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Visceral Adipose Tissue Area as an Independent Risk Factor for Elevated Liver Enzyme in Nonalcoholic Fatty Liver Disease

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Abstract: Chronic elevations in alanine aminotransferase (ALT) levels are associated with body composition. The aim of this study was to evaluate the relationship between elevated liver enzyme levels and the visceral tissue area in subjects with and without nonalcoholic fatty liver disease (NAFLD).

An observational cohort study was conducted with subjects undergoing general health examinations. To evaluate the visceral and subcutaneous abdominal adipose tissue area, a computed tomography scan was performed. NAFLD was diagnosed if a person demonstrated fatty liver on ultrasonography without a history of significant alcohol consumption or chronic liver disease. Abnormal liver enzyme levels were based on ALT elevations according to the updated Asian definition.

Of the 5100 subjects, 3712 (72.8%) met the inclusion criteria, and NAFLD was found in 1185 subjects. Elevated ALT values were positively correlated with body mass index, waist circumference, and subcutaneous and visceral adipose tissue area. These relationships were attenuated, although they remained significant in a dose-dependent manner, after adjusting for multiple liver injury risk factors. In addition, when body mass index and subcutaneous and visceral tissue areas were finally considered in combination, only visceral adipose tissue remained independently associated with elevated ALT levels in the ultrasonographically diagnosed NAFLD group (P for trend <0.001 for men and women).

Elevated ALT levels were independently and dose-dependently associated with visceral fat accumulation in the healthy general population, especially in ultrasonographically diagnosed NAFLD patients. These results reemphasize the importance of visceral fat in the pathogenesis of NAFLD.

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Abbreviations: ALT = alanine aminotransferase, BMI = body mass index, CT = computed tomography, HbA1c = hemoglobin A1c, HDL = high-density lipoprotein, MS = metabolic syndrome, NAFLD = nonalcoholic fatty liver disease, SAT = subcutaneous adipose tissue, VAT = visceral adipose tissue, WC = waist circumference.

INTRODUCTION

The serum concentration of alanine aminotransferase (ALT), which is considered to be the most specific marker for liver damage,[1] is associated with body mass index (BMI) and progressively increases with increasing BMI values.[2–4] A population-based study using data from the Third National Health and Nutrition Examination Survey (NHANES III) in the United States revealed that central adiposity, hyperleptinemia, and hyperinsulinemia are important factors in the association between overweight and increased ALT levels.[5] Another study reported a role of central adiposity in predicting increased liver enzyme levels.[6] A study using data from a ultrasonography (US) population survey also determined that trunk fat was associated with increased serum ALT levels independently of BMI and waist circumference (WC).[7] However, in this study, trunk fat was not differentiated into visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). Several studies have used computed tomography (CT) to determine the association between serum ALT levels and VAT area; however, these studies were limited by selection bias and small sample sizes.[8,9]

Nonalcoholic fatty liver disease (NAFLD), a common cause of chronic liver disease, with an increasing prevalence (20%–30%) worldwide,[10,11] is the most common cause of elevated serum ALT levels.[10] An association between hepatic fat and VAT has been suggested,[12] and hepatic steatosis, as measured by proton magnetic resonance spectroscopy, was found to be closely related to central obesity.[13] In addition, the severity of fatty liver has been linked to the VAT area as evaluated by CT.[14] Furthermore, the VAT area assessed by magnetic resonance imaging has also been directly associated with the severity of hepatic inflammation and fibrosis, independent of insulin resistance and hepatic steatosis.[15] However, few studies have investigated the relationship between liver injury and VAT in terms of NAFLD. Therefore, the aim of this study was to determine the relationship between the elevation of liver enzyme levels, VAT, and anthropometric indexes in subjects with and without NAFLD.

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PATIENTS AND METHODS

Study Population

For our study, we analyzed the database from a previously described cohort.[16,17] Briefly, a total of 5100 subjects who underwent abdominal ultrasonography, abdominal fat CT scans for adipose tissue areas, and blood samplings for a routine health checkup at the Seoul National University Hospital Gangnam Healthcare Center, Seoul, Korea, were recruited into the study. A total of 280 subjects who were positive for hepatitis B surface antigen, 56 who were positive for hepatitis C antibodies, 949 with alcohol consumption >140 g/wk, and 14 with other hepatitis histories, as identified by a questionnaire, were excluded. Additionally, we excluded 99 subjects who in the past year had taken medications known to provoke fatty liver. Finally, 3712 subjects met the inclusion criteria. Ethical approval for this study was obtained from the institutional review board of the Seoul National University Hospital with an informed consent waiver prior to the study.

Measurement of Clinical and Laboratory Parameters

Briefly, the details of clinical and laboratory measurement were based on the previous description.[17] Each subject completed questionnaires regarding his/her past medical and medication history. For women, questions regarding the presence of menopause and a history of hormone replacement therapy were included. A woman was considered to be menopausal if her menstrual periods had stopped >1 year prior to the study. The participants underwent an anthropometric assessment as well as laboratory and radiological exams on the day of tests. Measurements of height and body weight were measured while the subjects were wearing a light gown, and the BMI was calculated by dividing the weight (kilogram) by the square of the height (square meter). WC was measured at the midpoint between the lower costal margin of the rib cage and the iliac crest using a tape measure. The systolic and diastolic blood pressure was measured twice, and the average values were obtained for data analysis. Hypertension was defined as treatment with an antihypertensive drug, a systolic blood pressure >140 mm Hg, or a diastolic blood pressure >90 mm Hg.

The laboratory tests included serum aspartate aminotransferase, ALT, γ-glutamyl transpeptidase, triglycerides, total cholesterol, high-density lipoprotein (HDL)-cholesterol, glucose, uric acid, hepatitis B surface antigen, and hepatitis C virus antibody, and were performed on an Architect Ci8200 (Abbott Laboratories, Abbott Park, IL). Measurements of serum insulin levels were performed using immunoradiometric assays (Biosource, Nivelles, Belgium), and hemoglobin A1c (HbA1c) was measured with a COBAS INTEGRA 400 (Roche Diagnostics GmbH, Mannheim, Germany).

