

# Effects of Weight Loss on Nonalcoholic Fatty Liver Disease

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## ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is one of the most prevalent liver diseases worldwide, affecting men, women, and children. This is due, in part, to the obesity epidemic, which is associated with increased prevalence of NAFLD. The NAFLD spectrum ranges from simple steatosis to nonalcoholic steatohepatitis (NASH), which is the potentially progressive form. NAFLD is associated with metabolic syndrome and insulin resistance. Treatment recommendations include weight reduction through both diet and physical activity, and weight-loss surgery for extreme obesity. Most medical regimens target components of the metabolic syndrome or oxidative stress associated with the pathogenesis of NASH. These include antiobesity regimens, insulin sensitizers, antihyperlipidemics, and antioxidants. Bariatric surgery is effective for achieving and maintaining weight loss and reversing the complications of metabolic syndrome. On the other hand, the literature lacks well-designed, randomized control trials that assess the efficacy of anti-obesity regimens on histologic and long-term outcomes of NAFLD.

**KEYWORDS:** Nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), weight loss

Obesity is increasingly recognized as a major health issue throughout the world. Worldwide ~1 billion people are overweight and 300 million are obese.<sup>1</sup> In the United States, obesity is an epidemic, affecting 93 million people; this number is expected to rise to 120 million in the next 5 years.<sup>2</sup> According to the National Health and Nutrition Examination Survey (NHANES), the prevalence of obesity has risen from 15 to 32.9% in adults between 20 and 74 years old.<sup>3</sup>

Obesity is defined as a body mass index (BMI) > 30 kg/m<sup>2</sup> and morbid obesity > 40 kg/m<sup>2</sup>. Obese patients are known to have increased morbidity and mortality. The major factors contributing to obesity are behavior, environment, and genetics. Accumulating data indicate that in recent decades, our society has adopted a more sedentary lifestyle; people are consuming more calories and decreasing their physical activity. For exam-

ple, in 1995, almost double the number (34%) of people ate outside their homes (e.g., in restaurants) than in 1978 (18%).<sup>4</sup>

Health risks associated with obesity include insulin resistance, type II diabetes, hypertension, dyslipidemia, coronary heart disease, stroke, sleep apnea, and nonalcoholic fatty liver disease (NAFLD), which are components or complications of metabolic syndrome. Recently, the Center for Disease Control (CDC) has reported that over the past 30 years the number of patients with diabetes has increased in the United States from 5.6 million to 15.8 million.<sup>5</sup>

The hepatic manifestation of metabolic syndrome, NAFLD, affects people of all ages and ethnicities. NAFLD represents a wide spectrum of clinicopathologic conditions consisting of simple steatosis, steatosis with nonspecific inflammation, and

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Fatty Liver Disease; Guest Editor, Arun J. Sanyal, M.B.B.S., M.D.

Semin Liver Dis 2008;28:427–433. Copyright © 2008 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.

DOI 10.1055/s-0028-1091986. ISSN 0272-8087.

nonalcoholic steatohepatitis (NASH). The potentially progressive form of NAFLD or NASH can progress to cirrhosis, end-stage liver disease, and hepatocellular carcinoma. An estimated 25% of the general population has NAFLD and 3 to 5% has NASH. The prevalence of NAFLD and NASH is much higher in obese or morbidly obese individuals. In 1990, Wanless and coworkers found hepatic steatosis in 70% of 351 obese patients at autopsy. This study differentiated 18.5% of these patients with steatonecrosis and 13.8% with severe fibrosis compared with lean patients, of whom 2.7% had NASH and 6.6% had severe fibrosis.<sup>6</sup>

An estimated 9 to 15% of patients with NASH progress to more serious liver disease, as indicated by data from tertiary care centers and sequential biopsy studies. Community-based population studies and general population studies based on NHANES databases further confirm these observations.<sup>7</sup> Increasing evidence indicates that patients with NASH are at increased risk for liver-related mortality as well as increased risk for cardiovascular mortality.<sup>8</sup>

