REVIEWS

Is Weight Reduction an Effective Therapy for Nonalcoholic Fatty Liver?
A Systematic Review

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PURPOSE: To assess the evidence supporting the efficacy of weight reduction for patients with nonalcoholic fatty liver.

METHODS: Potentially relevant studies were identified by a computerized search of databases and a manual search of abstracts from scientific meetings. Studies were included if they reported histology, serum aminotransferase levels, or radiological imaging of the liver in obese adult patients who had undergone weight reduction. Weight reduction regimens included diet, exercise, antiobesity medications, gastric bypass, gastropasty, or any combination of these interventions. Studies involving jejunoileal or small bowel bypass surgery were excluded.

RESULTS: We identified 517 potentially relevant studies, of which 15 met the inclusion criteria: one randomized controlled trial (in abstract form), two nonrandomized controlled trials, nine case series, one retrospective review, and two case reports. Three studies included more than 50 patients, whereas nine studies had 25 or fewer patients. Twelve studies used behavioral, dietary, or pharmacologic therapy for weight reduction, and three studies used surgical interventions. Although all 15 studies demonstrated overall improvement in the measurements of liver outcome after weight reduction, more than half did not report histologic results.

CONCLUSION: Despite general acceptance that weight reduction is an effective therapy for nonalcoholic fatty liver, this systematic review found little data to support or refute this recommendation. Am J Med. 2003;115:554–559. ©2003 by Excerpta Medica Inc.

Nonalcoholic fatty liver represents a spectrum of disorders defined by the presence of hepatic steatosis in the absence of alcohol use or another chronic liver disease (e.g., viral hepatitis, autoimmune hepatitis, hereditary hemochromatosis). It is the most common liver disorder in industrialized countries, and affects about 15 million persons in the United States (1,2). Evidence suggests that nonalcoholic steatohepatitis, a more severe subtype of nonalcoholic fatty liver, progresses to cirrhosis in 25% of patients (3–6). Moreover, nonalcoholic fatty liver is now thought to be the predominant cause of cryptogenic cirrhosis in patients requiring liver transplantation (7).

Obesity has been described in 39% to 90% of patients with nonalcoholic fatty liver (4–6,8). Conversely, at least 20% of persons with a body weight >140% have hepatic steatosis (9). Nonalcoholic fatty liver is also associated with type 2 diabetes mellitus and hyperlipidemia, which themselves are linked to obesity. The pathophysiological mechanisms linking obesity to nonalcoholic fatty liver are not clear, but have been proposed to be mediated by the development of insulin resistance and the suppression of beta oxidation (10). Based on the relation between obesity and nonalcoholic fatty liver, weight reduction has been suggested as an effective treatment for overweight patients with nonalcoholic fatty liver (11). The objective of this paper was to assess the evidence supporting this recommendation.

METHODS

Potentially relevant studies were identified by searching the Cochrane Hepato-Biliary Group Controlled Trials Register (February 2002), the Cochrane Controlled Trials Register on The Cochrane Library (Issue 1, 2002), MEDLINE (1965 to 2001), EMBASE (1985 to 2001), the Science Citation Index (1980 to 2001), Biological Abstracts (1980 to 2001), Current Contents (1980 to 2001), the Papers First database (1980 to 2001), and the Proceedings database (1980 to 2001). In addition, manual searches were performed of the bibliographies of relevant published articles and the published abstracts of the annual...
meetings of the European Association for the Study of Liver and the American Association for the Study of Liver Disease (1980 to 2001). The following search terms (text and Medical Subject Headings) were used: steatohepatitis, NASH, nonalcoholic steatohepatitis, nonalcoholic fatty liver disease, fatty liver, weight loss, obesity, diet (fat-restricted), antiobesity agents, body mass index, body composition, diet therapy, surgery, behavior modification, pharmacotherapy, drug treatment, overweight, weight reduction, energy restriction, and very low-calorie diets. The closing date of the search protocol was February 2002.

Studies were included if they reported histology, serum aminotransferase levels, or radiological imaging of the liver in obese adult patients who had undergone weight reduction. Weight reduction methods included caloric restriction, increase in activity, other behavior modification, antiobesity medications, gastroplasty, gastric bypass, or any combination of these interventions. Studies involving jejunooileal or small bowel bypass were excluded, because these procedures have been shown to worsen liver outcome (12,13).