The presence of diabetes mellitus was defined as a fasting serum glucose level ≥126 mg/dL or as the use of blood glucose-lowering agents. Current smokers were defined as those who had smoked at least 1 cigarette/d during 1 year prior to the study. Former smokers were defined as those who had previously smoked cigarettes regularly.[18] Blood samples were collected before 10:00 AM after a 12-hour overnight fast. All of the laboratory tests were performed using standard laboratory methods. Homeostasis model assessment (HOMA)-estimated insulin resistance was used to evaluate insulin resistance, and was obtained by multiplying the fasting insulin by the fasting glucose.[19] Abnormal liver enzyme levels were defined as ALT elevation above the strict cutoff point based on the updated Asian definition by Lee *et al.*[20] (ALT >33/25 IU/L).

Metabolic syndrome (MS) was diagnosed if patients met 3 or more of the following 5 criteria: central obesity (WC >90 cm [men] or >80 cm [women], based on the definition by the Regional Office for the Western Pacific Region of the World Health Organization criteria), HDL-cholesterol <40 mg/dL (men) or <50 mg/dL (women), a triglyceride level ≥150 mg/dL, pressure ≥130/85 mm Hg or treatment for hypertension, and hyperglycemia (fasting glucose ≥100 mg/dL) or treatment for diabetes.[21]

Measurement of Adipose Tissue Areas

The method for measuring adipose tissue area using CT cross-sectional images has been described previously.[22,23] The subjects were examined with a 16-detector row CT scanner (Somatom Sensation 16; Siemens Medical Solutions, Forchheim, Germany). The cross-sectional surface area (in square centimeter) of the abdominal fat tissue was calculated at the level of the umbilicus using a CT software program (Rapidia 2.8; INFINITT, Seoul, Korea) by specifying the attenuation values for fatty tissues [−250 to −50 Hounsfield unit (HU)]. Because of a lack of a cutoff value for an appropriate healthy amount of abdominal adipose tissue, we used the lowest sex-specific quartile of the VAT and SAT areas as reference values.

Ultrasonographic Assessments and Definition of NAFLD

The ultrasonographic examinations of the liver were carried out by experienced radiologists blinded to the patients' clinical characteristics. Fatty liver was diagnosed based on the findings of ultrasonography (Acusion, Sequoia 512; Siemens, Mountain View, CA) according to the criteria previously described.[24] NAFLD was diagnosed in subjects who showed the findings of fatty liver on ultrasonography, in the absence of the following: a positive serologic marker for hepatitis B surface antigen or hepatitis C virus serological marker, excessive alcohol intake (>30 g/d for men and >20 g/d for women), medications known to produce fatty liver disease, and other specific hepatic disease.

Statistical Analysis

Comparisons of continuous variables between the 2 groups were performed using Student *t* test and analysis of variance (ANOVA) or ANOVA with post hoc analysis for multiple comparisons, and categorical data was compared using the χ^2 test or Fisher exact test. Variables significant in univariate analysis and previously known risk factors were included in the multivariate models to determine independent predictors of NAFLD. The statistical analyses were performed using SPSS 19.0 (SPSS Inc, Chicago, IL). The statistical significance was achieved at $P < 0.05$.

RESULTS

A total of 3712 subjects were analyzed. The mean age was 51.6 ± 9.7 years, and 55.5% of the subjects were men. NAFLD was found in 1185 (31.9%) of the 3712 subjects. In men, elevations of ALT were positively correlated with obesity, MS, higher BMI, WC, systolic blood pressure, triglyceride, fasting insulin, uric acid, HOMA index, SAT and VAT values, lower HDL-cholesterol levels, and younger age in the ultrasonographically normal and NAFLD groups. In men, obesity,

BMI, WC, triglycerides, fasting insulin, HOMA index, MS, SAT, and VAT were significantly increased in a dose-dependent manner in the ultrasonographically diagnosed normal group with normal ALT levels compared with the ultrasonographically diagnosed normal group with elevated ALT levels, the ultrasonographically diagnosed NAFLD group with normal ALT levels, and the ultrasonographically diagnosed NAFLD group with elevated ALT levels ($P < 0.001$, Table 1). In women, elevated ALT levels showed a significant association with higher BMI, WC, triglycerides, HbA1c, fasting insulin, HOMA index, MS, uric acid, VAT and SAT in the ultrasonographically diagnosed normal and NAFLD groups. The presence of diabetes mellitus, hypertension and MS, BMI, WC, triglyceride level, total adipose tissue, SAT, and VAT were higher, and showed a dose-dependent increase in the ultrasonographically diagnosed normal group with normal ALT levels, ultrasonographically diagnosed normal group with elevated ALT levels, ultrasonographically diagnosed NAFLD group with normal ALT levels, and the ultrasonographically diagnosed NAFLD group with elevated ALT levels (Table 2).

Relationship Between Abdominal Adipose Tissue Area and Elevated ALT Levels

We evaluated the risk for ALT elevation according to body measurement indices such as VAT, SAT, WC, and BMI. The

TABLE 1. Clinical Characteristics of Study Population (Men)

