Relationship of Liver Enzymes to Insulin Sensitivity and Intra-Abdominal Fat

TARA M. WALLACE, MD[1]
KRISTINA M. UTZSCHNEIDER, MD[1]
JENNY TONG, MD[1]
DARCY B. CARR, MD[2]
SAKENEH ZRAIKA, PHD[1]
DANIEL D. BANKSON, MD[3]
ROBERT H. KNOPP, MD[4]
STEVEN E. KAHN, MB, CHB[1]

OBJECTIVE — The purpose of this study was to determine the relationship between plasma liver enzyme concentrations, insulin sensitivity, and intra-abdominal fat (IAF) distribution.

RESEARCH DESIGN AND METHODS — Plasma γ-glutamyl transferase (GGT), aspartate transaminase (AST), alanine transaminase (ALT) levels, insulin sensitivity (insulin sensitivity index [S_I]), IAF area, and subcutaneous fat (SCF) area were measured in 177 nondiabetic subjects (75 men and 102 women, aged 31–75 years) with no history of liver disease. On the basis of BMI ($<$ or $\geq$27.5 kg/m^2) and S_I ($<$ or $\geq 7.0 \times 10^{-5}$ min/pmol) subjects were divided into lean insulin sensitive (LIS, $n = 53$), lean insulin resistant (LIR, $n = 60$), and obese insulin resistant (OIR, $n = 56$) groups.

RESULTS — Levels of all three liver enzymes were higher in men than in women ($P < 0.0001$ for each). In men, GGT levels were higher in insulin-resistant than in insulin-sensitive subjects ($P < 0.01$). In women, GGT levels were higher in the OIR than in the LIS group ($P < 0.01$) but no different in the LIR group. There was no difference in ALT and AST levels among the LIS, LIR, and OIR groups. GGT was associated with S_I ($r = -0.26$, $P < 0.0001$), IAF area ($r = 0.22$, $P < 0.01$), waist-to-hip ratio (WHR) ($r = 0.25$, $P = 0.001$), BMI ($r = 0.17$, $P < 0.05$), and SCF area ($r = 0.16$, $P < 0.05$) after adjustments for age and sex. In men, only S_I ($r = -0.29$, $P < 0.05$) remained independently correlated with GGT in multiple regression analysis. In women, IAF area ($r = 0.29$, $P < 0.01$) and WHR ($r = 0.29$, $P < 0.01$) were independently associated with GGT, but S_I was not.

CONCLUSIONS — In nondiabetic men GGT but not AST or ALT levels, are inversely related to insulin sensitivity independent of IAF area. However in women, GGT is related to measures of central body fat rather than to insulin sensitivity.

Diabetes Care 30:2673–2678, 2007

Relatively recently, the liver has been recognized as a major target of injury in patients with insulin resistance or the metabolic syndrome. Nonalcoholic fatty liver disease (NAFLD) is characterized by accumulation of hepatic fat in the absence of significant alcohol intake. In a proportion of patients, NAFLD may progress to nonalcoholic steatohepatitis (NASH), characterized by the presence of hepatic inflammation and hepatocellular damage, which may eventually progress to cirrhosis (1). The prevalence of NAFLD is about 20% and that of NASH is 2–3% in adults (2,3).

NAFLD is strongly associated with insulin resistance, dyslipidemia, obesity, and hypertension (4) and is probably the most common cause of abnormal liver function tests in diabetes (5). In nondiabetic subjects, elevated plasma liver enzyme levels are risk factors for the development of type 2 diabetes; however, γ-glutamyl transferase (GGT) may be a stronger predictor than aspartate transaminase (AST) or alanine transaminase (ALT) (6–8). Although GGT has been widely used as a marker of alcohol consumption, it has recently been found to be associated with an increased risk of development of type 2 diabetes independent of alcohol intake (9) as well as an increased risk of hypertension and cardiovascular mortality (10,11).

Because diabetes, dyslipidemia, hypertension, cardiovascular disease, and NAFLD have all been shown to be associated with central adiposity and insulin resistance (12), we hypothesized that differences in liver enzyme levels in healthy subjects are related in part to differences in fat distribution and insulin sensitivity. To test this hypothesis, we analyzed the relationship between liver enzymes, insulin sensitivity, and body fat distribution in a large cohort of apparently healthy normal subjects.

