



Serum aminotransferase changes with significant weight loss: sex and age effects

Ayako Suzuki^{a,*}, Martin Binks^{b,c}, Ronald Sha^{b,d}, Amy Wachholtz^{b,c,e},
Howard Eisenon^{b,d}, Anna Mae Diehl^a

^aDivision of Gastroenterology, Department of Medicine, Duke University, Durham, NC 27710, USA

^bDuke Diet and Fitness Center, Duke University Health System, Durham, NC 27705, USA

^cDivision of Medical Psychology, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 27710, USA

^dDepartment of Community and Family Medicine, Duke University Medical Center, Durham NC 27710, USA

^eDepartment of Psychiatry, University of Massachusetts Medical School, Worcester, MA 01655, USA

Received 18 December 2008; accepted 24 June 2009

Abstract

In obese subjects, the liver may be differentially affected by significant weight loss depending on as yet unknown factors. We explored clinical factors associated with serum alanine aminotransferase (ALT) changes during significant weight loss in a residential weight loss program. Clinical data from 362 adults who received a comprehensive weight loss intervention (ie, diets, physical fitness, and behavioral modification) in the program were analyzed. Serum ALT was used as a surrogate marker of liver injury. The ALT changes during the program were calculated to create study outcome categories (improvement, no change, or deterioration of ALT during significant weight loss). Variables of demography, lifestyle, and comorbidities at baseline, and total/rate of weight change during the program were explored for associations with the ALT change categories using multiple logistic regression models. Variation by sex was apparent among predictors of ALT deterioration; men with rapid weight loss and women with higher initial body mass index were more likely to experience ALT deterioration, whereas men with prior alcohol consumption were less likely to experience ALT deterioration even after adjusting for baseline ALT ($P_s < .03$). Variation by age was apparent among predictors of ALT improvement; younger patients with current smoking and older patients with rapid weight loss, diabetes or impaired fasting glucose, or sleep apnea or who followed a reduced-carbohydrate diet were less likely to experience ALT improvement ($P_s < .05$). A number of clinical factors influence ALT changes during weight loss in sex- and age-specific manners. The patterns that we detected may have pathophysiologic significance beyond the practical implications of our findings in clinical practice related to underlying changes in fat metabolism.

© 2009 Elsevier Inc. All rights reserved.

1. Introduction

In recent decades, obesity has become a significant public health problem in the United States [1–3]. The National Health and Nutrition Examination Survey showed that 66% of US adults were overweight, of whom half were obese [2]. This epidemic has led to a significant increase in

various disease conditions, such as insulin resistance, diabetes mellitus, cardiovascular disease, and nonalcoholic fatty liver disease (NAFLD), which is increasingly recognized as the most common chronic liver disease in the United States [4].

Weight reduction is known to benefit multiple organs including the liver [5]. Previous studies using patient populations in bariatric surgery suggested that weight reduction is effective in treating NAFLD among morbidly obese patients even when they have considerable fibrosis [6]. However, a subset of patients (12%–40%) may experience worsening of necroinflammation and/or fibrosis in the liver during long-term follow-up [7–10]. Rapid weight loss was suggested as a predictor for histologic deterioration in a

Institutional approval: This study was approved as exempt by the Internal Review Board of Duke University.

* Corresponding author. Division of Gastroenterology, Duke University Medical Center, Box 3913, Durham, NC 27710, USA. Tel.: +1 919 668 8891; fax: +1 919 681 8147.

E-mail address: suzuk004@mc.duke.edu (A. Suzuki).

small study using patients who received very low calorie diets [7]. However, there may be other potential predictors for liver outcomes after significant weight reduction.

In this study, we explored potential clinical factors influencing liver outcomes (deterioration and improvement in hepatic inflammation) during significant weight reduction by using serum alanine aminotransferase (ALT) as a surrogate marker of liver injury. Using a large clinical data set of severely obese subjects who were evaluated before and after a 4-week residential weight loss program, we conducted a comprehensive statistical analysis that revealed sex- and age-specific factors influencing ALT response to weight loss. Furthermore, we discuss possible underlying mechanisms based on the identified clinical factors and propose a working hypothesis (kinetic mechanisms) that may explain the different responses to significant weight loss.

2. Methods

2.1. Design and population

This study is a retrospective analysis of a large cohort (N = 362) of patients who participated in a multidisciplinary residential weight loss program; it was approved as exempt by the Institutional Review Board of Duke University.

In the residential weight loss program, a comprehensive intervention including diets, physical fitness, and behavioral modification was provided by the trained multidisciplinary teams in the Duke Diet and Fitness Center. Upon entry into the program, patients were prescribed a reduced-calorie diet (1000-1500 kcal/d) from among 3 levels of carbohydrate (as a percentage of total caloric intake)—high (55%), moderate (35%), and low (15%-25%)—by a registered dietitian.

The equation of Mifflin et al [11] with adjustment for physical activity was used to provide an estimate of basic caloric requirements for each patient. A calorie goal designed to produce weight loss at an average weekly rate of 1 to 3 lb was determined based on this estimate. The typical female client consumed 1100 to 1300 kcal daily; the typical male, 1200 to 1600 kcal daily. Patients were provided a nutritionally balanced diet based on “volumetric” principles that emphasize foods that promote satiety (eg, less processed, whole grain, high fiber), but are lower in energy density [12,13]. All diets were low in saturated fat and provided 1500 mg of sodium.

Patients were asked not to consume alcohol during the program. A personalized fitness plan was developed with each patient by an exercise physiologist. Patients were encouraged to participate in daily exercise. Routine fasting blood tests were performed pre- and postprogram. Medical evaluation, intervention, and monitoring were provided for obesity-related conditions (eg, hypertension, diabetes, and hyperlipidemia). Behavioral support was also provided.