	US-Normal			US-NAFLD			
ALT	**≤33 (n = 1036)**	**>33 (n = 161)**	***P* Value**	**≤33 (n = 513)**	**>33 (n = 352)**	***P* Value**	***P* Value**
Age, y	52.7 ± 10.1	50.9 ± 9.7	0.029	52.3 ± 9.2	48.5 ± 9.2	<0.001	<0.001*
Diabetes mellitus, %	74 (7.1%)	14 (8.7%)	0.482	71 (13.8%)	47 (13.4%)	0.837	<0.001†
Diabetes medication, %	59 (5.7%)	12 (7.5%)	0.380	60 (11.7%)	38 (10.8%)	0.681	<0.001†
Hypertension, %	202 (19.5%)	39 (24.2%)	0.164	134 (26.1%)	86 (24.4%)	0.575	0.016†
HT medication, %	170 (16.4%)	36 (22.4%)	0.063	120 (23.4%)	74 (21.0%)	0.412	0.005†
Smoking, %			0.884			0.519	0.140†
Current	485 (46.8%)	72 (44.7%)		246 (48.0%)	155 (44.0%)		
Former	279 (26.9%)	45 (28.0%)		159 (31.0%)	116 (33.0%)		
Never	272 (26.3%)	44 (27.3%)		108 (21.1%)	81 (23.0%)		
Obesity			<0.001			<0.001	<0.001†
Normal (BMI < 23)	411 (39.7%)	32 (19.9%)		69 (13.5%)	11 (3.1%)		
Overweight (23 ≤ BMI < 25)	374 (36.1%)	55 (34.2%)		157 (30.6%)	73 (20.7%)		
Obese (BMI ≥ 25)	251 (24.2%)	74 (46.0%)		287 (55.9%)	268 (76.1%)		
BMI, kg/m^2	23.52 ± 2.27	24.80 ± 2.40	<0.001	25.34 ± 2.27*	26.90 ± 2.67	<0.001	<0.001*
WC, cm	84.70 ± 6.23	88.82 ± 6.55	<0.001	89.80 ± 6.21	92.90 ± 6.21	<0.001	<0.001*
Total body fat, %	20.64 ± 4.02	22.48 ± 3.46	<0.001	23.71 ± 3.86	25.37 ± 4.02	<0.001	<0.001*
SBP, mm Hg	117.4 ± 13.2	120.0 ± 13.9	0.024	119.7 ± 13.4	122.6 ± 13.1	0.002	<0.001*
DBP, mm Hg	76.5 ± 10.4	78.0 ± 10.6	0.090	78.5 ± 10.1	81.0 ± 11.2	0.001	<0.001*
Total cholesterol, mg/dL	188.7 ± 32.8	189.0 ± 32.4	0.902	192.4 ± 33.3	201.2 ± 34.5	<0.001	<0.001*
Triglycerides, mg/dL	105.8 ± 51.4	131.2 ± 68.0	<0.001	147.4 ± 73.6	174.7 ± 97.5	<0.001	<0.001*
HDL-cholesterol, mg/dL	51.7 ± 12.3	46.6 ± 10.4	<0.001	46.2 ± 10.2	44.2 ± 8.8	0.002	<0.001*
Lipid lowering medication, %	71 (6.9%)	15 (9.3%)	0.260	44 (8.6%)	37 (10.5%)	0.337	0.145†
Fasting glucose, mg/dL	96.1 ± 17.9	100.3 ± 24.1	0.037	103.7 ± 23.7	104.4 ± 22.1	0.660	<0.001*
HbA1c, %	5.91 ± 0.63	6.10 ± 0.92	0.010	6.17 ± 0.89	6.25 ± 0.91	0.206	<0.001*
Insulin	7.79 ± 3.04 (874)	8.90 ± 3.45 (148)	<0.001	9.71 ± 3.86 (414)	12.54 ± 5.70 (282)	<0.001	<0.001*
HOMA index	1.89 ± 0.93	2.28 ± 1.29	0.001	2.50 ± 1.11	3.24 ± 1.69	<0.001	<0.001*
ALT	20.0 ± 5.9	46.4 ± 18.3	<0.001	23.3 ± 5.9	56.2 ± 26.6	<0.001	<0.001*
AST	21.0 ± 5.0	36.0 ± 39.6	<0.001	21.9 ± 4.98	37.6 ± 23.3	<0.001	<0.001*
GGT	30.2 ± 23.9	54.6 ± 40.5	<0.001	36.9 ± 26.4	64.1 ± 83.5	<0.001	<0.001*
MS	136 (13.1%)	48 (29.8%)	<0.001	187 (36.5%)	178 (50.6%)	<0.001	<0.001†
Uric acid	5.96 ± 1.18	6.19 ± 1.26	0.022	6.37 ± 1.26	6.75 ± 1.27	<0.001	<0.001*
TAT, cm^2	231.1 ± 80.0	280.3 ± 74.0	<0.001	302.6 ± 79.8	345.7 ± 80.1	<0.001	<0.001*
VAT area, cm^2	113.1 ± 46.0	138.0 ± 45.1	<0.001	151.8 ± 44.0	170.7 ± 44.9	<0.001	<0.001*
SAT area, cm^2	118.0 ± 44.5	142.3 ± 45.1	<0.001	150.8 ± 53.2	174.9 ± 59.8	<0.001	<0.001*

Data are means ± SD and range (in brackets) when appropriate. ALT = alanine aminotransferase, ANOVA = analysis of variance, AST = aspartate aminotransferase, BMI = body mass index, DBP = diastolic blood pressure, GGT = γ-glutamyl transpeptidase, HbA1c = hemoglobin A1c, HDL = high-density lipoprotein, HOMA = homeostasis model assessment, HT = hypertension, MS = metabolic syndrome, NAFLD = nonalcoholic nonalcoholic fatty liver disease, SAT = subcutaneous adipose tissue, SBP = systolic blood pressure, TAT = total adipose tissue, US = ultrasonography, VAT = visceral adipose tissue, WC = waist circumference.

* *P* value for the test of ANOVA comparing 4 groups.

† *P* value for the χ^2 test comparing 4 groups.

TABLE 2. Clinical Characteristics of Study Population (Women)