One investigator (RTW) reviewed all references, citations, and abstracts. The same investigator also corresponded with the other investigators to identify additional studies. Two investigators (RTW, HFY) then independently assessed each study for inclusion criteria.

Studies were classified as case reports, retrospective reviews, case series, controlled clinical trials, or randomized controlled trials using definitions from the Cochrane Reviewers’ Handbook Glossary (14).

RESULTS

The database search identified 500 citations and the manual search identified 17 studies. Communication with principal authors did not uncover any new studies. Of the 517 potentially relevant studies identified, only 15 met inclusion criteria (four abstracts, 11 published papers), which included one randomized and two nonrandomized controlled trials, and 12 case series, retrospective reviews, or case reports (Table 1). Three of the studies included more than 50 patients, of which only one has been published as a paper (21), and nine studies included 25 or fewer patients (15–19,24,25). Behavioral, dietary, or pharmacological interventions to reduce weight were used in 12 studies, whereas three studies used surgical interventions. Both of the controlled trials used behavioral, dietary, or pharmacological interventions for weight loss (15,16).

Although all 15 studies meeting inclusion criteria reported overall improvements in liver outcome measurements (serum aminotransferase levels, radiological imaging, histology) after weight reduction (Table 1), worse outcomes were observed in two subgroups. In one study (20), worsened liver histology was observed in patients who had lost more than 1.6 kg per week. In another study (21), there was a twofold increase in the number of patients who developed lobular hepatitis after bariatric surgery.

DISCUSSION

The goal of this paper was to evaluate the evidence supporting the recommendation of weight reduction in overweight patients with nonalcoholic fatty liver (1,2,11) by means of a meta-analysis. However, our systematic review of the existing data determined that the studies were inadequate to permit such a formal data combination. Indeed, the evidence supporting the recommendation was limited and sometimes of lower quality.

First, only 15 studies met the inclusion criteria, of which four were available only in abstract form. Second, more than half of the studies did not assess liver histology, which is considered the gold standard (8,26). Many studies used surrogate measures of liver outcome, such as serum aminotransferase levels or radiographic imaging, which do not correlate with clinical outcome. Consequently, the clinical importance of a substantial proportion of the included studies was uncertain. Third, most studies had small samples. Only three studies comprised more than 50 patients, whereas four studies consisted of 5 or fewer patients, which may explain why none of the studies provided power calculations. Finally, only three studies were controlled, of which only one was a randomized trial that did not have an untreated control group. Indeed, even the two controlled trials suggesting that weight reduction improved measurements of liver outcome had several limitations (15,16). The study samples were small. Park et al (15) used ultrasound-proven fatty liver as a criterion instead of the gold standard, liver biopsy. The studies were not randomized; hence, patients may have been subject to selection bias. In the uncontrolled trials, the purported benefits of weight reduction for patients with nonalcoholic fatty liver could be explained by regression artifact. Also termed regression to the mean, this phenomenon arises anytime two distinct measurements are made from a nonrandomized sample of the population. Because these studies enrolled only patients with evidence of hepatic abnormalities, it is predictable that measurements made after weight reduction would show apparent improvements. Therefore, in the absence of proper control groups, determination of the true benefit of weight reduction is problematic.

Furthermore, two reports suggested that weight reduction might be harmful. Anderson and colleagues reported that 5 patients who had relatively large and rapid loss in weight (>1.6 kg per week) developed more portal fibrosis (20). Luyckx et al observed a twofold increase in the number of patients with lobular hepatitis after bariatric surgery (21).
Table 1. Characteristics and Results of the 15 Eligible Studies