The pathogenesis of NAFLD and NASH is covered elsewhere in this issue of the *Seminars in Liver Disease*. Although the multihit hypothesis appears to involve insulin resistance and its impact on  $\beta$ -oxidation, influx of free fatty acid, oxidative stress, apoptosis, and inflammatory cytokines, other pathways are certainly involved in this progressive course. Specifically, recent work suggests that white adipose tissue (WAT) in the visceral fat is associated with the development of NAFLD. In fact, WAT is now considered to be an endocrine organ that secretes adipokines and cytokines responsible for the inflammatory milieu associated with obesity and its complications including NAFLD. Adipokines such as adiponectin, leptin, resistin, visfatin, vaspin, and apelin may be associated with insulin resistance, hepatic steatosis, and hepatic fibrogenesis. In addition to these adipokines, cytokines that are released from WAT, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), and interleukin-8 (IL-8), also contribute to these proinflammatory, proinsulin-resistant, and profibrogenic processes.

### WEIGHT LOSS IN THE CONTEXT OF TREATING NAFLD

In the absence of an approved treatment for NASH, potential treatments target associated risk factors such as obesity, insulin-resistance, type II diabetes, hyperlipidemia, and the pathogenic targets of oxidative stress, TNF, and cytoprotection. Weight loss interventions are summarized in Table 1.

First-line treatment for weight loss in overweight and obese patients is lifestyle modification (diet and exercise). Unfortunately, weight loss is hard to achieve and hard to maintain in most cases. Alternatives to diet

**Table 1 Weight Loss Methods for Treatment of Nonalcoholic Steatohepatitis**

Lifestyle modifications
Nutritional counseling
Calorie restriction
Exercise
Diet
Atkins diet
Zone diet
Weight Watchers
Antiobesity drugs
Orlistat
Sibutramine
Rimonabant
Weight loss surgery
Roux-en-Y gastric bypass
Laparoscopic adjustable gastric bypass
Biliopancreatic diversion/biliopancreatic diversion with duodenal switch
Gastrectomy

and exercise are antiobesity medications that may be effective in some patients. Orlistat and sibutramine are the two weight loss medications in use. Bariatric surgery is also offered to morbidly obese patients. In the following sections, we summarize specific medical and surgical treatment approaches to NAFLD that target some of the pathogenic pathways described above, focusing specifically on the impact of weight loss on the biochemical and histologic outcomes of NAFLD.

### WEIGHT LOSS AND DIET

In overweight or obese patients, recommendations for treatment of NAFLD include lifestyle modifications and weight loss (Table 2). Lifestyle changes include calorie restriction, exercise, and nutritional counseling. The goal of dieting is to decrease calorie intake while increasing energy consumption, resulting in weight loss, a reduction of adipose tissue, and improvement of insulin resistance.

The majority of patients has difficulty losing weight. In addition, a study of 74 obese NAFLD patients with a detailed diet history and liver biopsy revealed no association between steatosis, inflammation, or fibrosis in relation to total calorie or protein intake. This study pointed out a greater association between inflammation and increased carbohydrate intake. The authors concluded that a low fat, high carbohydrate diet may actually exacerbate NAFLD.<sup>9</sup> In another study, 23 patients with biopsy-proven NASH underwent nutritional counseling for 1 year. The diet was designed so patients would obtain 40 to 45% of their calories from carbohydrates, 35 to 40% from fat, and 15 to 20% from