	US-Normal			US-NAFLD			
ALT	≤25 (n = 1112)	>25 (n = 218)	*P* Value	≤25 (n = 188)	>25 (n = 132)	*P* Value	*P* Value
Age, years	49.6 ± 9.5	54.2 ± 8.2	<0.001	55.3 ± 8.7	55.3 ± 9.1	0.962	<0.001*
Diabetes mellitus, %	20 (1.8%)	7 (3.2%)	0.176	11 (5.9%)	21 (15.9%)	0.003	<0.001†
Diabetes medication, %	16 (1.4%)	5 (2.3%)	0.355	8 (4.3%)	20 (15.2%)	0.001	<0.001†
Hypertension, %	134 (12.1%)	43 (19.7%)	0.002	54 (28.7%)	45 (34.1%)	0.307	0.016†
HT medication, %	105 (9.4%)	38 (17.4%)	<0.001	46 (24.5%)	41 (31.1%)	0.192	0.005†
Smoking, %			0.037			0.779	0.067†
Current	54 (4.9%)	7 (3.2%)		7 (3.7%)	7 (5.3%)		
Former	45 (4.0%)	2 (0.9%)		5 (2.7%)	3 (2.3%)		
Never	1013 (91.1%)	209 (95.9%)		176 (93.6%)	122 (92.4%)		
Postmenopausal, %	474 (42.6%)	144 (66.1%)	<0.001	130 (69.1%)	97 (73.5%)	0.400	<0.001†
Hormone replacement therapy, %	115 (10.3%)	35 (16.1%)	0.015	22 (11.7%)	29 (22.0%)	0.014	<0.001†
Obesity			0.001			<0.001	<0.001†
Normal (BMI < 23)	790 (71.0%)	135 (61.9%)		54 (28.7%)	13 (9.8%)		
Overweight (23 ≤ BMI < 25)	217 (19.5%)	45 (20.6%)		60 (31.9%)	42 (31.8%)		
Obese (BMI ≥ 25)	105 (9.4%)	38 (17.4%)		74 (39.4%)	77 (58.3%)		
BMI, kg/ m^2	21.68 ± 2.43	22.51 ± 2.72	<0.001	24.61 ± 2.74	26.04 ± 2.96	<0.001	<0.001*
WC, cm	79.45 ± 6.99	82.13 ± 7.35	<0.001	86.68 ± 7.35	90.39 ± 7.88	<0.001	<0.001*
Total body fat, %	27.25 ± 4.78	28.61 ± 5.10	<0.001	31.93 ± 4.40	33.94 ± 4.38	<0.001	<0.001*
SBP, mm Hg	111.7 ± 15.0	113.7 ± 14.4	0.070	119.3 ± 14.6	122.0 ± 12.6	0.076	<0.001*
DBP, mm Hg	70.3 ± 11.0	70.0 ± 10.1	0.756	75.0 ± 11.0	75.4 ± 9.2	0.768	<0.001*
Total cholesterol, mg/dL	191.4 ± 32.3	198.8 ± 38.2	0.008	204.2 ± 33.3	208.5 ± 41.2	0.304	<0.001*
Triglycerides, mg/dL	82.1 ± 42.1	92.7 ± 42.7	0.001	115.5 ± 53.5	143.9 ± 84.6	0.001	<0.001*
HDL-cholesterol, mg/dL	60.9 ± 13.6	60.7 ± 15.2	0.807	54.4 ± 12.0	52.1 ± 12.4	0.098	<0.001*
Lipid lowering medication, %	54 (4.9%)	19 (8.7%)	0.022	22 (11.7%)	13 (9.8%)	0.601	0.027†
Fasting glucose, mg/dL	88.2 ± 12.2	90.6 ± 19.1	0.074	98.1 ± 15.4	103.7 ± 20.9	0.009	<0.001*
HbA1c, %	5.85 ± 0.41	6.00 ± 0.62	0.001	6.15 ± 0.68	6.45 ± 1.02	0.004	<0.001*
Insulin	7.51 ± 2.87 (957)	8.10 ± 3.77 (191)	0.040	9.32 ± 3.49 (161)	11.01 ± 4.42 (122)	0.001	<0.001*
HOMA index	1.66 ± (957)	1.88 ± 1.10 (191)	0.011	2.29 ± 0.97 (161)	2.88 ± 1.55 (122)	<0.001	<0.001*
ALT	15.3 ± 4.6	40.0 ± 25.9	<0.001	18.2 ± 4.0	42.7 ± 21.5	<0.001	<0.001*
AST	19.6 ± 4.5	34.5 ± 14.4	<0.001	20.0 ± 3.7	33.0 ± 13.1	<0.001	<0.001*
GGT	16.7 ± 10.5	35.8 ± 31.7	<0.001	21.0 ± 12.6	39.3 ± 32.6	<0.001	<0.001*
MS	141 (12.7%)	47 (21.6%)	0.001	71 (37.8%)	80 (60.6%)	<0.001	<0.001†
Uric acid	4.41 ± 0.89	4.76 ± 1.11	<0.001	4.87 ± 0.96	5.16 ± 1.01	0.009	<0.001*
TAT, cm^2	231.8 ± 84.6	260.0 ± 89.2	<0.001	330.4 ± 89.7	374.2 ± 90.4	<0.001	<0.001*
VAT area, cm^2	70.1 ± 33.9	87.2 ± 39.7	<0.001	117.9 ± 39.2	139.0 ± 38.3	<0.001	<0.001*
SAT area, cm^2	161.7 ± 59.3	172.7 ± 61.0	0.012	212.5 ± 68.8	235.1 ± 71.4	0.005	<0.001*

Data are means ± SD and range (in brackets) when appropriate. ALT = alanine aminotransferase, ANOVA = analysis of variance, AST = aspartate aminotransferase, BMI = body mass index, DBP = diastolic blood pressure, GGT = γ-glutamyl transpeptidase, HbA1c = hemoglobin A1c, HDL-cholesterol = high-density lipoprotein cholesterol, HOMA = homeostasis model assessment, HT = hypertension, MS = metabolic syndrome, NAFLD = nonalcoholic fatty liver disease, SAT = subcutaneous adipose tissue, SBP = systolic blood pressure, TAT = total adipose tissue, US = ultrasonography, VAT = visceral adipose tissue, WC = waist circumference.

* *P* value for the test of ANOVA comparing 4 groups.

† *P* value for the χ^2 test comparing 4 groups.

associations between elevated ALT and the body measurement indices that were observed in the univariate analysis were attenuated in the multivariate analysis; however, the associations were still significant. After adjusting for multiple liver injury risk factors including age, smoking status, systolic blood pressure, fasting glucose, triglycerides and HDL-cholesterol, and postmenopausal status and use of hormone replacement therapy (in women), elevation of ALT showed positive relationships with BMI, WC, and VAT in ultrasonographically diagnosed NAFLD individuals and in the ultrasonographically normal group. Though the odds ratios of the VAT quartiles were similar between the ultrasonographically diagnosed normal and NAFLD groups in men, the odds ratios of the VAT quartile in the ultrasonographically diagnosed NAFLD group were higher than in the normal group in women (Tables 3 and 4).

