ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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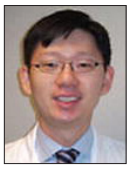
The Role of Bariatric Surgery in the Management of Nonalcoholic Steatohepatitis



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G&H What are the guidelines for the treatment of nonalcoholic steatohepatitis?

JL In 2012, a consensus statement was published by the American Association for the Study of Liver Diseases (AASLD), the American College of Gastroenterology (ACG), and the American Gastroenterological Association (AGA) for the diagnosis and management of fatty liver disease, including nonalcoholic steatohepatitis (NASH). The consensus guidelines recommend that first-line treatment for NASH consist of weight loss through lifestyle intervention, specifically a hypocaloric diet (calorie restriction with 30% energy reduction) and/or exercise. Weight loss of 3% to 5% may improve hepatic steatosis, but more significant weight loss of 10% or more is likely necessary to achieve an improvement in histologic necroinflammatory activity, steatohepatitis, and fibrosis. Exercise alone may have some benefit in reducing hepatic steatosis, but data confirming direct effects on steatohepatitis and/or fibrosis are limited.

Agents such as metformin and thiazolidinediones have been evaluated for a potential role in the treatment of NASH due to their role as insulin-sensitizing agents. Although multiple studies have demonstrated favorable effects on insulin resistance and liver enzymes, metformin has not been associated with significant improvements in liver histology. According to a recent meta-analysis, 6 to 12 months of metformin plus lifestyle change did not demonstrate greater change in liver histology than lifestyle change alone. On this basis, metformin is not recommended by the consensus guidelines for the treatment of NASH.

In contrast, thiazolidinediones such as pioglitazone have been demonstrated in several randomized, controlled trials to be associated with improvements in steatosis, ballooning, inflammation, aminotransferases, and liver fibrosis. In the largest study, the National Institutes of Health–sponsored multicenter PIVENS (Pioglitazone Vs Vitamin E Vs Placebo for Treatment of Non-Diabetic Patients With Nonalcoholic Steatohepatitis) trial, 247 nondiabetic patients with NASH were randomized to pioglitazone (30 mg/day), vitamin E (800 IU/day), or placebo for 24 months. The primary endpoint (improvement in NASH Activity Score ≥2 with no worsening of fibrosis) was achieved in 34% of the pioglitazone group, compared with 19% of the placebo group (P=.04) and 43% of the vitamin E group (P=.001); however, a P-value of .025 was considered significant due to 2 primary comparisons. A recent meta-analysis demonstrated that pioglitazone improves steatosis (odds ratio [OR], 4.05; 95% CI, 2.58-6.35) and inflammation (OR, 3.53; 95% CI, 2.21-5.64), but is not associated with an improvement in fibrosis (OR, 1.40; 95% CI, 0.87-2.24). Per the consensus guidelines, pioglitazone may be used to treat NASH in patients with biopsy-proven NASH, but it should be kept in mind that the evidence base is largely limited to nondiabetic patients.

The only medication currently recommended for first-line treatment of biopsy-proven NASH in nondiabetic patients is the antioxidant vitamin E at a dose of 800 IU/day based on the results of the PIVENS trial. However, due to concerns regarding a potential link to an increased risk for prostate cancer and all-cause mortality, careful discussion with patients regarding the relative benefits and risks of vitamin E administration is essential.

G&H When should vitamin E be used in nondiabetic NASH patients?

JL Vitamin E represents a first-line recommendation for the treatment of nondiabetic NASH as per the consensus guidelines. However, considering the need to balance benefits and risks, vitamin E is not universally recommended by

hepatologists for patients with NASH. In my clinical practice, I have a frank discussion with patients regarding the expected benefits and potential risks, and engage patients in this decision. Although 800 IU/day is the studied dose in randomized, controlled trials and what is endorsed by hepatologists and the AASLD guidelines, some patients have opted to use a lower 400 IU/day formulation, which is the dose typically found in a daily multivitamin. However, it is important to keep in mind that inadequate data are available to support this lower dose and that the use of vitamin E is restricted to patients with nondiabetic NASH.

G&H What, specifically, is the effect of weight loss on NASH?

