Effect of a dietary-induced weight loss on liver enzymes in obese subjects1–3

Christoph Gasteyger, Thomas Meinert Larsen, Frank Vercruysse, and Arne Astrup

ABSTRACT

Background: Weight loss was shown to be associated with improvements in liver enzymes and improvements of nonalcoholic fatty liver disease. However, some evidence also shows that liver enzymes may transiently increase immediately after a dietary-induced weight loss.

Objective: The aim was to assess the outcome of liver enzymes after a low-calorie diet (LCD) as well as during a follow-up period and to identify predictors for potential changes in these liver enzymes.

Design: In this post hoc analysis of an existing database, liver enzymes were assessed before and immediately after a highly standardized soy-based meal replacement LCD providing 800 kcal/d, as well as 32 and 60 wk after the end of the LCD.

Results: Data emanating from 147 obese subjects (104 women and 43 men) without known hepatic disease were included in this study. The LCD led to a median weight loss of 12.1 kg (range: 7.7–27.6 kg). In men, a significant decrease in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was observed immediately after the LCD, whereas, in women, these enzymes increased significantly, although mildly; however, this increase was transient. Sex was the only identifiable predictor of these changes in liver enzymes.

Conclusions: This study showed that mild, transient increases in ALT and AST values can be observed immediately after an LCD in women, but not in men. These changes are probably of multifactorial origin and may be considered as benign as long as they remain transient. Am J Clin Nutr 2008;87:1141–7.

INTRODUCTION

Overweight and obesity are major risk factors for diseases such as type 2 diabetes, coronary heart disease, sleep apnea, cancer, and liver disease such as nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) (1). NAFLD and NASH are recognized as being predominantly associated with insulin resistance, which is commonly found in obese subjects, especially those with a high accumulation of visceral fat (2). Therefore, many studies were conducted to examine the effect of weight loss on NAFLD and NASH. Wang et al (3) recently conducted a review of these studies and showed an overall improvement in liver outcome measurements. Thus, weight loss led as well to biological (decrease in serum aminotransferase values), radiologic (decrease in fatty liver score as evaluated by ultrasound scanning), and histologic (decrease in steatosis, necrosis, and portal inflammation) improvements. However, in 2 of the studies examined by that review, a worsening of liver histology (higher occurrence of mild lobular hepatitis or increased portal fibrosis) was reported in patients with particularly rapid weight loss after bariatric surgery (4, 5). Other researchers report a transient increase in liver enzymes during the weeks after the initiation of low-calorie diets (LCDs) (6–8). Improvements in liver enzymes during weight loss were shown by some (4, 9, 10) but not all (5, 11) researchers to be positively correlated with improvements in the radiologic or histologic appearance of the liver.

Liver enzymes are by far the most accessible and cheapest paraclinical examination when assessing liver state, even if they do not constitute the most reliable investigation to diagnose diseases such as NAFLD and NASH (2). In fact, they are much cheaper than radiologic examinations such as ultrasound scanning, computed tomography scanning, or magnetic resonance scanning (MR scan) of the liver. They are also less invasive than liver biopsy, which is the only way to establish a diagnosis of a given liver disease with certainty (2). Consequently, liver enzymes are measured in many different clinical contexts.

Our study aimed to assess changes in liver enzymes after an 8-wk dietary-induced weight loss and to identify predictors of these changes. To the best of our knowledge, we are the first to address this question in a relatively large cohort of subjects with normal or near normal liver enzymes [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] at baseline.

