

Low Right Care

Reducing Overuse and Underuse

Overdiagnosis of Nonalcoholic Fatty Liver Disease

Andy Lazris, MD, CMD, Personal Physician Care, Columbia, Maryland

Alan R. Roth, DO, FAAFP, FAAHPM, Jamaica Hospital Medical Center, Jamaica, New York

Patient perspective by Helen Haskell and John James

Case Scenario

A 52-year-old woman was employed as a busy engineer and often traveled for work, frequently ate fast food, and reported having no time for exercise. She had a body mass index of 29 kg per m² and borderline hypertension that she attributed to white coat syndrome. A few years ago, her A1C was high (6.5%), and type 2 diabetes mellitus was diagnosed. Her physician recommended a healthier diet and regular exercise for diabetes management. The patient tried to adhere to the recommendations, but her weight and A1C did not decrease.

Last year, her A1C increased to 7.1%, and her aspartate and alanine transaminase levels increased to nearly 100 U per L (1.67 μ kat per L). She agreed to start metformin, be more careful about what she ate, and stop drinking wine with dinner. Three months later, her A1C improved to 6.6%, but her weight and transaminase levels were stable. She had not consumed alcohol, although she admitted to not adhering to a diabetes-friendly diet. She did not have abdominal pain, nausea, or changes in bowel movements. Liver ultrasonography showed hepatic steatosis consistent with non-alcoholic fatty liver disease (NAFLD). Results of tests for other causes of liver dysfunction, including viral hepatitis, were normal. The patient was

very concerned that she had liver disease. She insisted on being referred to a hepatologist and was so worried about the possibility of developing cirrhosis that she broke down in tears.

Clinical Commentary

NAFLD is a diagnosis first recognized in the 1980s, with detection increasing as technology advanced during the following decades. NAFLD is defined by a fatty liver with a similar histologic appearance to alcoholic liver disease. The cardinal finding is macrovesicular hepatic steatosis on biopsy. Higher levels of inflammation and fibrosis are linked to worse outcomes.¹ The condition is invariably associated with metabolic syndrome and obesity, with most people having some insulin resistance. The prevalence of NAFLD is estimated to be as high as 30%.² When a biopsy shows inflammation, the condition is called nonalcoholic

TAKE-HOME MESSAGES FOR RIGHT CARE

Most patients with NAFLD eventually die from vascular rather than hepatic causes because NAFLD is a manifestation of metabolic syndrome.

The primary treatment for NAFLD is a diet and exercise regimen that alleviates metabolic syndrome.

Prognostic studies of people who are symptomatic and referred to tertiary care centers are not representative of the disease course of NAFLD in people who are asymptomatic with normal liver transaminase levels.

Screening for NAFLD with serum transaminase levels or periodic imaging in people with known NAFLD is unlikely to improve prognosis and could lead to overdiagnosis and overtreatment because of the low hepatic mortality, high false-positive rates, and lack of viable pharmacologic treatment.

NAFLD = nonalcoholic fatty liver disease.

Lown Institute Right Care Alliance is a grassroots coalition of clinicians, patients, and community members organizing to make health care institutions accountable to communities and to put patients, not profits, at the heart of health care.

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CME This clinical content conforms to AAFP criteria for CME. See CME Quiz on page 618.

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steatohepatitis (NASH), which has a worse prognosis than NAFLD. Approximately 60% of people with NAFLD who undergo a biopsy are found to have NASH.³ Within the next decade, NAFLD is projected to become the leading cause of liver-related death and disability and the primary diagnosis leading to liver transplantation.³

Elevated transaminase levels and hepatic steatosis on ultrasonography are the hallmarks of NAFLD, especially in people who are obese and have high blood glucose levels.⁴ People with NAFLD are generally not symptomatic, and because liver biopsy is the only definitive way to diagnose and distinguish mild NAFLD from NASH, the true prevalence is unknown. Elevated transaminase levels alone are not diagnostic of NAFLD, and ultrasonography has a 15% false-positive rate for NAFLD, which can lead to significant overdiagnosis if performed on all people with predisposing factors.⁵

EPIDEMIOLOGY

One study that sampled more than 8 million people in 22 Western countries found a prevalence of 25%, mostly among people with obesity (51%), type 2 diabetes (23%), hyperlipidemia (69%), and metabolic syndrome (43%).⁶ Prevalence and poor outcomes increase with age, possibly because of a longer duration of living with the condition and the additive effect of declining hepatic function with age.³ Because many people with NAFLD never seek medical attention or receive a liver biopsy, the prevalence and prognosis of NAFLD and NASH are based on limited, highly selective studies in tertiary care settings and modeling projections.⁶

PROGNOSIS

If 25% of adults have NAFLD, and approximately one-half of them develop NASH as the selective data indicate, the population burden of liver disease could be huge. However, the lack of prospective population-based studies and the scarcity of biopsy evidence make these estimates unreliable.⁶ The prognosis of an individual with NAFLD cannot be accurately predicted because liver disease progresses very slowly (typically over decades), and there is no correlation between ultrasound findings or the extent of increase in transaminase level and outcome.³

One retrospective study in Iceland found that people with NAFLD had a mean survival of 24 years after diagnosis. Although 7% ultimately progressed to cirrhosis, virtually none died of liver-related disease, with more than one-half dying of heart disease.⁷ Other data suggest that only people with symptomatic liver disease or who seek specialty care are likely to be enrolled in clinical studies or undergo biopsies. Others are less likely to progress to cirrhosis or develop serious liver disease.² The most common cause of death in people with NAFLD is vascular disease because NAFLD is a manifestation of metabolic syndrome, a common risk factor for vascular disease.⁵