JL As mentioned above, weight loss is currently the first-line therapy for patients with NASH. Weight loss is associated with direct effects on hepatic triglyceride (as measured by intrahepatic triacylglycerol concentrations on magnetic resonance spectroscopy) and favorable improvements in biochemical (serum alanine aminotransferase) and metabolic (fasting glucose, insulin sensitivity) parameters that lead to a reduction in steatosis, necroinflammation, and fibrosis on liver biopsy. In one of the largest prospective studies, 25% of the 293 patients who underwent lifestyle weight loss intervention over 52 weeks achieved resolution of steatohepatitis, 47% had a reduction in NASH Activity Score, and 19% experienced regression of liver fibrosis. As expected, the greatest effect was observed in patients who lost 10% or more of weight, with 90% achieving resolution of NASH and 45% achieving fibrosis regression. Importantly, only a minority of patients in this study (30%) successfully achieved meaningful weight loss through lifestyle intervention alone, and even fewer sustained this weight loss long term, matching real-world clinical practice.

Thus, the challenge that clinicians face is how to best advise patients in achieving weight loss: through standard medical diet and exercise, pharmacologic weight loss, and/or bariatric weight loss. Recognizing this challenge, many centers with a focus on NASH use a multidisciplinary approach in which patients see a team of health professionals (a hepatologist, dietician, health psychologist, bariatric physician, and so on) who work together to develop a personalized program for each patient depending on the stage of liver disease and the patient's unique medical needs.

G&H Have any weight loss drugs been examined for the treatment of NASH patients?

JL A number of weight loss drugs have been studied in the context of obesity, but very few have addressed obesity specifically in the setting of biopsy-proven NASH. Of these various medications, very few have adequate safety and efficacy data that incorporate liver histology outcomes. There is one notable exception: liraglutide, which is a glucagon-like peptide (GLP)-1 analogue. Liraglutide taken once daily for 48 weeks has been demonstrated in the randomized, controlled LEAN (Liraglutide Efficacy and Action in NASH) trial to reduce weight, fasting glucose, and body mass index (BMI). Importantly, it was found on paired biopsies to result in NASH resolution in 39% of patients (compared with 9% of patients on placebo; $P<.019$). Additional clinical trials are currently in progress to further examine whether this may represent a viable pharmacotherapy for NASH.

G&H How effective are surgical procedures for weight loss for the treatment of NASH?

JL Bariatric surgery represents an important treatment option for patients with NASH and obesity. Although the majority of patients with NASH are diabetic and obese, some patients are lean and nondiabetic. For these patients, weight loss may be necessary but inadequate to reverse the histologic changes associated with this disease. For the majority of patients who have obesity and metabolic syndrome, bariatric surgery—through Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric banding (LAGB), laparoscopic sleeve gastrectomy (LSG), or other methods—has been demonstrated to have a clear benefit in reducing all of the components of NASH, including steatosis, steatohepatitis, and fibrosis.

In terms of specific studies, there are several that have been impactful. One of the larger studies prospectively examined a series of 381 patients with severe obesity who underwent biopsies at baseline, 1 year postsurgery, and 5 years postsurgery. There was significant improvement in both fat and inflammation at the 1- and 5-year time points. One large meta-analysis that pooled 15 studies and 766 paired liver biopsies after bariatric surgery demonstrated improvement in steatosis (91.6%), steatohepatitis (81.3%), and fibrosis (65.5%), and 69.5% of patients achieved complete resolution of NASH. However, due to the absence of prospective, randomized, controlled trials addressing the role of bariatric surgery, these efficacy outcomes should be interpreted with caution.

G&H Are all bariatric surgical techniques equally effective for weight loss in NASH patients?