**Table 2** Effects of Weight Loss with Diet and Exercise

Author	Study Design	N	Outcome
Palmer and Schaffner, 1995 <sup>20</sup>	1-arm intervention with low calorie diet (25–30 kcal/kg) and low-impact aerobics for 1 year	39	Improved liver enzymes in those who lost weight vs. those who did not
Ueno et al, 1997 <sup>19</sup>	Nonrandomized controlled trial of diet and exercise versus no treatment	25	Improved steatosis in treated group
Samaha et al, 2003 <sup>14</sup>	Obese patients placed on low carbohydrate versus low fat restricted diet	132	Low carbohydrate group—greatest weight loss, improved insulin resistance in nondiabetics, reduced triglycerides
Huang et al, 2005 <sup>10</sup>	1 year dietary counseling in biopsy-proven NASH	23	NASH improved in 9 of 15 patients
Dansinger et al, 2005 <sup>16</sup>	Randomized trial of overweight/obese placed on diets: Atkins (carbohydrate restriction); Zone (macronutrient balance); Weight Watchers (calorie restriction); Ornish (fat restriction)	160	Reduced body weight (3–4.8 kg)

NASH, nonalcoholic steatohepatitis.

protein. A liver biopsy repeated 12 months later showed that 9 of 15 patients showed improvement in NASH histologic features, which were associated with a greater degree of weight loss.<sup>10</sup> Low carbohydrate diets are considered beneficial because of the weight loss associated with a reduced BMI and as well as improved insulin sensitivity. However, more research is needed to determine the long-term impact of this diet on NAFLD.

Several other diet regimens have been considered for NAFLD. Current rat models designed to study hepatic steatosis have shown the benefits of a diet high in fiber and rich in olive and fish oil.<sup>11–13</sup>

Furthermore, Samaha and coworkers randomized 132 obese patients with a mean BMI of 43 to a low carbohydrate versus a low-fat calorie restricted diet. At 6 months, the metabolic profile of the low carbohydrate group showed greater weight loss and reduced triglycerides than the low fat group. In addition, the fasting glucose of diabetics decreased in the low carbohydrate group and insulin sensitivity improved in the nondiabetic group.<sup>14</sup> The one-year follow-up showed no significant weight loss between the 2 groups.<sup>15</sup> Another study compared 4 popular diets: Atkins, Zone, Weight Watchers, and the Ornish diets. The results showed no difference between the diets because all decreased weight and reduced the low-density lipoprotein/high-density lipoprotein (LDL/HDL) ratio.<sup>16</sup> Neither one of these studies carefully assessed NAFLD. Although diets that improve insulin resistance are expected to improve NAFLD, future diet studies require measuring appropriate outcomes for patients with NAFLD.

## WEIGHT LOSS AND EXERCISE

Exercise has a positive impact on the risk factors for NAFLD including obesity, metabolic syndrome, dyslipidemia, insulin resistance, and type II diabetes. Exercise helps patients achieve weight loss and also improves

muscular insulin sensitivity. Specifically, aerobic exercise prevents the development of steatosis independently of weight loss. Researchers assume that these results are achieved by increasing insulin sensitivity through a reduction of peripheral lipolysis, inhibition of lipid synthesis, and stimulation of fatty acid oxidation.<sup>17</sup> For example, Gauthier and colleagues demonstrated the effects of exercise training and a high fat diet in active rats compared with sedentary rats. Unlike the sedentary rats, the physically active rats did not develop hepatic steatosis.<sup>18</sup> Furthermore, Ueno and coworkers describe the effects of lifestyle modifications on NAFLD in 25 obese Japanese patients. Fifteen patients were placed on a restricted diet and exercise for 3 months and compared with the controls, who did not receive treatment. The treated group showed a reduction in BMI, aminotransferases, total cholesterol, and fasting glucose. Liver biopsy showed improved steatosis, but no change in fibrosis or inflammation.<sup>19</sup> Finally, Palmer and colleagues placed 39 patients on a very low-calorie diet (600 to 800 kcal/day) with exercise. Twelve patients lost more than 10% of ideal body weight and had normalized liver enzymes, and 71% had a decreased liver span.<sup>20</sup>