In addition, when SAT and VAT were considered together, VAT was significantly associated with elevated ALT in men and women. However, the dose dependence was stronger in the ultrasonographically diagnosed NAFLD group than in the normal group. SAT showed a significant association only in men in the ultrasonographically diagnosed normal and NAFLD groups and not in women (Table 5). Finally, after a further adjustment for BMI as a surrogate marker of general obesity, a statistically significant association remained between VAT and

TABLE 3. Risk of the Body Measure Indices and Abdominal Adipose Tissue Areas for Elevated Serum ALT in Men (Cutoff 33)

	US-Normal (n = 1197)				US-NAFLD (n = 865)			
	Univariate	*P* Value	Multivariate	*P* Value	Univariate	*P* Value	Multivariate	*P* Value
VAT area								
1st	1	<0.001*	1	<0.001*	1	<0.001*	1	<0.001*
2nd	2.27 (1.22–4.21)	0.009	1.94 (1.03–3.64)	0.039	1.86 (1.24–2.79)	0.003	1.98 (1.30–3.02)	0.002
3rd	3.62 (2.01–6.52)	<0.001	2.95 (1.59–5.45)	0.001	1.98 (1.32–2.97)	0.001	2.14 (1.39–3.29)	0.001
4th	4.44 (2.49–7.91)	<0.001	3.35 (1.80–6.23)	<0.001	3.10 (2.07–4.64)	<0.001	3.40 (2.20–5.26)	<0.001
SAT area								
1st	1	<0.001*	1	<0.001*	1	<0.001*	1	<0.001*
2nd	1.05 (0.57–1.96)	0.874	0.99 (0.53–1.87)	0.982	1.41 (0.94–2.13)	0.102	1.35 (0.89–2.06)	0.162
3rd	2.71 (1.59–4.64)	<0.001	2.30 (1.33–4.00)	0.003	2.48 (1.66–3.71)	<0.001	2.12 (1.40–3.21)	<0.001
4th	3.82 (2.27–6.43)	<0.001	3.04 (1.77–5.23)	<0.001	3.22 (2.15–4.82)	<0.001	2.45 (1.61–3.75)	<0.001
WC								
1st	1	<0.001*	1	<0.001*	1	<0.001*	1	<0.001*
2nd	1.01 (0.54–1.88)	0.972	0.82 (0.44–1.55)	0.543	1.39 (0.93–2.09)	0.972	1.51 (0.99–2.31)	0.055
3rd	2.17 (1.25–3.77)	0.006	1.68 (0.95–2.98)	0.073	1.86 (1.24–2.78)	0.003	1.87 (1.23–2.84)	0.003
4th	4.63 (2.77–7.75)	<0.001	3.55 (2.07–6.10)	<0.001	3.22 (2.16–4.79)	<0.001	3.02 (1.99–4.60)	<0.001
BMI								
1st	1	<0.001*	1	<0.001*	1	<0.001*	1	<0.001*
2nd	1.80 (1.01–3.21)	0.048	1.56 (0.87–2.82)	0.140	1.91 (1.26–2.91)	0.003	1.82 (1.18–2.82)	0.007
3rd	2.16 (1.24–3.79)	0.007	1.67 (0.94–2.96)	0.081	2.51 (1.66–3.81)	<0.001	2.34 (1.52–3.59)	<0.001
4th	4.29 (2.52–7.28)	<0.001	3.01 (1.74–5.23)	<0.001	5.30 (3.49–8.06)	<0.001	4.25 (2.74–6.59)	<0.001

Multivariate model was adjusted for age, smoking status, systolic blood pressure, fasting glucose, triglyceride, and HDL-cholesterol. ALT = alanine aminotransferase, BMI = body mass index, HDL = high-density lipoprotein, NAFLD = nonalcoholic fatty liver disease, SAT = subcutaneous adipose tissue, US = ultrasonography, VAT = visceral adipose tissue, WC = waist circumference. VAT: 1st quartile, 0–98.58; 2nd quartile, 98.83–132.05; 3rd quartile, 132.06–167.79; 4th quartile, ≥167.84. SAT: 1st quartile, 0–101.78; 2nd quartile, 101.97–129.89; 3rd quartile, 129.91–164.39; 4th quartile, ≥164.40. WC: 1st quartile, 0–83.0; 2nd quartile, 83.1–87.5; 3rd quartile, 87.6–92.0; 4th quartile, ≥92.1. BMI: 1st quartile, 0–22.9; 2nd quartile, 23.0–24.5; 3rd quartile, 24.6–26.2; 4th quartile, ≥26.3.

* *P* value for the test of trends of odds.

elevated ALT in the ultrasonographically diagnosed NAFLD group (*P* for trend < 0.001 for men and women). This association was attenuated and no longer reached statistical significance in the ultrasonographically normal group (*P* for trend 0.079 for men and 0.114 for women, Table 6). The SAT had no significant association with ALT elevation, and BMI was associated with elevated ALT only in men in the ultrasonographically diagnosed NAFLD group (Table 6). These results indicate that VAT is an independent risk factor for elevated ALT in ultrasonographically diagnosed NAFLD.

Next, we analyzed the data regarding the relationship with elevated ALT levels defined by higher cutoff values. Using the cutoff value of ALT >40, a significant association was found between VAT and elevated ALT in the ultrasonographically diagnosed NAFLD group (*P* for trend 0.017 for men and <0.001 for women, Supplementary Table 1, http://links.lww.com/MD/A212). When the cutoff value of ALT was set at >2 times the upper normal limit, VAT had an association with elevated ALT only in women in the ultrasonographically diagnosed NAFLD group (Supplementary Table 2, http://links.lww.com/MD/A212).

DISCUSSION

In the present study, visceral fat accumulation was significantly associated with elevated ALT levels even after adjusting for metabolic components in the ultrasonographically diagnosed normal and NAFLD groups. The relationship between VAT and elevated ALT remained after adjusting for BMI, a surrogate marker of general obesity, in the ultrasonographically diagnosed NAFLD group.

A large population-based study using NHANES III data in the US showed that central adiposity, as measured by the waist-to-hip circumference ratio, was more strongly associated with elevated serum ALT levels than with BMI.[5] In addition, a study of recent NHANES III data revealed that trunk fat, as measured by dual x-ray absorptiometry, was associated with increased serum ALT levels, and this association was independent of BMI, WC, and other risk factors for liver injury.[7] Previous methods of measuring central fat could not differentiate between VAT and SAT.