In a global meta-analysis of 86 studies, people with NAFLD had a liver-specific mortality rate of less than 1 per 1,000 person-years, whereas people with NASH had a higher rate of approximately 12 per 1,000 person-years.⁶ Studies show that more severe fibrosis portends a worse prognosis; people with NAFLD without significant fibrosis have a higher risk of death from nonhepatic causes. People with fibrosis are overrepresented in studies compared with those without fibrosis because they are more likely to seek specialty care and be enrolled in studies.⁸ A cohort study showed that in people with NAFLD who were biopsied and had fibrosis, 65% had stabilization or improvement of fibrosis over time, with the most decline occurring in people with NASH and more severe fibrosis.⁹ Many people are likely unaware of their diagnosis because the condition often does not progress or resolves without the patient seeking medical attention.

TREATMENT

Alleviating metabolic syndrome with diet and exercise has been shown to improve pathology; however, it is unknown whether reducing metabolic syndrome or sugar reduces hepatic complications.⁶ There is some observational evidence from one U.S. study that a Mediterranean diet and bariatric surgery can decrease the burden of disease and pathologic fibrosis, with 85% of people who had bariatric surgery experiencing resolution of NASH to more benign fatty liver pathology.¹ Some studies have found that exercise and intensive lifestyle changes improve transaminase levels and pathology.¹⁰

Metformin has not been shown to improve liver pathology in NAFLD. Several short-term studies of pioglitazone showed pathologic improvement, but none measured clinical outcomes.¹¹ Pioglitazone may cause cardiovascular adverse effects and includes a U.S. Food and Drug Administration boxed warning about congestive heart failure exacerbations.¹² A placebo-controlled trial examined the use of the lipase inhibitor orlistat with nutrition counseling in people who have NAFLD. In both arms of the study, participants lost weight and had improvement of fatty liver on ultrasonography and reduced transaminase levels, with better outcomes occurring in the orlistat arm.¹³ A recent double-blind placebo-controlled study that evaluated the use of the peroxisome proliferator-activated receptor α agonist fenofibrate in people with NASH for 24 weeks found that 48% of study participants and 29% of the control group had improvement in fibrosis.¹⁴ The number of people taking a placebo who improved in a short amount of time is notable.

SHOULD WE TEST ASYMPTOMATIC PATIENTS FOR NAFLD?

A 2018 *Lancet* article concluded that the risks of overdiagnosis and overtreatment would exceed any benefit of

screening for NAFLD or periodic imaging in people with known NAFLD because of the low hepatic mortality, high false-positive rate of ultrasonography, selection bias of current studies, and lack of viable treatment.⁵ People with metabolic syndrome should be counseled about diet and exercise regardless of their liver condition. No evidence suggests that the diagnosis of NAFLD improves adherence to weight loss interventions and healthy eating. Data suggest that labeling someone with NAFLD can harm their quality of life without imparting any benefit.⁶

CONCLUSION

NAFLD is one of many manifestations of obesity and metabolic syndrome. Most people with NAFLD do not develop clinically significant liver disease. It is unclear how many and how quickly people with NAFLD progress to cirrhosis due to the absence of prospective, population-based studies, and current treatments have not been studied for patient-oriented outcomes. It is unlikely that diagnosing NAFLD benefits patients or predicts their prognosis. The best approach to patients with metabolic syndrome is not labeling them with more diseases, but addressing the root causes of their poor health.

Patient Perspective

It is hard for a patient not to be alarmed at a complicated-sounding diagnosis like NAFLD, especially if it is based on a laboratory test result or imaging finding, which most people do not question. This perception leaves some patients vulnerable to potential overtreatment and emotional upheaval as they try to fit new information into a knowledge base that may consist primarily of worst-case scenarios. This seems to be the case for this patient as she seeks to assimilate the news of her NAFLD diagnosis. Presenting bad news that has a wide margin of error and is not necessarily medically actionable may have unintended consequences. For every patient “scared straight,” another may fall into despair. A motivated patient like this one, who has already taken small steps, may take her physician’s advice to heart. Further improvements in her condition may reinforce her will to maintain a healthy lifestyle.

This story highlights family physicians’ key role in managing health without medical intervention by helping patients make lifestyle changes. People have busy lives and face difficult choices influenced by factors not necessarily evident to their physicians. Everyone wants to be healthy, but patients’ circumstances—such as this patient’s demanding job and frequent travel—can make it difficult to prioritize personal fitness and health. Patients seek advice that fits into their lives. This reinforces the importance of careful communication and listening. Physicians who understand a patient’s situation may offer more targeted resources or solutions, and the patient will be more amenable to trying them.

Resolution of Case

The physician showed the patient data about NAFLD and explained that it rarely causes cirrhosis and is only one complication of the patient’s poor diet and lack of exercise. The physician explained that the patient’s overall health would likely improve with faithful adherence to a diet and exercise plan. Three months later, the patient had lost 15 lb and felt much better. She went to the gym when at home and while staying in hotels and ate fruits and vegetables when she craved snack food. Her A1C was 6.4%, and her transaminase levels were near normal. Her physician told her there was no reason to repeat liver ultrasonography, although he would check her laboratory findings periodically. The patient was relieved and decided to push the NAFLD diagnosis out of her mind, focusing instead on maintaining good health.

Address correspondence to Andy Lazris, MD, CMD, at alazris50@gmail.com. Reprints are not available from the authors.

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