## ANTIOBESITY MEDICATIONS

Two medications currently used for weight loss are orlistat (Xenical<sup>®</sup>; Hoffman LaRoche, Nutley, NJ) and sibutramine (Meridia<sup>®</sup>; Abbott Laboratories, Abbott Park, IL). Orlistat inhibits gastric and pancreatic lipase, therefore blocking the absorption of long chain fatty acids and cholesterol. It decreases fat absorption by ~30% and unabsorbed fat is excreted in the stool.<sup>21</sup> This treatment may result in malabsorption of fat-soluble vitamins, requiring vitamin supplementation. Treatment benefits include a reduction in systolic blood pressure, waist circumference, fasting serum insulin and glucose levels, total cholesterol, and LDL cholesterol.<sup>22</sup>

In a study of 10 obese patients with biopsy-proven NASH, patients were given orlistat 120 mg orally three times a day with meals and dietary counseling with support. At the end of the 6-month trial, the mean average weight loss was 22.7 pounds and BMI, hemoglobin A1C, and transaminases were all decreased. Repeat liver biopsy showed improved steatosis in 6 patients and fibrosis improved in 3 patients. However, steatosis worsened in 2 patients and fibrosis worsened in one patient.<sup>23</sup> Hatzilios and colleagues studied 21 patients with NAFLD and hyperlipidemia who were given orlistat, omega 3 fatty acid, or atorvastatin for 6 months. All three groups showed decreased liver enzymes and 86% showed echogenicity normalization in their follow-up ultrasound scan.<sup>24</sup>

Another weight loss medication, sibutramine, enhances satiety by inhibiting serotonin and norepinephrine reuptake.<sup>21</sup> A study of 25 obese patients comparing sibutramine to orlistat resulted in transaminase reduction in the sibutramine group; steatosis improved in both groups after 6 months.<sup>25</sup>

Rimonabant (Acomplia<sup>®</sup>; Sanofi Aventis Pharmaceuticals, Paris, France), another antiobesity medication, is an antagonist of the cannabinoid receptor type 1 (CB1). Obese (fa/fa) rats were given rimonabant (30 mg/kg) for 8 weeks. Hepatic steatosis disappeared, and liver enzymes, triglycerides, and free fatty acids were all reduced. In addition, the proinflammatory cytokine TNF- $\alpha$  decreased while adiponectin levels increased.<sup>26</sup>

The Rimonabant in Obesity (RIO)-Europe group randomized a double-blinded trial comparing a placebo with rimonabant at 5 mg and 20 mg; all patients were also placed on a low-calorie diet (600 kcal/day). After 1 year, the 5 mg group lost 3.4 kg, the 20 mg group lost 6.6 kg, and the placebo group lost 1.8 kg. The greatest benefits appeared among the group receiving 20 mg of rimonabant, as they demonstrated improved waist circumference, HDL, triglycerides, insulin resistance, and metabolic syndrome.<sup>27</sup> In four large trials (Rimonabant in Obesity (RIO)-Lipids, RIO-Europe, RIO-North America, and RIO-Diabetes) patients were treated with rimonabant 20 mg/day for 1 to 2 years. The authors report significant weight reduction, and improvements in blood pressure, lipid disorders, and serum glucose. They also report an increase in adiponectin and decrease in C-reactive protein.<sup>28</sup>

A meta-analysis of 30 randomized trials from 2002 to 2006 examined 3 antiobesity drugs. Compared with placebo, sibutramine decreased weight by 4.2 kg (95% CI, 3.6 kg to 4.7 kg), orlistat by 2.9 kg (2.5 kg to 3.2 kg), and rimonabant by 4.7 kg (4.1 kg to 5.3 kg). The side effect of sibutramine included increased heart rate and blood pressure and decreased serum triglycerides and HDL. Orlistat improved blood pressure, total cholesterol, LDL, and decreased the likelihood of diabetes. Finally, rimonabant improved blood pressure and

cholesterol. However, these patients showed an increased risk of mood disorders.<sup>29</sup>

Despite some encouraging results, randomized controlled trials of antiobesity agents are required to determine whether their benefits on NAFLD can be proven in both the short term and the long term.