SUBJECTS AND METHODS

This study is a post hoc analysis of an existing database emanating from a large, multicenter, randomized, previously published trial, which examined the efficacy of topiramate compared with placebo on long-term maintenance of weight loss induced by an LCD (12). After an initial run-in phase of 8 wk consisting of an LCD, subjects were allocated either to topiramate treatment or to placebo for 60 wk. In addition to this treatment, all subjects participated in a standardized commercially available behavioral

1 From the Department of Human Nutrition, Centre for Advanced Food Studies, Faculty of Life Sciences, University of Copenhagen, Copenhagen, Denmark (CG, TML, and AVA), and Johnson & Johnson, Pharmaceutical Research & Development, Division of Janssen Pharmaceutica NV, Beerse, Belgium (FV).
2 Supported by a grant from the Program for Exchange in Endocrinology Expertise, which is supported by NovoNordisk.
3 Address reprint requests to A Astrup, Department of Human Nutrition, Faculty of Life Sciences, University of Copenhagen, Rolighedsvej 30, DK-1958 Frederiksberg C, Denmark. E-mail: ast@life.ku.dk.
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modification program known as Pathways to Change (Johnson & Johnson Healthcare Systems Inc, Piscataway, NJ), which continued throughout the remainder of the study. Pathways to Change focuses on lifestyle and self-management as related to weight loss and obesity. The LCD was replaced by an individualized diet with an energy content =600 kcal/d less than the subject’s calculated total energy requirement (13).

Study population

For the purpose of this study, we examined the nonpharmacologic part of the data collected at baseline (ie, before starting the LCD) and at the end of the LCD (ie, 8 wk after baseline) from a selected subgroup of the trial. We decided to include only those subjects who participated at the 2 Danish study sites, because they all received exactly the same type of LCD (see below), and who completed the LCD. We also retained the data available from those subjects who were allocated to the placebo treatment (but not from those allocated to the topiramate treatment) and who completed their follow-up visits at 32 wk (which will be called “32 wk after the end of LCD”) and 44–60 wk (which will be called “60 wk after the end of LCD”) after the end of the LCD.

Subjects were eligible for enrollment if they were between 18 and 75 y of age and had a body mass index (BMI; in kg/m²) ≥ 30 to < 50. Subjects in the same BMI range were eligible if they had controlled hypertension or dyslipidemia with a stable medication regimen or both. Subjects with diabetes were ineligible unless they were newly diagnosed with diabetes by oral glucose tolerance test at the enrollment visit, and anti-diabetic medication was not deemed necessary by the investigator. ALT and AST could not be higher than 2 times the upper limit of the normal range (ULN). Subjects with any significant hepatic disease (including but not limited to hepatitis B and C, autoimmune disorders) or condition potentially affecting the liver (including but not limited to metabolic disorders such as hemochromatosis, alcohol abuse) were excluded. Subjects were also ineligible if they had known significant cardiovascular or renal disease, a history or family history of kidney stones, uncontrolled thyroid disease, or significant central nervous system-related or psychiatric disorders. To be eligible, a subject’s weight had to be stable for at least 3 mo and smoking habits stable for at least 2 mo before enrollment. Female subjects of childbearing potential were required to use an approved method of contraception. The study was carried out from August 2000 to June 2002. It was conducted in accordance with the Declaration of Helsinki and approved by Ethics Committees at all sites. All subjects provided written informed consent before enrollment.

Concomitant medications

Medications that were not allowed during the study period included antiseizure medications, antidepressants, tranquilizers, sedatives, and agents that might affect weight or food absorption, such as glucocorticoids, anorexigenic agents (prescription or over the counter), orlistat, nonfiber laxatives, and thyroid hormones (except as part of a stable treatment regimen).

Measurements

Each of the above-mentioned visits included, among others, anthropometric measurements. Weight was measured with the use of a standardized calibrated balance throughout the study; subjects were weighed in similar attire (light clothing) at each visit and at approximately the same time of the day. Height was measured with the use of a wall-mounted stadiometer, with subjects not wearing shoes. Waist and hip circumferences were measured with the subject standing, wearing underwear, and with the measuring tape kept horizontal. Waist circumference was measured at a level midway between the superior aspect of the iliac crests and the lower lateral margins of the ribs. Hip circumference was measured at the level of the pubic symphysis anteriorly and the greater femoral trochanters laterally. Blood samples included the following analyses, among others: ALT, AST, γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), triacylglycerols, total cholesterol, HDL cholesterol, LDL cholesterol, fasting plasma blood glucose, and glycated hemoglobin. All biochemical markers were measured by a central core laboratory (Covance Central Laboratory services, Geneva, Switzerland). The normal reference ranges used in this study for ALT, AST, GGT, and ALP are shown in Table 1.

