# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Advances in the Diagnosis and Treatment of Nonalcoholic Steatohepatitis

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**G&H** How is steatosis diagnostically distinguished from nonalcoholic steatohepatitis?

**KK** Steatosis simply means "fatty liver." Liver biopsy is the most definitive method to differentiate steatosis from nonalcoholic steatohepatitis (NASH), which is the more serious form of fatty liver disease that may progress to cirrhosis.

A great deal of work is being done to develop noninvasive markers using a combination of either serum proteins to identify advanced disease in nonalcoholic fatty liver disease (NAFLD)/NASH or algorithms based on clinical, anthropometric, and routine laboratory data. For instance, older patients, those with type 2 diabetes, and those who have elevated liver enzymes are more likely to have NASH, but steatohepatitis is defined by histologic features, so, without a liver biopsy, steatosis and NASH cannot be definitively distinguished.

Although routine liver biochemical tests (aspartate aminotransferase [AST] and alanine aminotransferase) may be helpful in that they can identify patients at higher risk for development of NASH, the presence of normal liver enzymes does not exclude the presence of NASH or cirrhosis in patients with NAFLD.

**G&H** Which patients should be specifically encouraged to undergo screening for NAFLD and NASH?

**KK** Patients with the highest risk for NASH are those with all the features of the metabolic syndrome, defined as high cholesterol or hyperlipidemia, hypertension, type 2 diabetes, and increased waist circumference. If a patient has all 4 of these features, it is strongly recommended that the patient be screened for NASH; even in the absence of these features, patients with type 2 diabetes should be evaluated for NAFLD and NASH.

Older patients are more likely than younger patients to have NASH, and patients with more severe features of metabolic syndrome are more likely to have NASH. There are also racial differences in the prevalence of NASH that are not completely understood. Patients who are African American tend to be at a lower risk, and patients who are Mexican American tend to be at a higher risk.

**G&H** What is the most promising advancement in screening for NASH?

**KK** Several advances have been made recently in our understanding of the natural history, diagnosis, pathogenesis, and treatment of NASH. The first are noninvasive algorithms such as the FIB-4 score or the NAFLD fibrosis score. The most promising developments have focused on composite noninvasive tests or blood tests that might help distinguish NASH from NAFLD. An example is cytokeratin 18, which is a biomarker of hepatocyte apoptosis. Other noninvasive fibrosis staging systems also have started to gain broader recognition and are now being validated in large-scale studies.

**G&H** What is the most efficient method of staging NASH?

**KK** A lot of active research is going on regarding staging. This research includes transient liver elastography using FibroScan (Echosens/Sandhill), the use of which is widely

established in patients with hepatitis C virus infection but is also being studied in patients with NAFLD. As we gain more experience with FibroScan, it will probably play a greater role in our ability to stage fatty liver disease.

A biopsy, of course, has remained the gold standard to differentiate advanced from early-stage fibrosis, and noninvasive fibrosis staging systems have been studied. For example, a large study, reported at the recent annual meeting of the American Association for the Study of Liver Diseases, which was held in Washington, DC on November 1 to 5, 2013, compared noninvasive fibrosis scoring systems to predict advanced fibrosis. The NAFLD fibrosis score, the AST-to-platelet ratio index, the FIB-4, the HepaScore (Quest Diagnostics), and the BARD score were compared. Results showed that, in a large number of patients, the NAFLD fibrosis staging system had an area-under-the-receiver-operating-characteristic curve of .83, with good negative and positive predictive values.

In summary, these kinds of noninvasive staging systems will likely be more widely used, and I think that, in addition to FibroScan, we will soon have more broad-based data in terms of utility of noninvasive staging systems. Therefore, in the near future, we should be able to avoid liver biopsy for the purpose of staging in many patients. Although we have not found a definitive way to differentiate NASH from NAFLD without a biopsy, the focus more recently in NASH research has been on fibrosis stage rather than other histologic features so that, if we come up with noninvasive tools to stage patients with NAFLD, the need for biopsy may become less relevant.

### G&H What is known about the impact of diet on NASH?

**KK** This is an active area of research, and several key elements of the role of diet in the development of NASH have been uncovered in the past few years using both epidemiologic human data and animal studies. First and foremost, we recognize that excess caloric intake contributes to weight gain and obesity, and so an essential step in the prevention of fatty liver disease is caloric restriction.

With regard to the particular type of diet that should be implemented, reduction in carbohydrate content, especially simple sugars, is important because it is increasingly recognized that fatty liver disease is associated with insulin resistance, which is preceded by hyperinsulinemia.

Another aspect of diet that we have learned in the past few years is the role of saturated fat, particularly cholesterol. A large amount of data on the role of cholesterol and saturated fat (the so-called "Western diet") have been gathered from animal studies that have demonstrated that a diet rich in saturated fat and cholesterol has a proinflammatory effect on the liver in addition to causing steatosis (fatty change).

