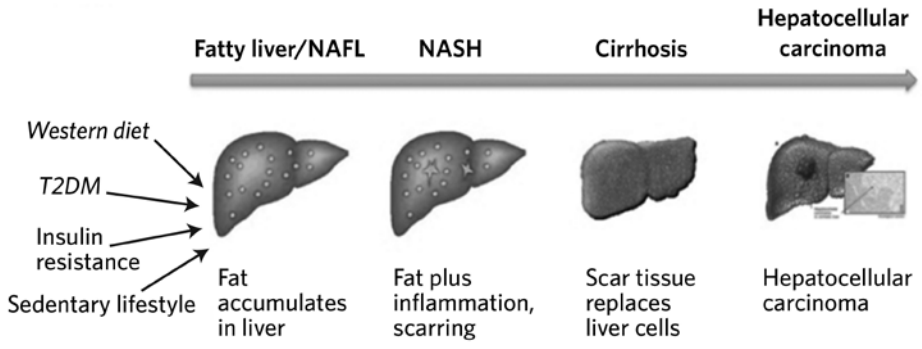
Although a liver biopsy is not required to establish a diagnosis of NAFLD, it may be indicated for accurate staging of the disease (ie, determining the presence of NASH and/or advanced hepatic fibrosis). Histology remains the gold standard for making the important distinction between simple steatosis, which is generally nonprogressive and readily reversible, versus steatohepatitis, which has the potential to progress to severe fibrosis or cirrhosis. A liver biopsy may also identify other causes of liver disease in patients thought

Electronically published May 6, 2016.

Address correspondence to Dr. Manal F. Abdelmalek, Duke University Medical Center, Division of Gastroenterology, PO Box 3913, Durham, NC 27710 (manal.abdelmalek@duke.edu).

N C Med J. 2016;77(3):216-219.
0029-2559/2016/77315

FIGURE 1.
Clinicopathologic Spectrum of Nonalcoholic Fatty Liver Disease



Note. NAFL, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

to have NAFLD or vice versa. Histologic grading and staging of NAFLD are potentially important for studying disease severity and progression, particularly in the context of clinical trials to assess novel therapeutic approaches [11].

Newer techniques for disease staging, including proton magnetic resonance spectroscopy and transient elastography, show promise but require further study before they will be ready for routine use [12]. Various clinical and laboratory markers have been shown to be associated with advanced fibrosis (bridging fibrosis or cirrhosis) in NAFLD patients: age greater than 45–50 years, body mass index above 30 kg/m^2, the presence of type 2 diabetes, and an aspartate aminotransferase-to-alanine aminotransferase ratio greater than 1 (AST:ALT > 1). At present, it would seem reasonable to restrict liver biopsy to patients with at least some of these risk factors.

Together with serum markers of inflammation and fibrosis, various risk factors have been combined into a number of different diagnostic algorithms. However, many of these algorithms currently require independent validation and comparison before they can be applied to routine clinical practice [12].

Current Management Strategies

Current management strategies are directed at treating the individual components of metabolic syndrome, when present. The cornerstone of treatment focuses on gradual and sustained weight loss. Any significant weight reduction—whether it is a result of dietary change, exercise, or bariatric surgery—has been shown to be effective at reducing liver enzyme levels and improving histology [13]. Several small, largely uncontrolled studies have shown an improvement in either alanine aminotransferase levels or steatosis following diet-induced weight loss (with or without exercise) [14-16]. There is less evidence that NASH or fibrosis can be improved with weight loss alone.

A recent randomized controlled trial that compared 48 weeks of intensive lifestyle intervention (a combination of diet, exercise, and behavior modification) versus structured education demonstrated significantly greater weight loss and improved NASH histological activity scores in the lifestyle intervention group [17]. This study also showed that patients who achieved greater than 7% weight loss had significantly greater improvements in all 3 components of the NASH activity score (steatosis, lobular inflammation, and ballooned hepatocytes) compared with those who lost less than 7% body weight. Therefore, aiming for a weight loss of 7% through diet and exercise appears to be a reasonable target in overweight and mildly obese patients [1, 12].

