ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Obesity and the Development of Nonalcoholic Steatohepatitis

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G&H How closely is the development of nonalcoholic steatohepatitis associated with obesity as a pre-existing condition?

BT The underlying disorder that is most closely linked to nonalcoholic steatohepatitis (NASH) is insulin resistance. Insulin resistance is a common problem among obese people, but it can occur independently of obesity, as can NASH. However, obesity remains a major risk factor, along with genetic and, possibly, environmental triggers. NASH is most often seen in the setting of type 2 diabetes, which develops as a result of insulin resistance and is also strongly associated with obesity.

Overall, although we are seeing a continuing escalation of the obesity epidemic, we are seeing a proportionally greater rise in NASH. Where obesity incidence may have doubled or tripled over a period of time, NASH prevalence has increased 10-fold. Therefore, we know some other pathophysiologic mechanism is, at least partially, driving NASH development.

G&H Could you explain the current understanding of NASH pathophysiology?

BT Our understanding of NASH pathophysiology is incomplete and currently evolving. Over a decade ago, two physicians in the United Kingdom, Drs. Christopher Day and Oliver James, described the "two-hit" theory of NASH pathogenesis. They published an editorial positing that the first step in the development of NASH was the build-up of fat in the liver. The second step was for that fat to cause oxidant stress and liver injury. However, ten years later, this theory has not been proven, nor has it provided the basis for any effective therapy.

If oxidant stress played a major role in NASH, we would expect that antioxidant approaches would be effective in treating the resultant liver injury, regardless of possible fat build-up. Quite a few small trials of antioxidant therapy have been conducted at institutions all over the world, and they have all shown negative results. Although recently released data suggest that vitamin E may be helpful, it is not uniformly so. I recently attended a large NASH-focused meeting in Italy, where the investigators who initially proposed the 2-hit hypothesis expressed their own doubts, as have many other investigators in liver disease and endocrinology.

Data coming from more recent animal studies, and even some human studies, suggest that NASH is caused by events that occur in tandem with fat build-up but is not necessarily caused by it. Instead, in a parallel process in the setting of insulin resistance, the liver needs to metabolize an excess of free fatty acids (FFAs) that are filtered from the bloodstream or are produced by the liver itself. Some of these FFAs are stored as triglycerides that become fat droplets in the liver. Others become toxic intermediates that cause the inflammation and scarring that are associated with NASH. This theory is known as the lipotoxicity model of NASH. I call it the nontriglyceride lipotoxicity model because triglycerides, and the resultant fat that builds up in the liver, may represent a protective response in the liver's processing of FFAs. By turning them into inert triglycerides, they can be stored and metabolized at a later time.

Thus, theoretically, the circulating FFAs generated by adipose tissue, as well as those made by the liver from carbohydrates like fructose, are the real culprit in NASH. This theory appeals because it explains both obesity and dietary contributors to disease, but there are still no hard data in humans to support it. However, the majority of current research is focused on exploring this idea.

Another observation that we have made from animal studies is that when we cause severe NASH in mice, the high-fat diet and the high-fructose corn syrup are not as great a contributing factor as the trans fats in their diet. This same observation has not yet been made in humans,

but we are working to confirm it currently. Trans fats were created in the 1940s and 1950s to make margarine and vegetable shortening. Many Americans grew up on them and were told that margarine was healthier than butter. Over the past ten years, an understanding has developed that trans fats pose a risk in terms of cardiovascular disease, stroke, and heart attack. Their possible role in NASH development needs to be more fully determined.

G&H What is the current prevalence of NASH in the United States, and is it contributing to the rising levels of cirrhosis and liver cancers that we are currently experiencing?

BT The Dallas Heart Study identified an excess of fat in the liver in approximately one third of all adults in the general population, when it was initially published in 2004. More recently, Dr. Stephen Harrison presented a study at the 2009 AASLD meeting where he found, via ultrasound examination, a prevalence of fatty liver in approximately 50% of adults coming into a large community-based clinic. Given the rapid escalation of the obesity epidemic, this rise in prevalence of fatty liver is not surprising.

With regard to NASH itself, where fat in the liver and concurrent injury are putting people at risk for cirrhosis, our current estimates range from 3% to 5% of adults in the general population. However, Dr. Harrison's study, which was conducted in a Texas community, showed a prevalence of 13%, which is a startling increase, but one that matches up with some of our clinical experience.

Currently, we have no way of predicting how many of these patients will develop liver cancer. However, we are seeing rare cases of cancer that develop in the setting of NASH without cirrhosis. Further, liver cancer is the fastest growing, in terms of prevalence, among all cancers in the United States. The large cohort of patients who contracted hepatitis C through intravenous drug use and transfusions in the 1960s and 1970s has led to a corresponding wave of cirrhosis and, now, liver cancer. This is a wave with a corresponding trough at the end. In 20 years, hepatitis C, and chronic liver disease caused by hepatitis C, will not be nearly as prevalent as they are now. However, there is no backside to the obesity epidemic, which continues to escalate with no end in sight. Therefore, if hepatocellular carcinoma proves to be closely related to cirrhosis from NASH, incidence will continue to rise.