Of 945 consecutive patients, 362 who met the following baseline criteria were used: (1) first-time attendee, (2) aged

18 to 79 years, (3) body mass index (BMI) of at least 30 kg/m², (4) no diagnosis of other liver diseases, (5) no history of alcohol abuse, (6) no current constitutional steroid or methotrexate medication, (7) current (preprogram) alcohol consumption not exceeding 7 servings (84 g) per week for women and not exceeding 14 servings (168 g) per week for men, (8) had baseline and posttreatment serum ALT, and (9) length of stay 10 to 30 days. Two subjects who presented with severe edema at baseline were excluded.

2.2. Variables

Information on age, sex, body weight (in kilograms), BMI (in kilograms per square meter), abdominal circumference (in centimeters), presence of hypertension, hypertriglyceridemia (plasma total triglycerides >150 mg/dL), low high-density lipoprotein (HDL) cholesterol (plasma HDL cholesterol <40 mg/dL for men and <50 mg/dL for women), diabetes mellitus, impaired fasting glucose (fasting plasma glucose ≥100 mg/dL), sleep apnea, alcohol consumption, smoking, aerobic exercise, carbohydrate level of diet followed during the program, and serum ALT (in international units per liter) and aspartate aminotransferase (AST) (in international units per liter) was collected through medical chart review. Serum AST/ALT ratios were calculated at baseline.

The presence/absence of comorbidities was based on baseline physician evaluation and laboratory data. Diabetes and impaired fasting plasma glucose were combined as 1 variable. Alcohol consumption, smoking, and aerobic exercise information was obtained via self-report questionnaire. Current average alcohol consumption was reported as total servings per week of beer (12 oz), wine (4 oz), and liquor (1 oz). Smoking status was dichotomized as (1) current and (2) other (including past smokers). Patient’s self-reported “regular participation” in aerobic exercise before admission was treated as a dichotomous variable. Dietary prescription was obtained from the nutrition assessment and classified as high-carbohydrate and reduced-carbohydrate (ie, moderate and low) diet (>55% and <35%, respectively, expressed as a percentage of total calorie consumption). Body weight, length of stay (in days), and serum ALT were collected at program completion. Total body weight change (in kilograms), rate of weight change (in kilograms per week), and serum ALT change (in international units per liter) were calculated.

Serum ALT was chosen as our primary surrogate marker of liver injury, although we recognize the limitations of this assay in determining histologic severity. However, it is a commonly used assay used to screen for evidence of liver injury and a common end point in assessing the efficacy of conservative measures used to treat NAFLD such as diet and exercise. Moreover, cross-sectional studies [14,15] and, more importantly, therapeutic trials that included follow-up biopsy using agents such as

thiazolidinediones [16,17] and bariatric surgery [18] have revealed an approximate relationship between ALT and histologic evidence of steatosis-related liver injury [19]. Thus, we felt justified in examining this readily available assay in the analysis.

2.3. Statistical analyses

Data are reported as mean \pm standard deviation or proportion of patients with a condition. The outcome variable in this study was serum ALT change and was classified into 3 categories: improvement (ALT decrease ≥ 10 IU/L), deterioration (ALT increase ≥ 10 IU/L), and no change (ALT increase or decrease < 10 IU/L change). The cutoff of 10 IU/L was conservatively chosen to account for possible error variance inherent in 2 consecutive biochemical measurements of ALT, previously reported as less than 3% [20]. Predictor variables were age, sex, BMI, abdominal circumference, total weight loss, rate of weight loss, baseline serum ALT and AST, AST/ALT ratio, presence of hypertension, hypertriglyceridemia, low HDL cholesterol, diabetes mellitus/impaired fasting plasma glucose, sleep apnea, reduced-carbohydrate diet, preprogram alcohol consumption, current smoking, and preprogram regular aerobic exercise.

To assess the association between serum ALT changes and each predictor variable, we first univariately examined the association of each predictor variable with serum ALT changes using analysis of variance with Tukey tests or χ^2 tests. Variables that were missing for more than 20% of patients were excluded from further analyses.

Each predictor variable was then assessed in an individual logistic regression analysis using ALT deterioration/improvement (vs others) as an outcome variable. Interactions with age group (separated by median age of the study population) and sex were also assessed for each predictor variable. Multiple logistic regression models were developed for serum ALT improvement/deterioration by backward elimination with the removal criterion at the .2 level of statistical significance. In cases where there was any significant interaction with sex and/or age groups, separate models were developed in subgroups. To assess prediction levels of the final models, an area under the receiver operating characteristic (ROC) curve (AUC) was used. For analyses, we used JMP version 6.0.0 (SAS, Cary, NC) and considered differences statistically significant when P values were less than .05.

Through the above analyses, we identified beneficial factors (variables either decreasing likelihood of ALT deterioration or increasing likelihood of ALT improvement) and detrimental factors (variables either increasing likelihood of ALT deterioration or decreasing likelihood of ALT improvement) (Fig. 1), both of which were discussed for underlying mechanisms and a working hypothesis explaining the differential response to significant weight loss.

3. Results

3.1. Clinical characteristics of patient population

We examined 362 adult participants in a 4-week, residential weight loss program (median length of stay, 27 days). Mean age of the study population was 53.6 ± 13.7 years; 57% were female. Mean BMI was 43.4 ± 9.4 kg/m²; 22.7% of patients followed a reduced-carbohydrate diet, whereas 77.3% chose a reduced-fat/higher-carbohydrate diet. Average total weight loss was 5.6 ± 3.2 kg (1.7 ± 0.9 kg/wk) for both diets combined, with no significant differences in weight loss among diets. Prevalence of obesity-associated comorbidities was as follows: diabetes/impaired fasting glucose, 63.5% (of which 7.4% were receiving insulin therapy and 36.1% were receiving oral antidiabetic drugs); hypertension, 52.4%; hypertriglyceridemia, 48.0%; low HDL cholesterol, 36.7%; and sleep apnea, 35.5%. At baseline, prevalence of hypertransaminasemia (serum ALT > 19 IU/L in women and > 30 IU/L in men) [21] was 61.9%; average serum ALT, AST, and AST/ALT ratio were 33.3 ± 20.9 IU/L, 27.8 ± 12.4 IU/L, and 0.93 ± 0.28 ; 10.1% of participants were current smokers, and 51.4% were alcohol consumers (45.1% reporting < 7 servings per week, 6.3% reporting at least 7 and less than 14 servings per week). About one quarter (28.6%) reported regular aerobic exercise at baseline. After the weight loss program, 17% of the population showed ALT deterioration, whereas 11% showed ALT improvement.