JL It is quite clear that each of these techniques have important differences, but bariatric surgery through any of the techniques is efficient for losing weight. Malabsorptive procedures such as RYGB and duodenal switch induce greater and faster weight loss than restrictive procedures such as LAGB or LSG, and this is believed to stem from fundamental differences in the effects on physiology. Whereas LAGB and LSG effectively promote satiation with partial removal of the fundus (the primary site of

ghrelin production) with activation of stretch mechanoreceptors, RYGB induces malabsorption via bypassing the absorption of nutrients in the duodenum, with first contact of nutrients occurring in the mid and distal small intestine. This leads to increased secretion of peptide YY hormone and incretins such as GLP-1 and GLP-2, which are important for insulin secretion to decrease hepatic glucose output and insulin resistance. This decreases inflammation through attenuation of tumor necrosis factor–alpha, interleukin (IL)-1–beta, and IL-6; reduces fatty acid–associated hepatocyte death; and activates genes such as peroxisome proliferator–activated receptor-alpha or -gamma, which are important for hepatic fatty oxidation, lipid export, and insulin sensitivity. Clinically, all bariatric surgery methods have demonstrated efficacy in reversing histologic features of NASH, but controlled trials comparing these methods head-to-head are lacking.

G&H Have endoscopic techniques for weight loss been studied in NASH patients?

JL A number of endoscopic methods for obesity have been studied. The best-known method is the intragastric balloon (IGB), which represents a space-occupying device that restricts stomach volume through implantation of a foreign device, promoting early satiety, delayed gastric emptying, and possibly impacting neurohormonal signaling pathways that affect metabolism. Multiple studies have confirmed the efficacy of IGBs in inducing weight loss, which in some cases have achieved outcomes similar to those of other restrictive surgical techniques such as LAGB or RYGB. A meta-analysis of 15 studies and 3608 patients treated with one commercially available IGB revealed an average BMI reduction of 5.7 at 6 months and excess weight loss of 32.1%. Very limited data addressing the role of IGBs in patients with NASH are available. One single-blinded, randomized, controlled trial revealed that patients randomized to IGB had a greater decrease in BMI (1.5 vs 0.8; P=.0008) and lower median NASH Activity Score on paired biopsy (2 vs 4; P=.03) vs a control group that received dietary intervention and sham endoscopy. Although several balloons have been approved by the US Food and Drug Administration (FDA) and are commercially available, more safety and efficacy data are needed using histology outcomes in patients with NASH to further clarify the role of IGBs and emerging endoscopic weight loss methods in NASH treatment.

G&H Should bariatric procedures be first-line therapy for NASH in morbidly obese patients?

JL Bariatric surgery is a highly effective treatment modality for patients with obesity and NASH. However, I generally consider these procedures to be treatments of last resort, in that the majority of patients may first benefit from either medical or pharmacologic weight loss or possibly from emerging pharmacotherapies for NASH. Although there is not a single FDA-approved drug that specifically targets NASH, 2 agents currently in phase 3 clinical trial development, obeticholic acid and elafibranor, have demonstrated histologic improvement within 48 to 72 weeks of therapy in phase 2b trials. There are several additional compounds that are currently in phase 2 development that are quite promising (eg, aramchol, emricasan, cenicriviroc, simtuzumab), which may allow physicians to use both medical weight loss and pharmacotherapy for the treatment of patients with NASH.

I view bariatric surgery as a treatment option that should be restricted to patients who have indications for bariatric surgery other than liver disease. In general, only patients with a BMI of 40 or a BMI of 35 with comorbidities such as diabetes mellitus or hypertension will qualify for bariatric surgery; liver disease due to NASH does not presently represent an independent indication for bariatric surgery. Bariatric surgery has been demonstrated to have significant benefits for patients with type 2 diabetes mellitus (42% remission post-RYGB), hyperlipidemia, hypertension, and obstructive sleep apnea, and is associated with improvements in health-related quality of life and life expectancy. Therefore, patients with NASH who have morbid obesity and/or other comorbidities should be given consideration for bariatric surgery. Special caution is warranted in patients with compensated and decompensated cirrhosis, in whom the postoperative mortality following bariatric surgery has been demonstrated to increase 2- and 21-fold, respectively.

Further studies to define the appropriate window for safe and effective bariatric surgery in patients with NASH are needed. In this context, the consensus guidelines of the AASLD, ACG, and AGA recommend that bariatric surgery should not be contraindicated in otherwise eligible obese patients with NASH, but more data are needed before it can be considered an established treatment option.

Dr Lim has no relevant conflicts of interest to disclose.

Suggested Reading

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