Finally, high fructose corn syrup has also been implicated, because of the impact of fructose on xanthine oxidase and other pathways, to have a deleterious effect in metabolic syndrome and associated conditions such as NAFLD, although there is ongoing debate on whether this is unique to fructose or all simple sugars. Therefore, our efforts in the clinical setting have been to focus on carbohydrate and simple sugar restriction to reduce caloric intake; reduction of saturated fat intake, particularly cholesterol; and recommending that patients restrict sweetened beverages.

There are unequivocal data that even a 10% weight loss can result in significant improvement in and resolution of NASH. We know this both from randomized trials of weight loss through diet and exercise as well as literature on bariatric surgery showing resolution of NASH.

Exercise is equally important as diet. Both diet and exercise have independent effects on insulin secretion, glucose disposal, and insulin resistance. Either exercise or weight loss through diet alone can independently improve insulin and glucose metabolism, and the effects of exercise are synergistic.

### G&H How can a hepatologist or other clinician relate the importance of diet and exercise to a patient with NAFLD?

**KK** Of particular importance is that hepatologists, gastroenterologists, and other clinicians be very specific when giving diet and exercise recommendations to patients. General statements given as "door-knob" comments when the physician is heading out of the door after patient evaluation are going to be much less effective than specific guidance regarding caloric restriction, carbohydrate restriction, and units of exercise needed. Very specific recommendations are provided to patients with NAFLD at our clinic. Patients are given instructions about the optimal number of grams of carbohydrates, fats, and protein per day and the types of fats that are acceptable in addition to concrete recommendations about exercise.

### G&H What is the role of vitamin D and E supplementation in the management of NASH?

**KK** Some intriguing data exist about vitamin D. Vitamin D deficiency has been shown to be associated with obesity and NASH. Therefore, vitamin D supplementation to maintain a serum 25-hydroxyvitamin D concentration at 30 ng/mL should be a goal in patient care.

More controversy exists with regard to the value of vitamin E. The controversy has largely been driven by research suggesting that vitamin E use may be associated with a slight increase in mortality and cancer. In our practice, we do use vitamin E supplementation in appropriately selected patients with NASH. The National

Institute of Diabetes and Digestive and Kidney Diseases Clinical Research Network study entitled the PIVENS (Pioglitazone vs Vitamin E vs Placebo for Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis) study, which we participated in, showed that natural vitamin E—that is, D-alpha tocopherol—in a dose of 400 IU twice a day was associated with improvement of liver enzymes and resolution of NASH in a large number of patients who had nondiabetic NASH.

In our practice for patients with active NASH, we weigh the risks and benefits of vitamin E supplementation with regard to coexistence of cardiovascular disease and the patients' knowledge about the existing data on the potential for adverse events associated with vitamin E use. We believe that the benefit of vitamin E supplementation in a patient with NASH at high risk for potential progression to liver disease outweighs the theoretical risk of complications, but informed consent is required. The treatment should be individualized based on the risks and benefits.

In our practice, we consider using a lower dose of vitamin E (400 IU a day) in patients with cardiovascular risk factors. In the PIVENS study, 40% of patients who responded to vitamin E supplementation therapy did so within the first 3 to 6 months; therefore, if the patient does not respond within 6 months, then discontinuation of therapy supplementation would be reasonable.

### **G&H** What is known about the role of statins/lipid-lowering drugs in reversing NASH and liver fibrosis?

**KK** There are no controlled clinical trial data that have shown that statins are effective as a specific treatment for NASH. However, it should be emphasized that, although primary care physicians are frequently concerned about liver-related toxicity from statins, large-scale databases have shown that patients with baseline elevations of liver enzymes are not at increased risk for statin hepatotoxicity compared with patients with normal baseline levels of liver enzymes. The data also show that there is no direct evidence that statins are associated with an increased risk of hepatotoxicity in patients with NAFLD. Because the treatment of NASH and NAFLD is to correct underlying metabolic abnormalities, statin use should not be discouraged in patients with NASH.

It is true that occasionally, albeit rarely, a rise in liver enzymes is observed in patients who are treated with statins. This rise generally occurs within the first few months of treatment. Therefore, monitoring liver enzymes after starting a patient on a statin is appropriate. If an unexpected rise in liver enzymes occurs that is coincident with starting the statin, a hepatotoxic reaction should be suspected.

It is also being increasingly recognized that NAFLD is the hepatic manifestation of the metabolic syndrome. Patients with metabolic syndrome, especially those with NAFLD, are at significant risk for atherosclerotic disease. Therefore, a central element in the management of these patients is to make sure that they are counseled about cardiovascular risk reduction.

*Dr Kowdley has no relevant conflicts of interest to disclose.*

## Suggested Reading


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