3.2. Clinical characteristics of patients by categories of serum ALT changes during weight loss

First, we analyzed the univariate associations between the categories of ALT change (deterioration, improvement, and no change) and the study variables. The results of the analyses are summarized in Table 1. As shown in the table, patients with “ALT deterioration” were younger, had higher initial BMI, had greater initial abdominal circumference, and lost more weight or lost it at a faster rate during the program compared with patients with “no ALT changes” during weight loss. Patients with “ALT improvement” were also younger than those with no ALT changes and had higher serum ALT and AST and lower AST/ALT ratio at baseline. Comorbidities, current smoking, preprogram alcohol use, preprogram aerobic exercise, and diet during the program were not associated with the categories of ALT change by the univariate analyses.

3.3. Likelihood of having ALT deterioration or improvement during weight loss and interactions with age and sex

We next univariately evaluated the likelihood of having ALT deterioration or improvement for patients with specific characteristics (study variables). We also evaluated whether the associations between ALT changes (ie, deterioration or improvement) and the study variables significantly differed

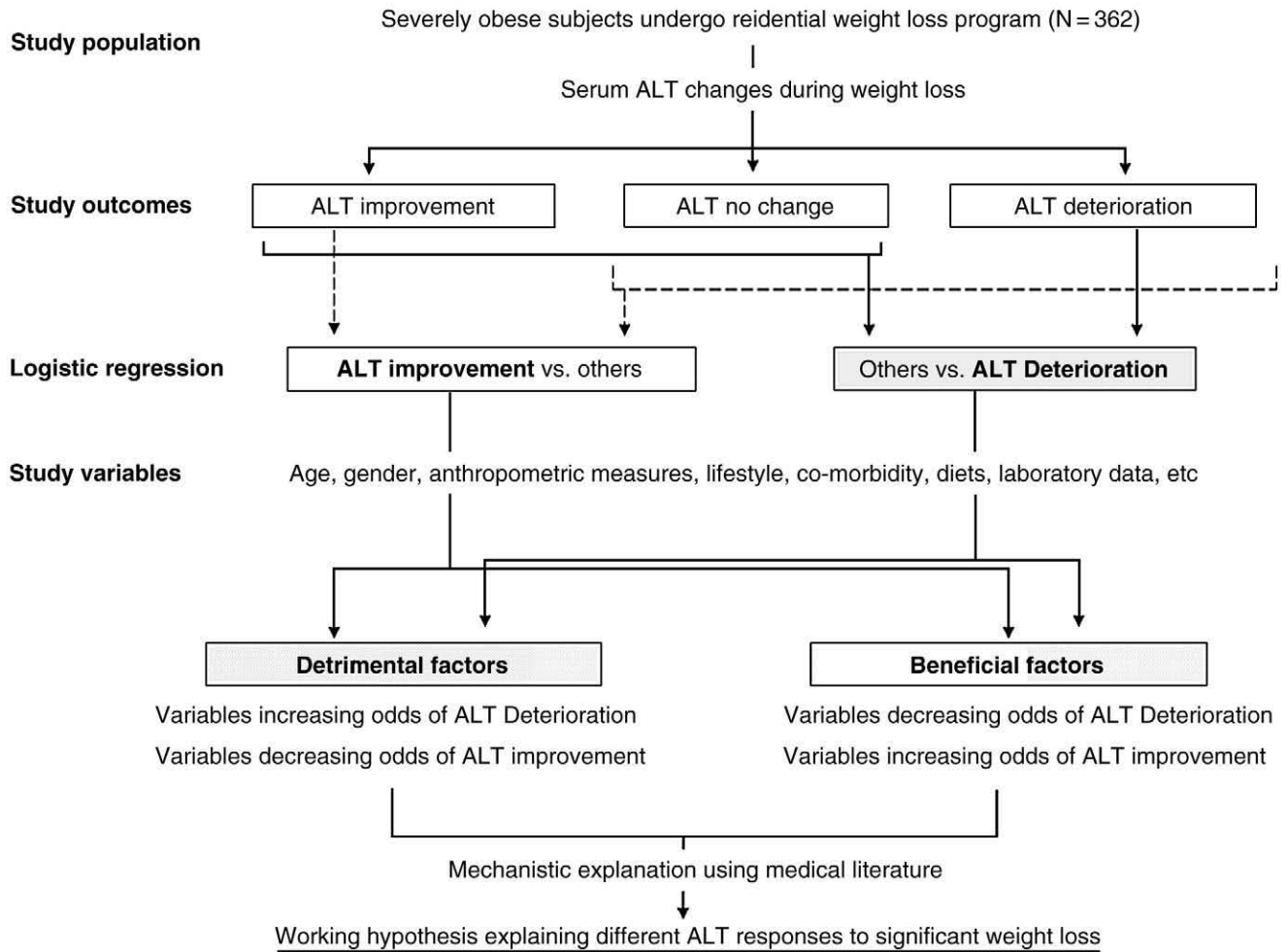


Fig. 1. Statistical exercise and hypothesis generation. In this study, the 362 participants were classified according to their serum ALT changes during the weight loss program. The study outcomes, that is, ALT deterioration (vs others) and ALT improvement (vs others), were then analyzed using logistic regression for associations with study variables. The study variables were then classified into beneficial factors (variables either decreasing likelihood of ALT deterioration or increasing likelihood of ALT improvement) and detrimental factors (variables either increasing likelihood of ALT deterioration or decreasing likelihood of ALT improvement). The factors in both groups were then discussed using medical literature for possible pathobiologic mechanisms explaining different responses to significant weight reduction.

between sexes or between the age groups (ie, interaction). The results are summarized in Table 2.