Several studies that have assessed the relationship between ALT levels and VAT area using CT scans showed results that are consistent with our study.[8,9] However, previous studies had limitations including small sample sizes and no consideration of the presence of fatty liver. In the present study, the visceral fat area was significantly associated with elevated ALT in subjects with NAFLD, suggesting a role for visceral fat in enhancing fatty infiltration and inflammation in NAFLD. In accordance with our findings, a previous study performed in Japan demonstrated that the severity of fatty liver, assessed by ultrasonography, was correlated with visceral fat accumulation and insulin resistance.[14]

Chronic ALT elevation is considered to be a marker of hepatocyte damage. Increased ALT activity was associated with the MS, and this association was graded across a number of metabolic components.[25,26] In addition, higher ALT levels were previously known to be associated with increased insulin

TABLE 4. Risk of the Body Measure Indices and Abdominal Adipose Tissue Areas for Elevated Serum ALT in Women (Cutoff 25)

	US-Normal (n = 1197)				US-NAFLD (n = 865)			
	Univariate	*P* Value	Multivariate	*P* Value	Univariate	*P* Value	Multivariate	*P* Value
VAT area								
1st	1	<0.001*	1	<0.001*	1	<0.001*	1	<0.001*
2nd	2.27 (1.22–4.21)	0.009	1.94 (1.03–3.64)	0.039	1.86 (1.24–2.79)	0.003	1.98 (1.30–3.02)	0.002
3rd	3.62 (2.01–6.52)	<0.001	2.95 (1.59–5.45)	0.001	1.98 (1.32–2.97)	0.001	2.14 (1.39–3.29)	0.001
4th	4.44 (2.49–7.91)	<0.001	3.35 (1.80–6.23)	<0.001	3.10 (2.07–4.64)	<0.001	3.40 (2.20–5.26)	<0.001
SAT area								
1st	1	<0.001*	1	<0.001*	1	<0.001*	1	<0.001*
2nd	1.05 (0.57–1.96)	0.874	0.99 (0.53–1.87)	0.982	1.41 (0.94–2.13)	0.102	1.35 (0.89–2.06)	0.162
3rd	2.71 (1.59–4.64)	<0.001	2.30 (1.33–4.00)	0.003	2.48 (1.66–3.71)	<0.001	2.12 (1.40–3.21)	<0.001
4th	3.82 (2.27–6.43)	<0.001	3.04 (1.77–5.23)	<0.001	3.22 (2.15–4.82)	<0.001	2.45 (1.61–3.75)	<0.001
WC								
1st	1	<0.001*	1	<0.001*	1	<0.001*	1	<0.001*
2nd	1.01 (0.54–1.88)	0.972	0.82 (0.44–1.55)	0.543	1.39 (0.93–2.09)	0.972	1.51 (0.99–2.31)	0.055
3rd	2.17 (1.25–3.77)	0.006	1.68 (0.95–2.98)	0.073	1.86 (1.24–2.78)	0.003	1.87 (1.23–2.84)	0.003
4th	4.63 (2.77–7.75)	<0.001	3.55 (2.07–6.10)	<0.001	3.22 (2.16–4.79)	<0.001	3.02 (1.99–4.60)	<0.001
BMI								
1st	1	<0.001*	1	<0.001*	1	<0.001*	1	<0.001*
2nd	1.80 (1.01–3.21)	0.048	1.56 (0.87–2.82)	0.140	1.91 (1.26–2.91)	0.003	1.82 (1.18–2.82)	0.007
3rd	2.16 (1.24–3.79)	0.007	1.67 (0.94–2.96)	0.081	2.51 (1.66–3.81)	<0.001	2.34 (1.52–3.59)	<0.001
4th	4.29 (2.52–7.28)	<0.001	3.01 (1.74–5.23)	<0.001	5.30 (3.49–8.06)	<0.001	4.25 (2.74–6.59)	<0.001

Multivariate model was adjusted for age, smoking status, systolic blood pressure, fasting glucose, triglyceride, HDL-cholesterol, menopause, and hormone replace therapy. ALT = alanine aminotransferase, BMI = body mass index, NAFLD = nonalcoholic fatty liver disease, HDL = high-density lipoprotein, SAT = subcutaneous adipose tissue, US = ultrasonography, VAT = visceral adipose tissue, WC = waist circumference. VAT: 1st quartile, 0–51.28; 2nd quartile, 51.34–77.43; 3rd quartile, 77.45–110.21; 4th quartile, ≥110.23. SAT: 1st quartile, 0–128.38; 2nd quartile, 128.45–167.57; 3rd quartile, 167.70–213.87; 4th quartile, ≥213.91. WC: 1st quartile, 0–76.0; 2nd quartile, 76.1–81.0; 3rd quartile, 81.1–86.5; 4th quartile, ≥86.6. BMI: 1st quartile, 0–20.4; 2nd quartile, 20.5–22.1; 3rd quartile, 22.2–24.1; 4th quartile, ≥24.2.

* *P* value for the test of trends of odds.

TABLE 5. Multivariate Analysis for Risk of the Abdominal Adipose Tissue Areas for Elevated Serum ALT

	Men				Women			
	US-Normal (n = 1197)		US-NAFLD (n = 865)		US-Normal (n = 1330)		US-NAFLD (n = 320)	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
VAT area								
1st	1	0.035*	1	<0.001*	1	0.028*	1	<0.001*
2nd	1.56 (0.80–3.04)	0.193	1.84 (1.19–2.83)	0.006	1.16 (0.68–1.97)	0.588	1.07 (0.49–2.34)	0.868
3rd	2.23 (1.13–4.39)	0.020	1.88 (1.21–2.93)	0.005	1.36 (0.77–2.40)	0.296	3.75 (1.74–8.08)	0.001
4th	2.19 (1.07–4.47)	0.032	2.82 (1.79–4.44)	<0.001	1.90 (1.02–3.54)	0.042	4.44 (1.94–10.18)	<0.001
SAT area								
1st	1	0.001*	1	0.002*	1	0.903*	1	0.172*
2nd	0.77 (0.40–1.51)	0.446	1.11 (0.72–1.72)	0.629	1.28 (0.78–2.09)	0.331	2.72 (1.29–5.77)	0.009
3rd	1.64 (0.89–3.01)	0.115	1.68 (1.09–2.60)	0.018	1.24 (0.74–2.09)	0.761	2.21 (1.05–4.66)	0.037
4th	2.08 (1.11–3.89)	0.022	1.85 (1.19–2.89)	0.007	1.02 (0.59–1.77)	0.931	2.07 (0.98–4.39)	0.058

Multivariate model was adjusted for age, smoking status, systolic blood pressure, fasting glucose, triglyceride, HDL-cholesterol, menopause (women only), hormone replace therapy (women only), VAT, and SAT. ALT = alanine aminotransferase, CI = confidence interval, HDL = high-density lipoprotein, NAFLD = nonalcoholic fatty liver disease, OR = odds ratio, SAT = subcutaneous adipose tissue, US = ultrasonography, VAT = visceral adipose tissue. VAT: men – 1st quartile, 0–98.58; 2nd quartile, 98.83–132.05; 3rd quartile, 132.06–167.79; 4th quartile, ≥167.84; women – 1st quartile, 0–51.28; 2nd quartile, 51.34–77.43; 3rd quartile, 77.45–110.21; 4th quartile, ≥110.23. SAT: men – 1st quartile, 0–101.78; 2nd quartile, 101.97–129.89; 3rd quartile, 129.91–164.39; 4th quartile, ≥164.40; women – 1st quartile, 0–128.38; 2nd quartile, 128.45–167.57; 3rd quartile, 167.70–213.87; 4th quartile, ≥213.91.