<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Type of Study</th>
<th>No. of Patients</th>
<th>Criteria</th>
<th>Intervention</th>
<th>Results</th>
<th>Notes</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Meryn (1990)</td>
<td>Randomized controlled trial</td>
<td>60</td>
<td>Inclusion: abnormal hepatic test results and obese patients; Exclusion: unable to determine if other causes of liver disease</td>
<td>Diet/placebo, diet/fluvoxamine, fluvoxamine/behavior therapy, behavior therapy/placebo (12 weeks)</td>
<td>Improvement in AST/ALT. Of patients with elevated levels, 55% of ALT and 100% of AST returned to normal.</td>
<td>No untreated control group. Absolute numbers of patients with normalization of aminotransferase levels not stated. No P values provided.</td>
<td>*</td>
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<tr>
<td>Park (1995)</td>
<td>Controlled clinical trial</td>
<td>25</td>
<td>Inclusion: ultrasound-proven fatty liver; Exclusion: alcohol, hepatitis B/C, medications, and other liver disease</td>
<td>Diet and exercise (1 year)</td>
<td>Improvement in AST/ALT in treated group (n = 13; P = 0.0002). Untreated group (n = 12) with worsened AST/ALT (P = 0.0005). Weight reduction &lt;10% of baseline weight showed improvement.</td>
<td>No between-group P values, no biopsy-proven nonalcoholic fatty liver.</td>
<td>15</td>
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<tr>
<td>Ueno (1997)</td>
<td>Controlled clinical trial</td>
<td>25</td>
<td>Inclusion: biopsy and clinically proven nonalcoholic fatty liver</td>
<td>Diet and exercise (3 months)</td>
<td>Improvement in AST/ALT in treated group (n = 15, P = 0.001). Histologic improvement (decreased steatosis) in treated group (n = 15; P = 0.05). Untreated group (n = 10) unchanged.</td>
<td>Only study to show histologic and biochemical improvement in clinically and biopsy-proven nonalcoholic fatty liver.</td>
<td>16</td>
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<tr>
<td>Rozental (1967)</td>
<td>Case series</td>
<td>5</td>
<td>Inclusion: liver biopsy-proven fatty liver; other causes not excluded</td>
<td>Diet</td>
<td>Histologic improvement (steatosis) in all 5 patients.</td>
<td></td>
<td>17</td>
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<tr>
<td>Eriksson (1986)</td>
<td>Case series</td>
<td>3</td>
<td>Inclusion: liver biopsy-and clinically proven nonalcoholic steatohepatitis</td>
<td>Diet</td>
<td>Histologic improvement (steatosis) in all 3 patients.</td>
<td></td>
<td>18</td>
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<tr>
<td>Ranlov (1990)</td>
<td>Case series</td>
<td>15</td>
<td>Inclusion: biopsy-proven fatty liver; unknown if excluded other factors for liver disease</td>
<td>Gastric bypass or gastroplasty followed by diet (12 months)</td>
<td>Histologic improvement (steatosis, necrosis, portal inflammation) in all 15 patients. Only reduction of steatosis showed statistical significance (P &lt; 0.01).</td>
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<td>19</td>
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<tr>
<td>First Author (Year)</td>
<td>Type of Study</td>
<td>No. of Patients</td>
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<td>Andersen (1991)</td>
<td>Case series</td>
<td>41</td>
<td>Exclusion: patients with alcohol use, diabetes, or use of medications that could cause liver disease</td>
<td>Diet followed by gastric bypass (mean follow-up of 261 days)</td>
<td>Improvement in AST after diet therapy in all 41 patients ($P = 0.02$). Histologic improvement in 36 patients: absent steatosis alone in 23 ($P &lt; 0.001$); decreased focal necrosis alone in 7 ($P = 0.001$); and both improvements in 6 (no $P$ value). Five patients had negative outcomes (increased portal fibrosis).</td>
<td>Negative outcomes associated with greater weight loss (&gt;1.6 kg/wk).</td>
<td>20</td>
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<tr>
<td>Loquercio (1997)</td>
<td>Case series</td>
<td>20</td>
<td>Inclusion: AST/ALT above normal for 2 years and liver biopsy with steatosis Exclusion: other risk factors for liver disease</td>
<td>Diet (2 months)</td>
<td>Improvement in ALT in 19 patients ($P &lt; 0.01$).</td>
<td>Unclear whether negative or unchanged outcome in 1 patient.</td>