## BARIATRIC SURGERY

Bariatric surgery is currently being recommended for morbidly obese patients.<sup>30-42</sup> Except for jejunoileal bypass surgery which is largely abandoned,<sup>32-34</sup> all the other types of bariatric surgical techniques seem to decrease excess body weight by at least 50%. This significant weight loss is associated with an improvement in insulin resistance and other components of the metabolic syndrome, including NASH. In fact, these improvements have been reported to occur after several bariatric procedures including biliopancreatic diversion,<sup>32,35</sup> gastroplasty,<sup>32,36</sup> Roux-en-Y gastric bypass,<sup>32,37,40-42</sup> and laparoscopic adjustable gastric band (LAGB).<sup>32,43,44</sup> Although the amount of weight loss may differ from procedure to procedure, they are all associated with some beneficial effects in reversing some of the components of metabolic syndrome (Table 3). Details of bariatric surgery and its impact on NASH are described elsewhere in this issue of *Seminars in Liver Disease*.

## CONCERNS ABOUT RAPID WEIGHT LOSS

Early studies assessing the impact of weight loss on liver disease suggest that weight loss > 1.6 kg per week places patients at risk for hepatic inflammatory changes and portal fibrosis. One explanation may be related to the fat mobilization that occurs with rapid weight reduction. Rapid fat mobilization increases visceral free fatty acids and accelerates the inflammatory process, which may negatively affect patients with advanced liver disease or cirrhosis. NASH patients with advanced fibrosis may be better off with LAGB than more drastic bariatric surgery procedures because the rate of weight loss can be controlled with the adjustable band.<sup>43</sup>

## WEIGHT LOSS SURGERY AND CIRRHOSIS

As noted previously, obese patients with cirrhosis secondary to NASH who are considering bariatric surgery can be at some perioperative risk. Those with well-compensated disease can be considered for the least invasive procedure, such as LAGB. Liver disease, including fibrosis, may in fact improve after weight loss in these patients.<sup>38</sup> One study showed that such patients benefit from weight loss surgery when compared with patients placed on a liver transplant list. On the other hand, patients with decompensated liver disease are at

**Table 3 Summary of Various Studies Comparing Surgical Weight Loss Procedures**

Author	Weight Loss Procedure	N	Outcome
Silverman et al, 1995 <sup>37</sup>	RYGB	106	Improvement of PSF and steatosis
Luyckx et al, 1998 <sup>36</sup>	Gastroplasty	528	Improved steatosis Increased inflammatory hepatitis
Kral et al, 2003 <sup>35</sup>	BPD	689 (104 paired bx)	Improved steatosis Decreased fibrosis in 28 Increased fibrosis in 42 Decreased fibrosis in 11 patients with cirrhosis
Dixon et al, 2004 <sup>43</sup>	LAGB	36	Average mean weight loss 34 ± 17 g Improved steatosis, inflammation, fibrosis Improved NASH
Mattar et al, 2005 <sup>38</sup>	RYGB, LAGB, Sleeve gastrectomy	70	Improved steatosis, inflammation, fibrosis Decreased MS
O'Brien et al, 2006 <sup>44</sup>	LAGB vs. Medical	80	Average mean weight loss 21.6% Decreased MS Improved quality of life
Liu et al, 2007 <sup>39</sup>	RYGB	39	Improved steatosis, ballooning and PSF No change in portal tract inflammation or fibrosis

BPD, biliopancreatic diversion; LAGB, laparoscopic adjustable gastric bypass; MS, metabolic syndrome; NASH, nonalcoholic steatohepatitis; PSF, perisinusoidal fibrosis; RYGB, Roux-en-Y gastric bypass.

significant operative risk from abdominal surgeries. For these patients, bariatric surgery may be considered after liver transplantation. Nevertheless, obesity carries an operative risk for liver transplantation, making a large number of these patients ineligible for transplantation. It is also important to remember that patients with obesity-related NASH are at risk for recurrence and progression of their liver disease after transplantation.<sup>45</sup>