Weight loss surgery is also effective in improving NASH. A 2008 meta-analysis of NAFLD and bariatric surgery–induced weight loss found that more than 90% of NAFLD patients with bariatric surgery–induced weight loss had improvement or resolution of hepatic steatosis. In addition, over 80% of patients with NASH showed improvement, with almost 70% showing complete resolution. Finally, 65.5% of patients with mild hepatic fibrosis showed improvement or resolution of hepatic fibrosis [18]. However, bariatric surgery may not be effective in reversing more advanced stages of hepatic fibrosis, and it may be associated with risk for postsurgical hepatic decompensation.

Pharmacologic Therapies

Currently, there are no pharmaceutical treatments approved by the US Food and Drug Administration for NAFLD. However, due to the strong association between NAFLD, type 2 diabetes, and dyslipidemia, therapies used to treat type 2 diabetes and/or dyslipidemia have been investigated as potential treatments for NAFLD. The rationale for NAFLD therapies is based on a growing understanding of disease pathogenesis, with a particular focus on several mechanisms: improving insulin resistance and levels of hepatic free fatty acids; reducing oxidative, endoplasmic reticulum, and cytokine-mediated stress; and optimizing the balance between liver injury and repair mechanisms [19-21].

Evidence that insulin resistance may contribute to both inflammation and fibrosis in NAFLD has led to several pilot studies of metformin and glitazones for treatment of

NAFLD. The most encouraging results have been reported for the glitazone class of drugs that acts as agonists for the peroxisome proliferator activated receptor γ. Five randomized controlled trials of glitazones have been reported, all of which showed an improvement in alanine aminotransferase levels and steatosis [22-26]; most studies also showed an improvement in NASH. Thus far, no study has shown a convincing benefit on fibrosis. In the largest randomized controlled trial to date, pioglitazone significantly improved each individual aspect of liver injury, but it failed to achieve the study's endpoint—a 2-point improvement in NASH activity score with no worsening of fibrosis more often than placebo [27]. The recently published FLINT trial examined the effect of obeticholic acid versus placebo in patients with NASH or borderline NASH. After 72 weeks of treatment, obeticholic acid was noted to be effective at improving liver histology, but this study showed no significant difference in resolution of NASH [28].

While lipid-lowering agents have not been extensively studied in NAFLD, there are scientific reasons to support the use of fibrates (conventional triglyceride-lowering agents) for this condition. To date, the only controlled study with histological follow-up reported that clofibrate had no effect on liver biochemistry or histology after 1 year of treatment [29]. While statins have not been extensively studied for NAFLD, they can be safely prescribed for treatment of hyperlipidemia in the setting of type 2 diabetes and high cardiovascular risk. There is no evidence that patients with preexisting NAFLD are at increased risk of statin-induced idiosyncratic hepatotoxicity, so clinicians should not withhold statin therapy in patients with NAFLD if there is some other indication for their use [30].

Oxidative stress is believed to be involved in liver injury in NASH patients. For this reason, antioxidants such as vitamin E have been investigated as potential treatments for NASH. Results from trials with vitamin E have been mixed. An Italian study published in 2005 compared the effect of metformin, vitamin E, and diet in NAFLD patients and found vitamin E to have no clinical benefit over weight loss [31]. However, a more recent study examined the efficacy of vitamin E or pioglitazone versus placebo. Both treatment arms showed significant improvements in both histology and serum enzyme levels. Vitamin E was effective for improving all histologic categories (steatosis, lobular inflammation, and ballooned hepatocytes), and pioglitazone showed improvements in both steatosis and inflammation [27]. Enthusiasm for the potential benefits of pioglitazone and vitamin E should be tempered by the finding that improvement in NASH was noted in only 34% of the subjects who received pioglitazone and 43% of those who received vitamin E, and steatohepatitis resolved in only 47% and 36%, respectively. Neither agent was associated with a significant improvement in the mean fibrosis score after 96 weeks of treatment [27].

The discovery of a safe and effective pharmacological intervention for NAFLD and/or NASH would have important implications for global public health. The evaluation of new pharmacologic targets for NASH is limited by the heterogeneous phenotype of the disease and the lack of noninvasive biomarkers for diagnosis and staging. Table 1 provides examples of investigational therapies that are in preclinical or clinical development for the treatment of NAFLD and/or NASH. More up-to-date data on therapies under investigation may be acquired from www.clinicaltrials.gov.