The LCD was a commercially available soy-based meal replacement (Nutriflett/Scan Diet; Nutri Pharma, Oslo, Norway). The LCD provided 800 kcal/d (45% from proteins, 38% from carbohydrates, and 17% from fat) and supplied all nutrients according to recommended dietary allowances.

At baseline and at the end of the LCD, a T1-weighted transaxial MR scan to determine subcutaneous and visceral adipose tissues was performed in a subset of subjects (42 women and 18 men). A single slice with a 5-mm slice thickness was obtained with no angulation at the level of the L4–L5 intervertebral disc space based on a sagittal localizer. The field of view of the sagittal localizer included all exterior boundaries of the abdomen; the field of view of the axial slice was ≥500 mm to encompass all the exterior boundaries of the abdomen.

Statistical analyses

Unless otherwise specified, all data are given as median (interquartile range; minimum to maximum) because their distribution was nonnormal. Paired data were compared with the use of the Wilcoxon’s signed-rank test and nonpaired data with the use of the Mann-Whitney U test. Spearman correlation test was used for bivariate correlations.

A stepwise linear regression analysis was used to identify factors independently predictive for changes in liver enzymes between baseline and the end of the LCD. Independent covariates included sex, age, smoking status, and change in BMI, waist circumference, or hip circumference (the 3 latter covariates were not deemed necessary by the investigator. ALT and AST could not be higher than 2 times the upper limit of the normal range (ULN). Subjects with any significant hepatic disease (including but not limited to hepatitis B and C, autoimmune disorders) or condition potentially affecting the liver (including but not limited to metabolic disorders such as hemochromatosis, alcohol abuse) were excluded. Subjects were also ineligible if they had known significant cardiovascular or renal disease, a history or family history of kidney stones, uncontrolled thyroid disease, or significant central nervous system-related or psychiatric disorders. To be eligible, a subject’s weight had to be stable for at least 3 mo and smoking habits stable for at least 2 mo before enrollment. Female subjects of childbearing potential were required to use an approved method of contraception. The study was carried out from August 2000 to June 2002. It was conducted in accordance with the Declaration of Helsinki and approved by Ethics Committees at all sites. All subjects provided written informed consent before enrollment.

### Table 1

| Normal reference ranges for liver enzymes, as used in this study |
|-----------------|----------------|
| Women | Men |
| ALT (U/L) | 6–34 | 6–43 |
| AST (U/L) | 9–34 | 11–36 |
| GGT (U/L) | 4–49 | 5–50 |
| ALP (U/L) | 18–50 | 31–106 |
| >50 y | 5–50 | 35–123 |

1 ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase.
entered in separate analyses to avoid confounding effects, because they cannot be considered as independent. Statistical significance levels for variables for entry in and removal from the model were set at \( P < 0.05 \) and \( P < 0.10 \), respectively.

After having identified sex as the only significant predictive variable of change in liver enzymes, we categorized our data by sex. Then, simple bivariate analysis assessed for correlations between the changes in liver tests (between baseline and the end of the LCD) and anthropometric baseline characteristics; moreover, simple bivariate analysis assessed also for correlations between the changes in liver tests and changes of the above-mentioned baseline characteristics. The significance level was determined as \( P < 0.05 \). SPSS version 15.0 (SPSS Inc, Chicago, IL) was used for all analyses.