As shown in the table, patients in the older group were 60% less likely to experience ALT deterioration (compared with patients in the younger group), whereas patients with higher BMI (40% more likely per 5-kg/m² increase in BMI) or abdominal circumference (40% more likely per 5-cm increase) at baseline were more likely to experience ALT deterioration during significant weight loss. Furthermore, patients who lost more weight (10% more likely per 1-kg increase in total weight loss) or lost weight at a faster rate (80% more likely per 1-kg/wk faster weight loss) were also more likely to experience ALT deterioration. Total/rate of weight loss showed significant interactions with sex; total/rate of weight loss was associated with ALT deterioration only among men, but not women (data not shown). The effects of rate of weight loss on the

probability of serum ALT deterioration in men and women are depicted in Fig. 2.

Patients in the older group were 50% less likely to experience ALT improvement. Patients who had higher aminotransferase at baseline (ALT or AST) were more likely to experience ALT improvement. Patients with higher AST/ALT ratio (where >1 is clinically considered an indicator of a more progressive form [or the presence of fibrosis] of NAFLD [22,23]) were less likely to experience ALT improvement. Total/rate of weight loss, baseline AST, and AST/ALT ratio showed significant interactions with age groups.

3.4. Clinical predictors of serum ALT deterioration during weight loss after adjusting for other factors

Because there was significant interaction between total/rate of weight loss and sex, multiple logistic regression

Table 1

Univariate associations between serum ALT changes during significant weight loss and the study variables

	Total n	Serum ALT change during significant weight loss			P value
		Deterioration	Improvement	No change	
		n = 64	n = 40	n = 258	
Age, y	362	46.8 ± 1.6*	49.8 ± 2.1*	55.9 ± 0.8	<.0001
Sex, % male	362	46.9%	50.0%	41.1%	.455
BMI, kg/m ²	362	48.3 ± 1.1 [†]	42.5 ± 1.5	42.3 ± 0.6	<.0001
Preintervention abdominal circumference, cm	354	53.2 ± 0.9*	50.4 ± 1.2	49.6 ± 0.5	.0028 ^b
Total weight loss, kg	360	−6.8 ± 0.4 [†]	−5.8 ± 0.5	−5.3 ± 0.2	.0052
Rate of weight loss, kg/wk	360	−2.1 ± 0.1 [†]	−1.7 ± 0.1	−1.6 ± 0.1	.0007
Baseline ALT elevation ^a	362	62.5%	95.0%	56.6%	<.0001
Baseline ALT, IU/L	362	38.5 ± 2.3	59.7 ± 2.9	27.9 ± 1.1	.0001 [‡]
Baseline AST, IU/L	361	30.2 ± 1.4	42.3 ± 1.8	25.0 ± 0.7	.0001 [‡]
Baseline AST/ALT	361	0.878 ± 0.034	0.743 ± 0.043	0.969 ± 0.017	.0001 [‡]
Diabetes/impaired fasting glucose	362	59.4%	60.0%	65.1%	.615
Hypertension	361	50.0%	47.5%	53.7%	.703
Hypertriglyceridemia	362	53.1%	62.5%	44.6%	.072
Low HDL cholesterol	362	39.1%	42.5%	35.7%	.619
Sleep apnea	359	34.4%	27.5%	35.7%	.599
Reduced-carbohydrate diets	344	14.5%	23.7%	24.6%	.236
Alcohol consumption, servings/wk	298	1.2 ± 0.4	2.2 ± 0.5	1.8 ± 0.2	.203
Current smoking	298	10.7%	11.1%	9.7%	.952
Aerobic exercise	133	25.0%	11.1%	31.0%	.401

Study variables evaluated include baseline clinical characteristics and total/rate of weight loss during the program.

^a Defined as serum ALT greater than 19 IU/L in women and greater than 30 IU/L in men.^b This association was only significant among men when analyzed in men and women separately.* *P* < .05 vs no change.[†] *P* < .05 vs others.[‡] *P* < .05 for all comparisons.

Table 2

Univariate associations between ALT deterioration/improvement during significant weight loss and study variables—individual logistic regression analysis and interactions with age and sex