### WEIGHT LOSS FOR TREATMENT OF NAFLD IN THE PEDIATRIC POPULATION

Between 1999 and 2002, 16% of the pediatric population (age 6 to 19 years) in the United States was overweight.<sup>46</sup> The overall rate of NAFLD in the obese pediatric population can be as high 53%.<sup>47,48</sup> In an investigation of the impact of weight loss in children, investigators enrolled 84 children with elevated liver enzymes and biopsy-proven NAFLD. The treatment consisted of diet and physical activity for one year. At the beginning of the study, the majority of patients had insulin resistance despite their BMI. After 12 months, these patients showed a reduction in BMI, serum insulin, glucose, lipids, liver enzymes, and decreased liver echogenicity on abdominal sonograms.<sup>49</sup> Additional studies are needed to assess the impact of weight loss on the pediatric population with NAFLD.

### WEIGHT LOSS FOR HEPATITIS C PATIENTS WITH OBESITY OR SUPERIMPOSED NAFLD

As described elsewhere in this issue of *Seminars of Liver Disease*, NAFLD may coexist with other liver diseases

such as chronic hepatitis C (HCV). Thirty to 70% of patients with HCV have hepatic steatosis on liver biopsy. The etiology of steatosis in patients with HCV may be host related because of conditions associated with metabolic syndrome, or it could originate with the virus itself. Superimposed fatty liver and the obesity and insulin resistance associated with it can affect the HCV-related outcome in several ways. First, obesity, insulin resistance, and hepatic steatosis may exacerbate HCV-related fibrosis. Additionally, these conditions may lower the efficacy of antiviral therapy for hepatitis C. Although several strategies are used to improve the outcome of obese patients with HCV, weight loss is an important option. Hickman and colleagues assessed the impact of weight loss in 19 obese HCV patients with hepatic steatosis. The study consisted of 3 months of weight reduction through increased physical activity, restricted energy intake, and weekly meetings with a dietician. The authors reported an average weight loss of 5.9 ± 3.2 kg and a reduction in waist circumference. Fasting insulin improved from 16 ± 7 to 11 ± 4 and alanine aminotransferase (ALT) improved in 6 out of 19 patients. Paired liver biopsies in 10 patients revealed reduced steatosis and improved fibrosis.<sup>50</sup>

In another study, patients with HCV and hepatic steatosis were placed in a 15-month diet and exercise program. After 15 months, 68% of these patients lost weight and sustained their weight loss. Reductions in serum insulin and ALT values were also noted. Additionally, these patients reported improved quality of life.<sup>51</sup>

Both studies suggest that weight loss for obese patients with HCV may be beneficial. Nevertheless,

well-designed controlled trials of different treatment regimens, including pharmacologic agents, for these patients are needed.

## CONCLUSIONS

To date, treatment options for patients with the potentially progressive form of NAFLD or NASH are limited and have not been tested in randomized clinical trials. Nevertheless, current recommendations target weight loss through lifestyle modifications with diet and exercise. Some studies have shown improvement in liver enzymes and evidence of hepatic steatosis by ultrasonography, but long-term histologic improvements have not been fully established. Additionally, most patients have difficulty losing weight and sustaining the weight loss. Medical treatment with antiobesity medications, diet with or without exercise, and bariatric surgery are currently being studied to determine whether they provide an effective treatment strategy for patients with NAFLD.

There is increasing evidence that bariatric surgery may improve conditions associated with metabolic syndrome and NAFLD in morbidly obese patients. Preliminary studies have shown that these patients are able to lose and sustain their weight loss. Benefits include reduced transaminases, serum insulin, glucose, and histologic improvement in some patients. In addition, components of metabolic syndrome resolve or improve after weight loss. However, the efficacy of these treatments needs to be further evaluated in well-designed clinical studies.

## ABBREVIATIONS

BMI	body mass index
HCV	hepatitis C
HDL	high-density lipoprotein
LDL	low-density lipoprotein
MS	metabolic syndrome
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
WAT	white adipose tissue

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