RESULTS

Baseline characteristics

One hundred forty-seven subjects (104 women and 43 men) were included in this analysis. Their baseline characteristics (before the LCD) are summarized in Table 2. Follow-up data at 32 and 60 wk after the end of the LCD were available for 67 subjects (47 women and 20 men) and 68 subjects (48 women and 20 men), respectively. Some baseline characteristics of the subjects with follow-up data differed from subjects without follow-up data. Thus, baseline BMI (follow-up data differed from subjects without follow-up data, respectively. Some baseline characteristics of the subjects with follow-up data differed from subjects without follow-up data. Thus, baseline BMI (follow-up data differed from subjects without follow-up data, respectively; \( P = 0.003 \), weight (108.3 ± 13.8 kg compared with 115.3 ± 16.1 kg, respectively; \( P = 0.02 \), and waist circumference (115 ± 11 cm compared with 119 ± 12 cm, respectively; \( P = 0.04 \) were significantly lower in subjects with follow-up data compared with subjects without follow-up data.

Overall, subjects lost 12.1 kg (4.0; 7.7–27.6 kg) during the LCD; men lost 14.0 kg (5.9; 8.7–27.6 kg) and women lost 11.5 kg (3.5; 7.7–21.9 kg). Waist circumference decreased by 12 cm (5; 1–25 cm) in men and by 8 cm (5; –5 to 20 cm) in women. A significant improvement in all characteristics mentioned in Table 2 was noted after the LCD in both sexes (\( P < 0.01 \) for all variables), except for HDL cholesterol, which diminished significantly in women (\( P < 0.001 \)) and did not change significantly in men (\( P = 0.07 \)).

Liver enzymes

No significant difference was observed in baseline liver enzymes (ALT, AST, GGT, ALP, and total bilirubin) between subjects who were followed up after the LCD and subjects who were not (data not shown). All but 2 female subjects had ALT and AST values below 2 times the ULN.

The outcome of liver enzymes from baseline to the last follow-up visit, according to sex, is shown in Table 3 (as mentioned below, we identified this factor as the only independent predictive factor of the outcome of liver enzymes after the LCD). The most important finding was that ALT and AST concentrations constantly decreased in men, whereas a significant but transient increase was observed in these enzymes at the end of the LCD in women. GGT decreased significantly in men after the LCD and did not change in women. No significant change was observed in ALP in either sex after the LCD. Finally, after the LCD statistically significant increases were also observed in total bilirubin in both sexes, which however cannot be considered as clinically significant. The median AST-to-ALT ratio never exceeded 1 in either sex.

The relative changes in ALT and AST according to sex when compared with baseline are shown in Figure 1. In men, the change in ALT was −20.5% (29.9; −62.2% to 60.5%) and the change in AST was −12.5% (29.0; −55.3% to 46.9%); in women, these changes were 52.2% (146.6; −35.7% to 505.0%) and 31.8% (67.5; −53.7% to 800.0%), respectively.

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**TABLE 2** Characteristics of the subjects before the low-caloric diet

<table>
<thead>
<tr>
<th></th>
<th>All subjects (n = 147)</th>
<th>Women (n = 104)</th>
<th>Men (n = 43)</th>
<th>P (women compared with men)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>44 (17; 20–69)</td>
<td>44 (17; 21–69)</td>
<td>41 (18; 20–62)</td>
<td>0.46</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>110 (20; 74–154)</td>
<td>106 (17; 74–146)</td>
<td>121 (19; 91–154)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>38 (5; 31–47)</td>
<td>38 (5; 31–47)</td>
<td>38 (5; 34–46)</td>
<td>0.30</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>118 (18; 93–149)</td>
<td>113 (13; 93–138)</td>
<td>125 (13; 104–149)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.92 (0.14; 0.76–1.22)</td>
<td>0.88 (0.07; 0.76–1.06)</td>
<td>1.06 (0.07; 0.92–1.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>130 (20; 105–165)</td>
<td>127 (20; 105–165)</td>
<td>133 (15; 113–160)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>80 (10; 59–103)</td>
<td>79 (10; 59–93)</td>
<td>83 (9; 67–103)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>5.5 (0.9; 4.3–11.6)</td>
<td>5.5 (0.7; 4.3–11.6)</td>
<td>5.6 (1.1; 4.6–9.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Glycated hemoglobin (%)</td>
<td>5.6 (0.6; 4.6–8.7)</td>
<td>5.6 (0.6; 4.7–8.7)</td>
<td>5.6 (1.0; 4.6–7.1)</td>
<td>0.59</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>15 (13; 6–96)</td>
<td>19 (19; 6–78)</td>
<td>14 (12; 6–96)</td>
<td>0.30</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.6 (1.5; 4.0–8.5)</td>
<td>5.6 (1.5; 4.0–8.5)</td>
<td>5.5 (1.5; 4.1–7.9)</td>
<td>0.69</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.3 (0.4; 0.6–2.8)</td>
<td>1.4 (0.5; 0.7–2.8)</td>
<td>1.1 (0.4; 0.6–1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.6 (1.4; 1.4–6.5)</td>
<td>3.5 (1.4; 1.4–6.5)</td>
<td>3.6 (1.2; 2.4–4.9)</td>
<td>0.38</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.5 (0.7; 0.5–5.5)</td>
<td>1.4 (0.7; 0.5–4.9)</td>
<td>1.5 (0.9; 0.7–5.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>24.7</td>
<td>22.1</td>
<td>30.2</td>
<td>0.29</td>
</tr>
</tbody>
</table>