	ALT deterioration				ALT improvement			
	Unadjusted		Interactions		Unadjusted		Interactions	
	OR	<i>P</i> value	Age ^a	Sex	OR	<i>P</i> value	Age ^a	Sex
Age group (>56, yes or no)	0.4 [0.2, 0.7]	.0013	–	NS	0.5 [0.3, 1.0]	.0427	–	.0958
Sex, male	1.2 [0.7, 2.1]	.5011	NS	–	1.4 [0.7, 2.7]	.3517	NS	–
BMI, 5 kg/m ²	1.4 [1.2, 1.6]	<.000	NS	NS	0.9 [0.8, 1.1]	.5194	.0932	NS
Abdominal circumference, 5 cm	1.4 [1.1, 1.6]	.0011	NS	.1287	1.0 [0.8, 1.3]	.9203	NS	NS
Total weight loss, 1 kg	1.1 [1.1, 1.2]	.0022	.1719	.0158	1.1 [0.6, 1.8]	.7930	.0186	NS
Rate of weight loss, 1 kg/wk	1.8 [1.3, 2.4]	.0003	NS	.0035	1.0 [0.1, 6.8]	.990	.0111	NS
Baseline AST, 5 IU/L	1.1 [1.0, 1.2]	.0994	NS	NS	1.5 [1.3, 1.7]	<.0001	.0375	NS
Baseline ALT, 5 IU/L	1.1 [1.0, 1.1]	.0376	NS	NS	1.3 [1.2, 1.4]	<.0001	NS	NS
Baseline AST/ALT, 1 U	0.4 [0.1, 1.2]	.1084	NS	NS	0.1 [0.0, 0.3]	<.0001	.0045	.074
Hypertension	0.9 [0.5, 1.5]	.6776	NS	NS	0.8 [0.4, 1.6]	.5147	NS	.1066
Hypertriglyceridemia	1.3 [0.7, 2.2]	.3721	NS	NS	1.9 [1.0, 3.9]	.0558	NS	.1720
Low HDL cholesterol	1.1 [0.6, 2.0]	.6721	NS	NS	1.3 [0.7, 2.5]	.4269	NS	NS
Diabetes/impaired glucose tolerance	0.8 [0.5, 1.5]	.4485	NS	.1523	0.8 [0.4, 1.7]	.6242	NS	NS
Sleep apnea	1.0 [0.6, 1.7]	.9755	NS	NS	0.7 [0.3, 1.4]	.3126	.1467	NS
Reduced-carbohydrate diet, %	0.5 [0.2, 1.1]	.0945	NS	.1058	1.1 [0.5, 2.3]	.8753	.0879	NS
Alcohol consumption, 1 serving/wk	0.9 [0.8, 1.0]	.1253	NS	.1538	1.1 [1.0, 1.2]	.2742	NS	NS
Current smoking	1.1 [0.4, 2.7]	.8583	NS	NS	1.1 [0.3, 3.1]	.8265	.1615	NS

Logistic regression models were developed using a dichotomous variable of ALT deterioration (vs others) or ALT improvement (vs others) as a dependent variable. Models were run including each one of the listed study variables as an independent variable to provide unadjusted OR. The models were also run with adding an interaction term with age (or sex) to assess potential interactions with age and/or sex. The values provided in the columns of age and sex interactions were *P* values of the interaction terms, indicating that the association between ALT deterioration/improvement and the study variable was significantly different by sex or age if the *P* value is < .05. NS indicates not significant.

^a Age interaction was assessed by using the 2 age groups (<56 or ≥56 years).

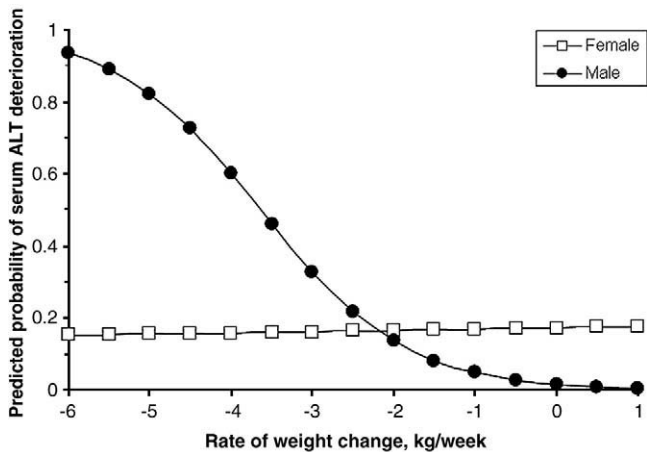


Fig. 2. Predicted probability of serum ALT deterioration and rate of weight change in men and women. The vertical axis shows predicted probability of serum ALT deterioration, and the horizontal axis shows rate of weight change in kilograms per week. Closed circles represent men, and open squares represent women.

models were developed in men and women separately to identify the predictors independently associated with ALT deterioration during weight loss. The adjusted odds ratios (ORs) of the predictors in the final models are summarized in Table 3. Based on the results, men who lost weight at a faster rate were more likely to experience ALT deterioration (about 7 times more likely per 1-kg increase in rate of weight loss per week), whereas patients who consumed alcohol (before the program) were less likely to experience ALT deterioration (30% less likely per 1-serving increase in weekly alcohol consumption). Adjusting for baseline serum ALT did not change the findings or add significant information to the model.

On the other hand, women who had higher BMI were more likely to experience ALT deterioration (30% more likely per 5-kg/m² increase in BMI). As described in the table footnote, the model developed for men accurately predicts ALT deterioration 88% of the time (AUC of 0.88), whereas the model for women presented a rather low performance (66% or AUC of 0.66, vs 50% for random guessing).

3.5. Clinical predictors of serum ALT improvement during weight loss after adjusting for other factors

For ALT improvement, multiple logistic regression models were developed in the younger and older groups separately based on the identified interactions between age groups and certain study variables. The adjusted ORs of the predictors in the final models (2 models using either baseline serum ALT or AST for each group) are summarized in Table 4.

In the younger group, after adjusting for baseline serum aminotransferase (ALT or AST), patients with higher AST/ALT ratio and current smoking were less likely to experience ALT improvement. In the older group, patients

with rapid weight loss, sleep apnea, or diabetes/impaired fasting glucose and those who followed a reduced-carbohydrate diet were less likely to experience ALT improvement after adjusting for baseline serum aminotransferase (ALT or AST).