* *P* value for the test of trends of odds.

TABLE 6. Risk of the Various Adipose Tissue Areas for Elevated Serum ALT (Including BMI)

	Men				Women			
	US-Normal (n = 1197)		US-NAFLD (n = 865)		US-Normal (n = 1330)		US-NAFLD (n = 320)	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
VAT area								
1st	1	0.079*	1	<0.001*	1	0.114*	1	<0.001*
2nd	1.56 (0.79–3.07)	0.200	1.79 (1.16–2.77)	0.009	1.09 (0.63–1.87)	0.765	0.96 (0.42–2.17)	0.913
3rd	2.14 (1.06–4.32)	0.034	1.67 (1.07–2.62)	0.025	1.22 (0.68–2.20)	0.508	3.29 (1.47–7.37)	0.004
4th	2.07 (0.98–4.36)	0.056	2.36 (1.48–3.76)	<0.001	1.61 (0.84–3.07)	0.149	3.70 (1.52–8.99)	0.004
SAT area								
1st	1	0.458*	1	0.696*	1	0.380*	1	0.554*
2nd	0.76 (0.39–1.51)	0.434	0.88 (0.56–1.39)	0.581	1.22 (0.74–2.00)	0.437	2.60 (1.20–5.66)	0.016
3rd	1.58 (0.83–3.01)	0.162	1.15 (0.72–1.86)	0.554	1.09 (0.63–1.87)	0.761	2.03 (0.90–4.54)	0.086
4th	1.86 (0.94–3.70)	0.075	1.01 (0.59–1.73)	0.963	0.81 (0.45–1.48)	0.498	1.57 (0.64–3.83)	0.324
BMI								
1st	1	0.384*	1	<0.001*	1	0.069*	1	0.192*
2nd	1.11 (0.59–2.11)	0.747	1.60 (1.01–2.53)	0.046	1.22 (0.73–2.04)	0.451	1.33 (0.58–3.01)	0.501
3rd	0.92 (0.47–1.78)	0.798	1.97 (1.21–3.21)	0.007	1.41 (0.81–2.46)	0.224	1.29 (0.53–3.14)	0.573
4th	1.34 (0.68–2.67)	0.401	3.17 (1.84–5.45)	<0.001	1.76 (0.95–3.26)	0.073	1.86 (0.68–5.14)	0.229

Multivariate model was adjusted for age, smoking status, systolic blood pressure, fasting glucose, triglyceride, HDL-cholesterol, menopause (women only), hormone replace therapy (women only), VAT, SAT, and BMI. ALT = alanine aminotransferase, BMI = body mass index, CI = confidence interval, HDL = high-density lipoprotein, NAFLD = nonalcoholic fatty liver disease, OR = odds ratio, US = ultrasonography, VAT = visceral adipose tissue, SAT = subcutaneous adipose tissue area. VAT: men – 1st quartile, 0–98.58; 2nd quartile, 98.83–132.05; 3rd quartile, 132.06–167.79; 4th quartile, ≥167.84; women – 1st quartile, 0–51.28; 2nd quartile, 51.34–77.43; 3rd quartile, 77.45–110.21; 4th quartile, ≥110.23. SAT: men – 1st quartile, 0–101.78; 2nd quartile, 101.97–129.89; 3rd quartile, 129.91–164.39; 4th quartile, ≥164.40; women – 1st quartile, 0–128.38; 2nd quartile, 128.45–167.57; 3rd quartile, 167.70–213.87; 4th quartile, ≥213.91. BMI: men – 1st quartile, 0–22.9; 2nd quartile, 23.0–24.5; 3rd quartile, 24.6–26.2; 4th quartile, ≥26.3; women – 1st quartile, 0–20.4; 2nd quartile, 20.5–22.1; 3rd quartile, 22.2–24.1; 4th quartile, ≥24.2.
* *P* value for the test of trends of odds.

resistance and the development of type 2 diabetes.[27,28] In accordance with previous studies, ALT elevations were significantly correlated with metabolic variables and insulin resistance in our study.

Adipocytes in the visceral fat promote the increased release of free fatty acids and the subsequent production of cytokines, such as adiponectin, interleukin-6, tumor necrosis factor-α, and leptin, and these adipocytokines flow directly into the liver because abdominal fat has a circulatory communication pathway to the liver via the portal vein.[29–31] In addition, these adipocytokines have been known to induce insulin resistance and enhance hepatic steatosis, and they may also induce nonalcoholic steatohepatitis.[32] Furthermore, visceral fat was directly associated with hepatic inflammation and fibrosis in a dose-dependent manner, independent of insulin resistance.[15]

A strength of our study is the relatively large sample size, which allowed for a high-powered analysis of associations. Moreover, the subjects in this study are representative of the healthy population due to the characteristics of a health checkup. Finally, an abdominal fat measurement by CT scan was performed on the same day that blood samples were collected, which allowed for the accurate evaluation of the association between visceral fat and ALT elevations.

However, there are limitations to our study. First, because of the cross-sectional design of this study, we could not identify the causal relationship between elevated ALT levels and visceral fat accumulation. Second, the method of hepatic ultrasonography used to diagnose NAFLD could not identify fatty infiltration below 30%.[33] Other blood parameters, as well as noninvasive methods such as magnetic resonance imaging or the controlled attenuation parameter, could be used to diagnose NAFLD. However, ultrasonography has the advantages of low cost, safety, satisfactory sensitivity, and specificity.[34] Therefore, hepatic ultrasonography is considered the first-line technique in clinical practice guidelines.[11,35] Third, the interpretation of the results is limited due to the lack of data on the serum levels of adiopocytokines. Finally, a single measurement of ALT levels could be influenced by acute liver injury with variable causes. However, we evaluated the presence of fatty liver with ultrasonography to overcome the limitation of a single ALT measurement.