1 BP, blood pressure. Mann-Whitney U test was used for all comparisons, except for the proportions of smokers, for which a 2-tailed Fisher’s exact test was used.

2 Median; interquartile range and minimum to maximum values in parentheses (all such values).
<table>
<thead>
<tr>
<th></th>
<th>Before the LCD</th>
<th>End of LCD</th>
<th>32 wk after the end of LCD</th>
<th>60 wk after the end of LCD</th>
<th>P (comparison between baseline and end of LCD)</th>
<th>P (comparison between baseline and 60 wk after the end of LCD)</th>
</tr>
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<tbody>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
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<tr>
<td><strong>Women</strong></td>
<td>37.8 (5.4; 31.4–47.0)</td>
<td>33.6 (4.7; 27.9–42.3)</td>
<td>31.6 (4.3; 25.3–43.9)</td>
<td>31.5 (4.5; 24.1–43.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>38.0 (4.9; 33.5–46.0)</td>
<td>31.9 (5.2; 29.6–40.8)</td>
<td>31.0 (5.5; 25.7–40.0)</td>
<td>32.4 (5.2; 26.3–40.4)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>ALT (U/L)</strong></td>
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<tr>
<td><strong>Women</strong></td>
<td>26 (13; 4–81)</td>
<td>43 (51; 13–392)</td>
<td>21 (14; 7–61)</td>
<td>21 (9; 10–67)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>38 (19; 19–79)</td>
<td>30 (11; 15–69)</td>
<td>22 (14; 13–89)</td>
<td>22 (9; 13–60)</td>
<td>0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>AST (U/L)</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Women</strong></td>
<td>22 (6; 10–46)</td>
<td>30 (18; 12–189)</td>
<td>19 (8; 8–35)</td>
<td>22 (6; 10–44)</td>
<td>&lt;0.001</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>27 (9; 15–61)</td>
<td>24 (8; 14–47)</td>
<td>20 (8; 14–102)</td>
<td>21 (7; 13–60)</td>
<td>0.001</td>
<td>0.002</td>
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<tr>
<td><strong>GGT (U/L)</strong></td>
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<tr>
<td><strong>Women</strong></td>
<td>30 (22; 10–242)</td>
<td>31 (20; 9–122)</td>
<td>24 (21; 10–143)</td>
<td>24 (16; 11–234)</td>
<td>0.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>37 (29; 18–124)</td>
<td>25 (16; 10–113)</td>
<td>30 (15; 12–81)</td>
<td>32 (30; 12–120)</td>
<td>&lt;0.001</td>
<td>0.001</td>
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<tr>
<td><strong>ALP (U/L)</strong></td>
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<tr>
<td><strong>Women</strong></td>
<td>74 (25; 40–173)</td>
<td>75 (25; 30–204)</td>
<td>68 (27; 42–119)</td>
<td>67 (23; 38–125)</td>
<td>0.58</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>81 (28; 21–114)</td>
<td>76 (38; 20–128)</td>
<td>81 (42; 25–135)</td>
<td>80 (37; 25–137)</td>
<td>0.76</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>Total bilirubin (µmol/L)</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Women</strong></td>
<td>7 (3; 4–31)</td>
<td>8 (3; 4–32)</td>
<td>9 (4; 4–32)</td>
<td>8 (4; 4–32)</td>
<td>&lt;0.001</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>9 (4; 4–27)</td>
<td>10 (5; 5–43)</td>
<td>11 (10; 6–41)</td>
<td>10 (6; 4–42)</td>
<td>0.003</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>AST to ALT ratio</strong></td>
<td></td>
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<tr>
<td><strong>Women</strong></td>
<td>0.8 (0.2; 0.4–5.3)</td>
<td>0.7 (0.3; 0.3–1.3)</td>
<td>0.9 (0.3; 0.4–3.4)</td>
<td>1.0 (0.5; 0.5–2.4)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>0.7 (0.2; 0.4–1.2)</td>
<td>0.8 (0.3; 0.4–1.3)</td>
<td>0.9 (0.3; 0.4–1.8)</td>
<td>1.0 (0.5; 0.4–1.8)</td>
<td>0.19</td>
<td>0.003</td>
</tr>
</tbody>
</table>