G&H Once a patient has developed obesity-associated NASH, is their physical ability to exercise and lose weight impaired?

BT Currently, we have no hard data on how NASH affects exercise. It is, nonetheless, an interesting question with a variety of permutations. Are people who are relatively intolerant of exercise, for genetic or metabolic reasons, at heightened risk for obesity and NASH, particularly given the diet of typical Americans? It is hard to know what comes first, the disease or the behavior. We do know that any form of chronic liver disease can cause fatigue and contribute to a feeling of malaise that could affect the patient's inclination to exercise.

G&H How do you approach counseling NASH patients regarding the need, and means, for exercise and weight reduction?

BT The reality is that we live in an environment of fairly inexpensive but very abundant food. The cheaper fast foods tend to be very high in calories, which is perceived as a value. We, as physicians, are pushing against the marketing of these ideas to children and adults, and it is a very powerful force that is difficult to reverse, or even affect, with short clinic visits.

When speaking with patients, I avoid the word "diet." Asking patients to go on a diet is counterproductive, as most people who are overweight have already tried dieting and the word has a very pejorative connotation. I focus on healthy eating, including the avoidance of junk food and the avoidance of an overabundance of food. For patients who are determined, it is easy to avoid bad foods by avoiding fast food restaurants and eliminating high-fructose corn syrup–containing beverages. Many patients lose weight simply by eliminating sugar-sweetened soft drinks from their daily intake. I point out to patients that a 12-oz can of soda contains the equivalent of 10 sugar cubes and then ask, "Would you give your kids 10 sugar cubes to eat, just for the fun of it? Then why give them a can of Coke?" Patients have told me that the only liquid they drink is soda and that they drink 3 or 4 20-oz, sugar-sweetened sodas daily. These choices have huge health implications, and they are easily fixed.

Despite recent cardiovascular concerns, trans fats remain in the foods of many restaurants and manufacturers. Even some foods that are labeled "zero trans fat" can have significant trans fat content. This is because the US Food and Drug Administration allows manufacturers to label foods as "zero trans fat" if their trans fat content is less than 0.5 g per serving. However, as most of us are aware, the designated serving size of most snack foods is unreasonably small. People can easily eat 4 or 5 servings at one sitting, making it easy to go over the recommended 2 g of trans fat per day, simply by eating foods that are labeled as having zero trans fats. I teach all of my patients how to look for trans fats on labels, as well as hydrogenated and partially hydrogenated vegetable oil, particularly in the context of foods labeled zero trans fat.

This is easily done when buying prepared foods but more difficult in restaurants. Restaurant Web sites may have information on trans fat content, and it can be impressive, and disturbing, to read.

In terms of exercise, I tell people to do what they can. Unfortunately, the American lifestyle has become very sedentary, although there are differences among the degrees of sedentary behavior. Some current research in exercise physiology is focused on the difference between people who do not exercise but are active during the day, compared to those who sit at desks all day, drive to and from work, and do not exercise or even move about on a regular basis. Researchers are finding that the people who are not active at all are at a significantly higher health risk than those who do not exercise but are still up and about in the course of their daily routine. None of these data have focused specifically on the relation of exercise and NASH, but I remain convinced, with regard to many of my patients, that their jobs are killing them, simply by requiring them to sit at a desk for 8–10 hours daily. It is very difficult to develop an effective exercise regimen to counteract that schedule. For patients who can afford it and have facilities available where they live, I also recommend joining a gym and working with a trainer, because a trainer is an additional person to provide positive feedback and guidance in terms of exercise.

G&H Do you perceive an emerging role for bariatric surgery or gastric banding in the setting of obesity-related NASH?

BT Current data support the bariatric surgery procedure as a treatment for obesity, with NASH improvement as an added benefit. Although I do not initially suggest it, some patients raise the idea themselves and I am supportive, if they want to pursue it. Gastric banding is less effective for weight loss but it is also a less risky procedure, which is a trade-off.

G&H How does successful weight loss affect NASH progression and outcomes?

BT Available data suggest that somewhere in the range of 10% weight loss can provide significant benefit in terms of the liver, which is encouraging to patients. For someone who is 100 lbs overweight, the goal does not need to be a drastic reduction in order to achieve benefit. In reality, the weight loss is likely not at the root of whatever benefit is achieved. It is more likely the change in dietary and exercise habits that provides benefit, while simultaneously achieving weight loss. This is something we have seen in the laboratory in mouse models. If we put mice on a Western, fast-food diet, they become obese and develop NASH. However, if we switch them back to regular food, although they remain obese, the NASH disappears.

Suggested Reading

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