4. Discussion

In this study, we statistically explored the predictors of serum ALT deterioration and improvement during significant weight loss among severely obese patients who participated in a residential weight loss program, after taking into account baseline values. By taking advantage of the size of the cohort, our analyses identified several clinical factors influencing changes in aminotransferase in sex- or age-specific manners. Identified clinical factors include current alcohol consumption before the program (as a beneficial factor) and rapid weight loss, higher BMI and higher AST/ALT ratio at baseline, current smoking, diabetes/impaired fasting glucose, and sleep apnea (as detrimental factors). Interestingly, reduced-carbohydrate diets showed different effects depending on subgroup analyzed. Because significant weight loss may exacerbate hepatic inflammation and/or

Table 3
Sex-specific clinical predictors of ALT deterioration during significant weight loss

	Male		Female	
	OR	P value	OR	P value
Age group (≥ 56 , yes or no)	–	–	0.5 [0.2, 1.1]	.092
BMI, 5 kg/m ²	–	–	1.3 [1.1, 1.7]	.017
Abdominal circumference, 5 cm	–	–	–	–
Total weight loss, 1 kg	–	–	–	–
Rate of weight loss, 1 kg/wk	6.9 [2.9, 16.4]	<.0001	1.7 [0.9, 3.4]	.123
Baseline AST, 5 IU/L	–	–	1.1 [1.0, 1.3]	.116
Baseline ALT, 5 IU/L	–	–	–	–
Baseline AST/ALT	–	–	–	–
Hypertension	2.3 [0.7, 7.5]	.172	–	–
Hypertriglyceridemia	–	–	–	–
Low HDL cholesterol	–	–	–	–
Diabetes/impaired glucose tolerance	–	–	–	–
Sleep apnea	–	–	–	–
Reduced-carbohydrate diet, %	0.1 [0.0, 1.8]	.132	–	–
Alcohol consumption, 1 serving/wk	0.7 [0.6, 1.0]	.023	–	–
Current smoking	–	–	–	–

Separate models were developed for men and women because associations between ALT deterioration and certain study variables were significantly different between sexes (ie, significant interactions with sex, Table 2). All the listed variables were included in the models (backward elimination). Variables with a hyphen in the table indicate that these variables were associated with P values of > .2 and had been excluded from the model. Prediction levels of the multiple logistic regression models expressed as AUC of the ROC curve were 0.88 for men and 0.66 for women.

Table 4
Age-specific clinical predictors of ALT improvement during significant weight loss

	Younger (<56 y) group				Older (\geq 56 y) group			
	Model 1		Model 2		Model 1		Model 2	
	OR	P value	OR	P value	OR	P value	OR	P value
Sex, male	–	–	–	–	–	–	–	–
BMI, 5 kg/m ²	–	–	–	–	–	–	–	–
Abdominal circumference, 5 cm	–	–	–	–	–	–	–	–
Total weight loss, 1 kg	–	–	–	–	–	–	–	–
Rate of weight loss, 1 kg/wk	–	–	–	–	0.3 [0.2, 0.6]	0.001	0.2 [0.1, 0.6]	.003
Baseline AST, 5 IU/L	–	–	1.4 [1.1, 1.7]	.001	–	–	1.3 [1.1, 1.5]	.000
Baseline ALT, 5 IU/L	1.2 [1.1, 1.4]	.003	–	–	1.9 [1.4, 2.6]	0.000	–	–
Baseline AST/ALT, 0.1 U	0.7 [0.4, 1.0]	.036	0.5 [0.3, 0.7]	.0004	1.2 [1.0, 1.5]	0.124	–	–
Hypertension	–	–	–	–	–	–	–	–
Hypertriglyceridemia	3.1 [0.9, 11.0]	.082	2.8 [0.8, 10.2]	.121	–	–	–	–
Low HDL cholesterol	–	–	–	–	–	–	–	–
Diabetes/impaired glucose tolerance	0.4 [0.1, 1.4]	.145	0.4 [0.1, 1.3]	.133	–	–	0.1 [0.0, 1.0]	.048
Sleep apnea	–	–	–	–	0.1 [0.0, 0.8]	0.027	0.1 [0.0, 0.6]	.016
Reduced-carbohydrate diet, %	–	–	–	–	–	–	0.1 [0.0, 1.0]	.047
Alcohol consumption, 1 serving/wk	–	–	–	–	–	–	1.2 [0.9, 1.7]	.169
Current smoking	0.03 [0.0, 0.9]	.046	0.03 [0.0, 0.6]	.040	–	–	–	–

Separate models were developed for the younger and older groups because associations between ALT improvement and certain variables were significantly different between age groups (ie, significant interactions with age groups, Table 2). All the listed variables were included in the models (backward elimination). Variables with a hyphen in the table indicate that these variables were associated with *P* values of $> .2$ and had been excluded from the model. Prediction levels of the multiple logistic regression models expressed as AUC of the ROC curve were 0.89 (model 1) and 0.90 (model 2) for the younger group and 0.91 (model 1) and 0.94 (model 2) for the older group.

fibrosis in a subset of patients after long-term follow-up [7-10], it is important to better understand who would likely experience worsening of necroinflammation in the liver after significant weight loss and, on the other hand, who would likely show improvement. Despite the preliminary nature of this study, the identified predictors of ALT deterioration/improvement during significant weight loss could aid future studies in discovering factors associated with worsening/improvement of hepatic inflammation (and/or fibrosis) during significant weight loss and in developing a clinical model to predict histologic liver outcomes. Furthermore, we believe that our findings may have pathophysiologic significance related to underlying changes in fat metabolism during significant weight loss.

The most significant finding in this study was a sexually dimorphic effect observed in rate of weight loss; rapid weight loss significantly increased the probability of ALT deterioration only among men, even after adjusting for differences in rate of weight loss (higher in men). This finding is intriguing because men have more β 3-adrenoreceptor and higher lipolytic activity in visceral adipose tissue compared with women [24,25], which may lead men to lose more visceral fat during weight loss. Enhanced lipolytic activity in visceral fat may result in an increased influx of nonesterified free fatty acid to the portal vein in men undergoing rapid weight loss, relative to women, and could overwhelm the pathways of fatty acid oxidation in the liver. Because free fatty acid is a well-known proinflammatory factor [26], rapid influx of free fatty acid to the liver could aggravate hepatic inflammation. Based on our prediction model developed for men (Fig. 2), weekly weight reduction

of less than 1.5 kg resulted in low likelihood of ALT deterioration ($<10\%$), whereas rate of weight loss exceeding 2 kg/wk increased likelihood exponentially. Besides the sexual dimorphism, this finding is consistent with that reported by Anderson et al [7] using histologic evaluation before and after significant weight loss.