1 LCD, low-calorie diet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase.
2 n = 104 women and n = 43 men.
3 n = 47 women and n = 20 men.
4 n = 48 women and n = 20 men.
5 Calculated by a Wilcoxon signed-rank test.
6 Calculated by a Wilcoxon signed-rank test, including only those subjects for whom data were available at baseline and at 60 wk after the end of the LCD.
7 Median; interquartile range and minimum to maximum values in parentheses (all such values).
LIVER ENZYMES DURING DIET-INDUCED WEIGHT LOSS

there is some, although little, empiric evidence supporting that weight loss through lifestyle modification, medication, or bariatric surgery has a role in the treatment of NAFLD (3, 14, 16, 17) (usually accompanied by a decrease in liver enzymes), our results showing a transient increase in liver enzymes in women may seem paradoxical. Methodologic differences differentiating our study from previous reports could explain this contradiction. First, almost all our subjects had normal or near-normal ALT and AST values (<2 times the ULN) at baseline. This does not exclude that some of them had NAFLD or even NASH, because liver enzymes were shown to be both insensitive and nonspecific for chronic liver disease (18). However, previous studies that examined the effect of lifestyle changes on liver enzymes and steatosis included subjects who already had abnormal liver enzymes and liver steatosis (as assessed by imaging or histology) at baseline (19–21). Those studies all noticed a decrease in ALT and AST concentrations after a dietary-induced weight loss. This could be explained by the fact that the improvement in steatosis (and the related decrease in liver enzymes) may have counterbalanced and masked a slight increase in liver enzymes of another unknown origin that would perhaps have occurred if these subjects had had normal liver enzymes at baseline.

The second difference was in scheduling the measurement of liver enzymes. In contrast to other researchers who performed the second measurement of liver enzymes after a weight-maintenance phase (10), we assessed liver enzymes immediately after the end of LCD, while subjects were still in a weight-loss phase.

Transient increase in ALT and AST during dietary weight loss: hypothetical causes

The cause of this transient rise in ALT and AST remains unclear and may be multifactorial. ALT is the most specific marker of hepatocellular injury and is confined to cytoplasm, whereas AST can be identified to some extent in the heart, skeletal muscles, kidneys, brain, pancreas, and blood cells and is found in both mitochondria and cytoplasm (22). Therefore, our results showing more important changes in ALT than in AST concentrations suggest a transient injury to the liver.