Future Directives

There are many opportunities for improvement in the diagnosis and treatment of NAFLD. One important initiative is to identify noninvasive markers that can be used to diagnose and stage NAFLD and NASH. As previously mentioned, the current standard for diagnosis and staging is liver biopsy, which is invasive and requires a significant time investment from both patients and physicians. Noninvasive imaging methods are both expensive and nonspecific.

In addition to focus on biomarker discovery, development of pharmaceutical treatments for NAFLD and NASH is a pri-

TABLE 1.
Drugs Being Evaluated and/or in Preclinical or Clinical Development as Treatments for NAFLD or NASH

Type of drug	Drugs	Mechanism of action
Antifibrotics	Simtuzumab	Anti-LOX2 monclonal antibody
	Cenicriviroc	CCR2/CCR5 inhibitor
	Emricasan	Pas-caspase protease inhibitor
	GR-MD-02	Galactin-3 inhibitor
Modulators of nuclear receptor function	Obeticholic acid Px-104	Farnesoid X receptor agonist
	GFT-505	Peroxisome proliferator activated receptor α/δ agonist
Repurposed drugs for type 2 diabetes	Pioglitazone Rosiglitazone	Insulin sensitizers
	Exenatide Liraglutide	Glucagon-like peptide-1 receptor
	MK-0626 Vlidagliptin Sitagliptin	Dipeptidyl peptidase-4 inhibitors
	Remogliflozin	Sodium-glucose transport protein-2 inhibitors
Lipid-modifying agents	Atorvastatin Pitavastatin Simvastatin	Statins
	Fenofibrate	Fibrate
	Ezetimibe	Cholesterol absorption inhibitor
	Colesevelam	Bile acid sequestrant
Others	Vitamin E Omega-3 fatty acids	Antioxidants
	Amachol	Fatty acid/bile modifier
	Cysteamine bitartrate	Cysteine depletion
	Nalmefene (JKB-121)	Toll-like receptor 4 antagonist
	IMM-124E VLS#3	Probiotics

Note. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

ority for those patients who fail lifestyle modification and/or have NASH with fibrosis. Many of the therapeutic options presented in this review have plausible mechanisms for the treatment of NASH. While some therapies, including weight loss, may be able to reverse NASH, no treatments to date have shown the ability to significantly improve fibrosis, and many therapies have yet to be tested in patients with cirrhosis. Finally, the long-term effects of these treatments and their ability to have a lasting impact without long-term use will require future investigation. NCMJ

Tyler Thrasher, BS clinical trials assistant, Division of Gastroenterology and Hepatology, Department of Medicine, Duke University, Durham, North Carolina.
Manal F. Abdelmalek, MD, MPH associate professor of medicine, Division of Gastroenterology and Hepatology, Department of Medicine, Duke University, Durham, North Carolina.

Acknowledgments

Potential conflicts of interest. M.F.A. receives funding for research from NIH/NIDDK, Gilead, NGM Biopharmaceuticals, Bristol-Myers Squibb, TaiwanJ Pharmaceuticals, Immuron, Intercept, Galactin, Galmed, Arisaph, Genfit, and Conatus Pharmaceuticals; he also serves as a consultant to Genfit, Islet Sciences, and TaiwanJ Pharmaceuticals. T.T. has no relevant conflicts of interest.