Theoretically, the detrimental effect could also depend on downstream mechanisms in the liver, that is, ability to eliminate accumulated free fatty acids as well as cellular redox status in the liver to cope with generated reactive oxygen species through fatty acid oxidation. Based on our findings, we propose a working hypothesis explaining the different liver outcomes in response to significant weight loss; changes in aminotransferase levels during weight loss might be explained by an intricate kinetic balance among several mechanisms, including fatty acid oxidation pathways, triglyceride production and export, and cellular redox status, in response to rate of fatty acid influx to the portal vein. Possible explanation for each identified factor in line with the working hypothesis will be provided below.

Current alcohol consumption before the program showed a beneficial effect among men, whereas reduced-carbohydrate diets showed a borderline beneficial effect during weight loss. At baseline, there were no significant associations of serum ALT levels with alcohol consumption or reduced-carbohydrate diets among men (data not shown). Alcohol and low dietary carbohydrate may increase CYP2E1 activity in the liver [27-29]. Because enhanced fatty acid oxidation via CYP2E1 expedites the removal of toxic free fatty acid from hepatocytes, it would be conceivable that increased CYP2E1 could be beneficial during significant

weight loss. Our extended analysis further supports the theory: among rapid losers (mean rate of weight loss = 2.4 kg/wk), reduced-carbohydrate diets (adjusted OR = 0.1, $P = .036$) and moderate alcohol consumption (adjusted OR = 0.8 for 1-serving increase, $P = .08$) were associated with lower risk of ALT deterioration [30].

Because the fatty acid oxidation via CYP2E1 generates reactive oxygen species, the beneficial effect of enhancing this pathway may depend on available antioxidant reserves (ie, glutathione). Under a condition with reduced hepatic glutathione (eg, older age [31,32]), enhancing this pathway may, in turn, present a detrimental effect during significant weight loss. Diabetes directly affects mitochondrial energy metabolism [33-35] and the pentose phosphate pathway [36], which decreases β -oxidation and energy supply for glutathione disulfide reduction. Therefore, having diabetes could be detrimental under significant weight loss, especially among rapid losers [30]. Smoking is a well-known inducer of oxidative stress [37] and may therefore impair mitochondrial function and reduce antioxidant reserves, adversely affecting redox status in the liver. Based on our hypothesis, pacing the rate of weight reduction, especially among men, and eliminating the accumulation of toxic free fatty acid (eg, promoting fatty acid oxidation) with antioxidant supports may help decrease adverse histologic response of the liver during significant weight reduction. Nevertheless, mechanisms not yet discussed here (eg, potential influence of appetite-regulating hormones or hypothalamic controls) could also influence liver metabolism and hepatic inflammation during significant weight loss. Further studies are required to validate our hypothesis.

This study has several limitations. First, it did not include liver histology or imaging studies as outcome variables. Although it may not be optimal, this approach is justifiable given evidence that changes in serum aminotransferases within individuals have been shown to reflect changes in hepatic inflammation [19]; and there has been an approximate correlation between therapeutic interventions, ALT, and histology in past studies [16-18]. Second, alterations in medication were not taken into account in our analyses. In general, medications tend to be reduced and very few participants initiate new medications during the program. Nevertheless, we cannot deny a possibility that changes in medication might have modified the associations between serum ALT changes and the factors measured in this study. Third, the classification of diet in this study (high- vs reduced-carbohydrate diets) may not be optimal to address the influence of dietary composition on the liver. Further future studies using more precise measures of dietary carbohydrate should be done taking into consideration other potential variables (eg, age, rate of weight loss) that could modify the dietary influence on the liver. Finally, we observed aminotransferase changes only during an acute phase of weight loss (ie, 4 weeks). How aminotransferase response during such an acute phase reflects long-term histologic outcomes remains to be determined.

In summary, this study identified potential clinical predictors of changes in hepatic inflammation during significant weight loss using ALT changes as a surrogate marker. We believe the identified age- and sex-specific clinical predictors of ALT worsening/improvement may aid future studies in developing models to identify which obese individuals are likely to experience improved (or exacerbated) hepatic inflammation during significant and/or rapid weight loss and providing patients with more individualized weight loss recommendations. Furthermore, the working hypothesis developed here to explain the different responses of aminotransferase during weight loss may help inform future studies in delineating underlying mechanisms influencing hepatic inflammation during significant weight loss. Further studies with longer follow-up and histologic evaluation are warranted to verify our findings/theories and to further the goal of developing tailored diet/weight loss recommendations for obese individuals.

Acknowledgment

The authors would like to thank Eric Stewart for his editorial support.