The amount of energy provided per day by a weight-loss diet may influence the outcome of liver enzymes. We found 3 articles that described transient increases in ALT and AST similar to

FIGURE 1. Relative changes in alanine aminotransferase (ALT; □) and aspartate aminotransferase (AST; □) according to sex, when compared with the values of these enzymes at baseline. The lower and upper box boundaries mark the 25th and 75th percentiles, respectively. The heavy black line inside the boxes marks the 50th percentile. * and # mark cases with values between 1.5 and 3 box lengths and >3 box lengths from the upper or lower edge of the boxes, respectively. Note that the scale of the y axis is logarithmic. At the end of the low-calorie diet (LCD), n = 43 men and 104 women; at 32 and 60 wk after the LCD, n = 20 men and 47–48 women.

The percentage of subjects with abnormal (>2 times the ULN) ALT values is shown in Figure 2. ALT values were abnormal in 21% of women (0% of men) at the end of the LCD. At the same time, 17% of women had an ALT value ≥ 3 times higher than the ULN reference range (not shown in the figure). Finally, AST concentrations were abnormal in only 9% of women and 0% of men at the end of the LCD.

A multiple stepwise regression was performed to identify independent predictive baseline factors for the changes in liver enzymes after the LCD. Sex was predictive for the changes in enzymes after the LCD. Men at the end of the LCD.

First, almost all our subjects had normal or near-normal ALT and AST concentrations at baseline. This does not exclude that some of them had NAFLD or even NASH, because liver enzymes were shown to be both insensitive and nonspecific for chronic liver disease (18). However, previous studies that examined the effect of lifestyle changes on liver enzymes and steatosis included subjects who already had abnormal liver enzymes and liver steatosis (as assessed by imaging or histology) at baseline (19–21). Those studies all noticed a decrease in ALT and AST concentrations after a dietary-induced weight loss. This could be explained by the fact that the improvement in steatosis (and the related decrease in liver enzymes) may have counterbalanced and masked a slight increase in liver enzymes of another unknown origin that would perhaps have occurred if these subjects had had normal liver enzymes at baseline.

The second difference was in scheduling the measurement of liver enzymes. In contrast to other researchers who performed the second measurement of liver enzymes after a weight-maintenance phase (10), we assessed liver enzymes immediately after the end of LCD, while subjects were still in a weight-loss phase.

Transient increase in ALT and AST during dietary weight loss: hypothetical causes

The cause of this transient rise in ALT and AST remains unclear and may be multifactorial. ALT is the most specific marker of hepatocellular injury and is confined to cytoplasm, whereas AST can be identified to some extent in the heart, skeletal muscles, kidneys, brain, pancreas, and blood cells and is found in both mitochondria and cytoplasm (22). Therefore, our results showing more important changes in ALT than in AST concentrations suggest a transient injury to the liver.

The amount of energy provided per day by a weight-loss diet may influence the outcome of liver enzymes. We found 3 articles that described transient increases in ALT and AST similar to

FIGURE 2. Proportions of subjects with abnormal alanine aminotransferase (ALT) values from baseline to the last follow-up visit. Abnormal values were defined as being ≥2 times higher than the upper limit of normal. Because no subject had abnormal ALT values 60 wk after the end of the low-calorie diet (LCD), no bar appears in the graph at that time. For men, n = 43, 20, and 20 at baseline and end of LCD, at 32 wk after end of the LCD, and at 60 wk after end of the LCD, respectively. Similar values for women were 104, 47, and 48, respectively.
those observed in our study during or immediately after a hypercaloric diet (6–8): all 3 reported using an LCD or even a very-LCD (330–840 kcal/d). To the contrary, studies that used diets providing >1000 kcal/d did not describe such kind of changes (23). Moreover, the macronutrient composition of a diet also seems to influence the outcome of liver enzymes, as was recently suggested by Ryan et al (24). Those researchers reported a greater decrease in ALT values after a hypocaloric diet moderately restricted in carbohydrates (40% of total energy) than after a diet providing 60% carbohydrates, suggesting that carbohydrate restriction enhances hepatic lipid mobilization. However, this latter finding does not explain the transient increase in liver enzymes observed in our female subjects.