References

1. Chalasani N, Younossi Z, Lavine JE, et al; American Gastroenterological Association; American Association for the Study of Liver Diseases; American College of Gastroenterology. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology. 2012;142(7):1592-1609.
2. Day CP. Non-alcoholic fatty liver disease: a massive problem. Clin Med (Lond). 2011;11(2):176-178.
3. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002;346(16):1221-1231.
4. Newton JL, Jones DE, Henderson E, et al. Fatigue in non-alcoholic fatty liver disease (NAFLD) is significant and associates with inactivity and excessive daytime sleepiness but not with liver disease severity or insulin resistance. Gut. 2008;57(6):807-813.
5. Mofrad P, Contos MJ, Haque M, et al. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. Hepatology. 2003;37(6):1286-1292.
6. Ong JP, Pitts A, Younossi ZM. Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease. J Hepatol. 2008;49(4):608-612.
7. Stepanova M, Rafiq N, Makhlouf H, et al. Predictors of all-cause mortality and liver-related mortality in patients with non-alcoholic fatty liver disease (NAFLD). Dig Dis Sci. 2013;58(10):3017-3023.
8. Argo CK, Northup PG, Al-Osaimi AM, Caldwell SH. Systematic review of risk factors for fibrosis progression in non-alcoholic steatohepatitis. J Hepatol. 2009;51(2):371-379.
9. Sanyal AJ, Banas C, Sargeant C, et al. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. Hepatology. 2006;43(4):682-689.
10. Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology. 2005;129(1):113-121.
11. Nalbantoglu IL, Brunt EM. Role of liver biopsy in nonalcoholic fatty liver disease. World J Gastroenterol. 2014;20(27):9026-9037.
12. Ratziu V, Bellentani S, Cortez-Pinto H, Day C, Marchesini G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. J Hepatol. 2010;53(2):372-384.
13. Huang MA, Greenson JK, Chao C, et al. One-year intense nutritional counseling results in histological improvement in patients with non-alcoholic steatohepatitis: a pilot study. Am J Gastroenterol. 2005;100(5):1072-1081.
14. Gasteyger C, Larsen TM, Vercruysse F, Astrup A. Effect of a dietary-induced weight loss on liver enzymes in obese subjects. Am J Clin Nutr. 2008;87(5):1141-1147.
15. Promrat K, Kleiner DE, Niemeier HM, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology. 2010;51(1):121-129.
16. Hickman IJ, Jonsson JR, Prins JB, et al. Modest weight loss and physical activity in overweight patients with chronic liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life. Gut. 2004;53(3):413-419.
17. Promrat K, Kleiner DE, Niemeier, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology. 2010;51(1):121-129.
18. Mummadi RR, Kasturi KS, Chennareddygari S, Sood GK. Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2008;6(12):1396-1402.
19. Day CP. From fat to inflammation. Gastroenterology. 2006;130(1):207-210.
20. Angulo P, Machado MV, Diehl AM. Fibrosis in nonalcoholic fatty liver disease: mechanisms and clinical implications. Semin Liver Dis. 2015;35(2):132-145.
21. Boursier J, Diehl AM. Implication of gut microbiota in nonalcoholic fatty liver disease. PLoS Pathog. 2015;11(1):e1004559.
22. Ratziu V, Giral P, Jacqueminet S, et al; LIDO Study Group. Rosiglitazone for nonalcoholic steatohepatitis: one-year results of the randomized placebo-controlled Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) Trial. Gastroenterology. 2008;135(1):100-110.
23. Aithal GP, Thomas JA, Kaye PV, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. Gastroenterology. 2008;135(4):1176-1184.
24. Sanyal AJ, Chalasani N, Kowdley KV, et al; NASH CRN. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010;362(18):1675-1685.
25. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med. 2006;355(22):2297-2307.
26. Torres DM, Jones FJ, Williams CD, Harrison S. The effect of 48 weeks of rosiglitazone alone versus combination rosiglitazone and metformin (Avandamet) versus combination rosiglitzone and losartan in treatment of nonalcoholic steatohepatitis (NASH): a open-label prospective randomized clinical trial. Hepatology. 2009;50(4):390A-319A.
27. Sanyal AJ, Chalasani N, Kowdley KV, et al; NASH CRN. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010;362(18):1675-1685.
28. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al; NASH Clinical Research Network. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet. 2015;385(9972):956-965.
29. Laurin J, Lindor KD, Crippin JS, et al. Ursodeoxycholic acid or clofibrate in the treatment of non-alcohol-induced steatohepatitis: a pilot study. Hepatology. 1996;23(6):1464-1467.
30. Vuppalanchi R, Chalasani N. Statins for hyperlipidemia in patients with chronic liver disease: are they safe? Clin Gastroenterol Hepatol. 2006;4(7):838-839.
31. Bugianesi E, Gentilcore E, Manini R, et al. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. Am J Gastroenterol. 2005;100(5):1082-1090.