<td>*</td>
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<tr>
<td>Luyckx (1998)</td>
<td>Case series</td>
<td>69</td>
<td>Inclusion: liver biopsies performed during and after gastric bypass surgery; unclear if other risk factors for liver disease were excluded</td>
<td>Gastric bypass surgery (mean follow-up of 27 months)</td>
<td>Improvement in ALT ($P &lt; 0.05$); number of patients not mentioned. Reduction in steatosis from 83% to 38% of patients ($P &lt; 0.01$). Increase in patients with normal tissue from 13% to 45% ($P &lt; 0.01$). Increase in lobular hepatitis after surgery from 14% to 26% ($P &lt; 0.05$).</td>
<td>Gastric bypass surgery that induced rapid weight loss may cause mild lobular hepatitis.</td>
<td>21</td>
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<tr>
<td>Knobler (1999)</td>
<td>Case series</td>
<td>48</td>
<td>Inclusion: abnormal serum aminotransferase levels for &gt;6 months Exclusion: all other liver-related causes</td>
<td>Dietary therapy (6 months). If failed target weight goals, then statin therapy as well (2-year follow-up)</td>
<td>Biochemical improvement; 25 patients had positive outcomes (resolution of aminotransferase levels).</td>
<td>Some patients were taking diabetic agents, insulin, and statins, which may confound results. No $P$ values provided.</td>
<td>22</td>
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<tr>
<td>Hsiao (2000)</td>
<td>Case series</td>
<td>55</td>
<td>Inclusion: ultrasound-diagnosed fatty liver</td>
<td>Diet and exercise (12 weeks)</td>
<td>Biochemical and ultrasound improvement. ALT reduced or normalized in 32 patients ($P &lt; 0.01$). Ultrasound fatty liver score decreased ($P &lt; 0.01$).</td>
<td>Weight reduction &lt;10% of baseline weight. Unknown number of patients who had a decrease in ultrasound fatty liver score.</td>
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<td>First Author (Year)</td>
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<tr>
<td>Johnson (2000)</td>
<td>Case series</td>
<td>15</td>
<td>Inclusion: biopsy-proven nonalcoholic steatohepatitis in 13 patients; abnormal aminotransferase levels and ultrasound in 2 patients</td>
<td>Diet/exercise (3 months)</td>
<td>Improvement in AST/ALT in all 15 patients. AST reduced ($P = 0.04$); ALT reduced ($P$)</td>
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<tr>
<td>Palmer (1990)</td>
<td>Retrospective review</td>
<td>39</td>
<td>Inclusion: abnormal liver test or hepatomegaly Exclusion: other causes of liver disease</td>
<td>Diet/exercise (16 months)</td>
<td>Group 1 &gt;10% body weight loss. Group 2 &lt;10% body weight loss. 13/17 (group 1) vs. 7/18 (group 2) normalized AST/ALT ($P &lt; 0.03$). Greater biochemical improvement showed with &gt;10% weight reduction of baseline weight.</td>
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<tr>
<td>DeMeo (1997)</td>
<td>Case report</td>
<td>1</td>
<td>Inclusion: liver biopsy-and clinically proven nonalcoholic steatohepatitis</td>
<td>Diet/fenfluramine/ phentamine</td>
<td>Improvement in AST/ALT.</td>
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* Results are preliminary/study not published; available as meeting abstract.

ALT = alanine aminotransferase; AST = aspartate aminotransferase.
In summary, we conclude that there is little evidence to support the widely held belief that weight reduction is an effective therapy for nonalcoholic fatty liver. This unexpected conclusion has important clinical implications given the increasing recognition that nonalcoholic fatty liver is an emerging public health problem. We do not suggest that the paucity of evidence should affect current recommendations for weight loss. Certainly, numerous high-quality studies have demonstrated the medical benefits of weight reduction in obese patients (27,28). Our findings do, however, point to the need for quality data, particularly in the form of randomized controlled trials, to assess the effectiveness of weight reduction in patients with nonalcoholic fatty liver. With the recent establishment of the National Institutes of Health Clinical Research Network for the Study of NASH (nonalcoholic steatohepatitis), perhaps the question of weight reduction in nonalcoholic fatty liver will finally be answered.

REFERENCES