In conclusion, we have demonstrated that the elevation of ALT was independently and dose-dependently associated with visceral fat accumulation in the healthy general population, especially in ultrasonographically diagnosed NAFLD patients. These findings emphasize the importance of visceral fat in the pathogenesis and inflammation of NAFLD.

REFERENCES

1. Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *N Engl J Med.* 2000;342:1266–1271.

2. Burns CJ, Boswell JM, Olsen GW. Liver enzyme activity and body mass index. *J Occup Environ Med.* 1996;38:1248–1252.

3. Sull JW, Yun JE, Lee SY, et al. Body mass index and serum aminotransferase levels in Korean men and women. *J Clin Gastroenterol.* 2009;43:869–875.

4. Kim J, Jo I. Relationship between body mass index and alanine aminotransferase concentration in non-diabetic Korean adults. *Eur J Clin Nutr.* 2010;64:169–175.
5. Ruhl CE, Everhart JE. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. *Gastroenterology.* 2003;124:71–79.
6. Stranges S, Dorn JM, Muti P, et al. Body fat distribution, relative weight, and liver enzyme levels: a population-based study. *Hepatology.* 2004;39:754–763.
7. Ruhl CE, Everhart JE. Trunk fat is associated with increased serum levels of alanine aminotransferase in the United States. *Gastroenterology.* 2010;138:1346–1356.
8. Song HR, Yun KE, Park HS. Relation between alanine aminotransferase concentrations and visceral fat accumulation among nondiabetic overweight Korean women. *Am J Clin Nutr.* 2008;88:16–21.
9. Mochizuki K, Miyauchi R, Misaki Y, et al. Accumulation of visceral fat is positively associated with serum ALT and gamma-GTP activities in healthy and preclinical middle-aged Japanese men. *J Nutr Sci Vitaminol (Tokyo).* 2011;57:65–73.
10. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther.* 2011;34:274–285.
11. The Korean Association for the Study of the Liver (KASL). KASL clinical practice guidelines: management of nonalcoholic fatty liver disease. *Clin Mol Hepatol.* 2013;19:325–348.
12. Jakobsen MU, Berentzen T, Sorensen TI, et al. Abdominal obesity and fatty liver. *Epidemiol Rev.* 2007;29:77–87.
13. Thomas EL, Hamilton G, Patel N, et al. Hepatic triglyceride content and its relation to body adiposity: a magnetic resonance imaging and proton magnetic resonance spectroscopy study. *Gut.* 2005;54:122–127.
14. Eguchi Y, Eguchi T, Mizuta T, et al. Visceral fat accumulation and insulin resistance are important factors in nonalcoholic fatty liver disease. *J Gastroenterol.* 2006;41:462–469.
15. van der Poorten D, Milner KL, Hui J, et al. Visceral fat: a key mediator of steatohepatitis in metabolic liver disease. *Hepatology.* 2008;48:449–457.
16. Yim JY, Kim D, Lim SH, et al. Sagittal abdominal diameter is a strong anthropometric measure of visceral adipose tissue in the Asian general population. *Diabetes Care.* 2010;33:2665–2670.
17. Kwak MS, Kim D, Chung GE, et al. Role of physical activity in nonalcoholic fatty liver disease in terms of visceral obesity and insulin resistance. *Liver Int.* 2015;35:944–952.
18. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998;97:1837–1847.
19. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia.* 1985;28:412–419.
20. Lee JK, Shim JH, Lee HC, et al. Estimation of the healthy upper limits for serum alanine aminotransferase in Asian populations with normal liver histology. *Hepatology.* 2010;51:1577–1583.
21. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486–2497.
22. Chung SJ, Kim D, Park MJ, et al. Metabolic syndrome and visceral obesity as risk factors for reflux oesophagitis: a cross-sectional case–control study of 7078 Koreans undergoing health check-ups. *Gut.* 2008;57:1360–1365.
23. Kim D, Choi SY, Park EH, et al. Nonalcoholic fatty liver disease is associated with coronary artery calcification. *Hepatology.* 2012;56:605–613.
24. Choi SY, Kim D, Kim HJ, et al. The relation between non-alcoholic fatty liver disease and the risk of coronary heart disease in Koreans. *Am J Gastroenterol.* 2009;104:1953–1960.
25. Park HS, Han JH, Choi KM, et al. Relation between elevated serum alanine aminotransferase and metabolic syndrome in Korean adolescents. *Am J Clin Nutr.* 2005;82:1046–1051.
26. Oh SY, Cho YK, Kang MS, et al. The association between increased alanine aminotransferase activity and metabolic factors in nonalcoholic fatty liver disease. *Metabolism.* 2006;55:1604–1609.
27. Vozarova B, Stefan N, Lindsay RS, et al. High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. *Diabetes.* 2002;51:1889–1895.
28. Hanley AJ, Wagenknecht LE, Festa A, et al. Alanine aminotransferase and directly measured insulin sensitivity in a multiethnic cohort: the Insulin Resistance Atherosclerosis Study. *Diabetes Care.* 2007;30:1819–1827.
29. Degrace P, Demizieux L, Du ZY, et al. Regulation of lipid flux between liver and adipose tissue during transient hepatic steatosis in carnitine-depleted rats. *J Biol Chem.* 2007;282:20816–20826.
30. Czaja MJ. Liver injury in the setting of steatosis: crosstalk between adipokine and cytokine. *Hepatology.* 2004;40:19–22.
31. Kern PA, Ranganathan S, Li C, et al. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. *Am J Physiol Endocrinol Metab.* 2001;280:E745–E751.
32. Hui JM, Hodge A, Farrell GC, et al. Beyond insulin resistance in NASH: TNF-alpha or adiponectin? *Hepatology.* 2004;40:46–54.
33. Sanyal AJ. AGA technical review on nonalcoholic fatty liver disease. *Gastroenterology.* 2002;123:1705–1725.
34. Saadeh S, Younossi ZM, Remer EM, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. *Gastroenterology.* 2002;123:745–750.
35. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. *Gastroenterology.* 2012;142:1592–1609.