References

- [1] Morbidity and Mortality Weekly Report from the Centers for Disease Control and Prevention. State-specific prevalence of obesity among adults—United States, 2005. *JAMA* 2006;296:1959-60.
- [2] Ogden CL, Flegal KM, Carroll MD, et al. Prevalence and trends in overweight among US children and adolescents, 1999-2000. *JAMA* 2002;288:1728-32.
- [3] Olshansky SJ, Passaro DJ, Hershow RC, et al. A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med* 2005;352:1138-45.
- [4] Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med* 2002;346:1221-31.
- [5] Adams LA, Angulo P. Treatment of non-alcoholic fatty liver disease. *Postgrad Med J* 2006;82:315-22.
- [6] Kral JG, Thung SN, Biron S, et al. Effects of surgical treatment of the metabolic syndrome on liver fibrosis and cirrhosis. *Surgery* 2004;135:48-58.
- [7] Andersen T, Glud C, Franzmann MB, et al. Hepatic effects of dietary weight loss in morbidly obese subjects. *J Hepatol* 1991;12:224-9.
- [8] Luyckx FH, Desai C, Thiry A, et al. Liver abnormalities in severely obese subjects: effect of drastic weight loss after gastroplasty. *Int J Obes Relat Metab Disord* 1998;22:222-6.
- [9] Srivastava S, Younossi ZM. Morbid obesity, nonalcoholic fatty liver disease, and weight loss surgery. *Hepatology* 2005;42:490-2.
- [10] Stratopoulos C, Papakonstantinou A, Terzis I, et al. Changes in liver histology accompanying massive weight loss after gastroplasty for morbid obesity. *Obes Surg* 2005;15:1154-60.
- [11] Mifflin MD, St Jeor ST, Hill LA, et al. A new predictive equation for resting energy expenditure in healthy individuals. *Am J Clin Nutr* 1990;51:241-7.
- [12] Kral TV, Roe LS, Rolls BJ. Combined effects of energy density and portion size on energy intake in women. *Am J Clin Nutr* 2004;79:962-8.
- [13] Rolls BJ. *The volumetrics eating plan*. New York: HarperCollins Publishers; 2005.

- [14] Campos GM, Bambha K, Vittinghoff E, et al. A clinical scoring system for predicting nonalcoholic steatohepatitis in morbidly obese patients. *Hepatology* 2008;47:1916-23.
- [15] Machado M, Marques-Vidal P, Cortez-Pinto H. Hepatic histology in obese patients undergoing bariatric surgery. *J Hepatol* 2006;45:600-6.
- [16] Thomas EL, Potter E, Tosi I, et al. Pioglitazone added to conventional lipid-lowering treatment in familial combined hyperlipidaemia improves parameters of metabolic control: relation to liver, muscle and regional body fat content. *Atherosclerosis* 2007;195.
- [17] Ratziu V, Giral P, Jacqueminet S, et al. Rosiglitazone for nonalcoholic steatohepatitis: one-year results of the randomized placebo-controlled Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) Trial. *Gastroenterology* 2008;135:100-10.
- [18] Engl J, Sturm W, Sandhofer A, et al. Effect of pronounced weight loss on visceral fat, liver steatosis and adiponectin isoforms. *Eur J Clin Invest* 2008;38:238-44.
- [19] Suzuki A, Lymp J, Sauver JS, et al. Values and limitations of serum aminotransferases in clinical trials of nonalcoholic steatohepatitis. *Liver Int* 2006;26:1209-16.
- [20] Bellentani S, Saccoccio G, Masutti F, et al. Prevalence of and risk factors for hepatic steatosis in Northern Italy. *Ann Intern Med* 2000;132:112-7.
- [21] Prati D, Taioli E, Zanella A, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann Intern Med* 2002;137:1-10.
- [22] Angulo P, Hui JM, Marchesini G, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology* 2007;45:846-54.
- [23] Angulo P, Keach JC, Batts KP, et al. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology* 1999;30:1356-62.
- [24] Fried SK, Leibel RL, Edens NK, et al. Lipolysis in intraabdominal adipose tissues of obese women and men. *Obes Res* 1993;1:443-8.
- [25] Lonnqvist F, Thorne A, Large V, et al. Sex differences in visceral fat lipolysis and metabolic complications of obesity. *Arterioscler Thromb Vasc Biol* 1997;17:1472-80.
- [26] Feldstein AE, Werneburg NW, Canbay A, et al. Free fatty acids promote hepatic lipotoxicity by stimulating TNF- α expression via a lysosomal pathway. *Hepatology* 2004;40:185-94.
- [27] Lieber CS. Microsomal ethanol-oxidizing system (MEOS): the first 30 years (1968-1998)—a review. *Alcohol Clin Exp Res* 1999;23:991-1007.
- [28] Wang PY, Kaneko T, Wang Y, et al. Acarbose alone or in combination with ethanol potentiates the hepatotoxicity of carbon tetrachloride and acetaminophen in rats. *Hepatology* 1999;29:161-5.
- [29] Yoo JS, Ning SM, Pantuck CB, et al. Regulation of hepatic microsomal cytochrome P450IIE1 level by dietary lipids and carbohydrates in rats. *J Nutr* 1991;121:959-65.
- [30] Suzuki A, Sha R, Wachholtz A, Binks M, Diehl AM. Influence of impaired glucose tolerance, glucose control status, light to moderate alcohol consumption, and reduced carbohydrate diets on serum ALT change during rapid weight loss in the residential weight loss program. *Hepatology* 2007;46(Suppl 741):740A.
- [31] Toroser D, Sohal RS. Age-associated perturbations in glutathione synthesis in mouse liver. *Biochem J* 2007;405:583-9.
- [32] Vogt BL, Richie Jr JP. Glutathione depletion and recovery after acute ethanol administration in the aging mouse. *Biochem Pharmacol* 2007;73:1613-21.
- [33] Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. *Science* 2005;307:384-7.
- [34] Kristal BS, Koopmans SJ, Jackson CT, et al. Oxidant-mediated repression of mitochondrial transcription in diabetic rats. *Free Radic Biol Med* 1997;22:813-22.
- [35] Kristal BS, Jackson CT, Chung HY, et al. Defects at center P underlie diabetes-associated mitochondrial dysfunction. *Free Radic Biol Med* 1997;22:823-33.
- [36] Sudnikovich EJ, Maksimchik YZ, Zabrodskaya SV, et al. Melatonin attenuates metabolic disorders due to streptozotocin-induced diabetes in rats. *Eur J Pharmacol* 2007.
- [37] Scheffler E, Wiest E, Woehrle J, et al. Smoking influences the atherogenic potential of low-density lipoprotein. *Clin Investig* 1992;70:263-8.