Mild and transient changes in liver histology, which themselves could be induced by the modifications in liver physiology such as the increased ketone production or active mobilization of lipids from hepatocytes during dieting, could be the first and main explanation. In fact, we found 2 studies reporting an increased prevalence of mild steatohepatitis after weight loss. Luyckx et al (4) examined changes in liver histology before and after vertical ring gastroplasty or adjustable gastric banding in 69 patients. The mean weight loss averaged 32 ± 19 kg. The proportion of patients with normal liver histology increased after surgery, and the proportion of patients with steatosis decreased. However, the proportion of patients with steatohepatitis increased after surgery (14% before and 26% after surgery; P < 0.05). Andersen et al (5) studied the effects of weight loss induced by a very-LCD in 41 morbidly obese subjects (35 women and 6 men). They performed a liver biopsy both before and at the end of the diet; the median time interval between these 2 biopsies was 261 d (range: 127–681 d). The median weight loss was 34.0 kg (range: 17.4–88.6 kg). The researchers observed a significant increase in portal inflammation (6 patients with portal inflammation before weight loss and 14 patients after weight loss; P = 0.039). However, changes in biochemical variables (AST, ALP, LDH, and bilirubin) were not associated with histologic changes. The researchers suggested that a rapid mobilization of intra- and extrahepatic fat stores may represent a hepatotoxic factor that could explain the observed changes. A second explanation could be the formation of asymptomatic gallstones. Weight loss, especially in women, was shown to be a risk factor for gallstones (25). However, it is unlikely that this occurred in our subjects, because the observed elevation of hepatic enzymes was transient, and no increase in GGT and ALP was noted. Third, it was suggested that strenuous exercise can increase AST and ALT concentrations (26). We did not assess for physical activity during the LCD, but a spontaneous increase in physical activity was reported in women involved in a dietary-induced weight-loss program without recommendations to influence physical activity patterns (27). Fourth, the sex difference could also be explained by the fact that men lost more weight and especially more abdominal fat (as illustrated by the more important decrease in waist circumference) than did women; thus, a potential small increase in liver enzymes in men may have been masked by the overall improvement in liver steatosis, which was perhaps more important than in women.

Finally, it may seem surprising that we found no correlation between age and changes in liver enzymes during the LCD. In fact, many studies have shown correlations between age and liver enzymes (28–30), but their results are contradictory, which may explain our findings. Moreover, we found no study that specifically examined correlations between age and changes in liver enzymes during weight loss.

Strengths and limitations

Our study has several strengths and limitations. The first strength is that our cohort of subjects was larger than those of other studies mentioned earlier (6–8). Second, all subjects received exactly the same type of LCD. This is important, because the composition of a diet was shown to influence the outcomes of liver enzymes, as mentioned above. Thus, by standardizing the diet, we eliminated this potential confounding factor. The first limitation is that we assessed liver state only by measuring liver enzymes and did not perform computed tomography scans, MR scans, or liver biopsies. Despite this limitation, it cannot be denied that the increase in liver tests observed in women immediately after the LCD is significant. Second, alcohol consumption was not recorded during the LCD. Therefore, an increase in alcohol consumption during the LCD, which could explain the transient raise in liver enzymes in some subjects, cannot be totally excluded, although this seems to be unlikely because a significant caloric intake from alcoholic beverages would have impaired their weight loss. Moreover, the AST-to-ALT ratio remained <1 even after the LCD in women, suggesting that the raise in liver enzymes was not due to excessive alcohol consumption (31). Third, we did not assess physical activity during the LCD. Yet, changes in physical activity level could have influenced liver enzymes during the LCD. Finally, only subjects who completed the LCD were included in the analysis, which could have introduced a potential selection bias.

Conclusion

During a dietary-induced weight loss, a modest increase in ALT and AST can be observed. Sex seems to be a predictor for this transient increase, which was observed only in women and was not correlated with the amount of weight loss. The cause remains unclear, but it is probably benign. Further research to assess the exact cause of this increase is needed. However, in our opinion, patients with mild increases in liver enzymes during weight loss do not need further investigations as long as these changes are transient.

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