RESEARCH DESIGN AND METHODS

— The data presented are baseline measurements from 177 subjects (75 men and 102 women) from a study population of 234 subjects in whom data on insulin sensitivity, body fat distribution, and plasma liver enzyme concentrations were available. There were no significant differences in subject characteristics between all 234 subjects and the 177 who form the basis of the current analysis. The subjects, who had been recruited by advertisement to participate in a study of the effect of egg consumption on plasma lipids in people with various degrees of insulin sensitivity, were aged 31–75 years and were apparently healthy, had no history of diabetes, dyslipidemia, or uncontrolled hypertension, and had no known liver disease (13). Specific testing

From the [1]Department of Medicine, VA Puget Sound Health Care System, and University of Washington, Seattle, Washington; the [2]Department of Obstetrics and Gynecology, University of Washington, Seattle, Washington; the [3]Department of Pathology and Laboratory Medicine, VA Puget Sound Health Care System, and University of Washington, Seattle, Washington; and [4]Harborview Medical Center, University of Washington, Seattle, Washington.

Address correspondence and reprint requests to Steven E. Kahn, MB, ChB, VA Puget Sound Health Care System (151), 1660 S. Columbian Way, Seattle, WA 98108. E-mail: skahn@u.washington.edu.

Received for publication 18 August 2006 and accepted in revised form 29 June 2007.

Published ahead of print at http://care.diabetesjournals.org on 31 July 2007. DOI: 10.2337/dc06-1758.

T.M.W., K.M.U., and J.T. contributed equally to this work.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FSIGT, frequently sampled intravenous glucose tolerance test; GGT, γ-glutamyl transferase; IAF, intra-abdominal fat; IQR, interquartile range; LIR, lean insulin resistant; LIS, lean insulin sensitive; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OIR, obese insulin resistant; SCF, subcutaneous fat; S_I, insulin sensitivity index; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

for liver disease was not performed at the time of the study. Subjects with fasting plasma glucose ≥6.4 mmol/l (≥115 mg/dl), biochemical evidence of renal disease, uncontrolled thyroid disease, coronary or other vascular disease, or anemia were excluded, but formal oral glucose tolerance tests were not performed. The subjects were predominantly Caucasian: Caucasian ($n = 161$), Asian ($n = 5$), African American ($n = 7$), Native American ($n = 2$), and Hispanic ($n = 2$). The study was approved by the Human Subjects Review Committee of the University of Washington, and subjects provided written informed consent.

Subjects were divided a priori into three groups on the basis of BMI and insulin sensitivity index (S_I) to analyze the relationship between liver enzyme concentrations, obesity, and insulin sensitivity. These three groups were lean insulin sensitive (LIS) (BMI <27.5 kg/m^2 and $S_I \geq 7.0 \times 10^{-5}$ min/[pmol/l]), lean insulin resistant (LIR) (BMI <27.5 kg/m^2 and $S_I < 7.0 \times 10^{-5}$ min/[pmol/l]), and obese insulin resistant (OIR) (BMI ≥27.5 kg/m^2 and $S_I < 7.0 \times 10^{-5}$ min/[pmol/l]). The cutoff of 27.5 kg/m^2 was based on the criteria in place before the more recent definition of the criteria for overweight and obesity. The cutoff of 7.0×10^{-5} min/(pmol/l) for S_I represents the highest value for this parameter among a group of apparently healthy obese subjects studied in Seattle (14). Obese insulin-sensitive subjects were excluded from this analysis because of their small number ($n = 8$).

Measures of anthropometry and body fat distribution

The averages of two weight and height measurements were used to calculate BMI as weight in kilograms divided by the square of height in meters. Waist and hip circumferences were calculated as the average of two measurements. Waist circumference was measured at the smallest circumference of the waist, and hip circumference was measured at the widest level of the buttocks, using a previously described protocol (*National Health and Nutrition Examination Survey III Anthropometric Measurements.* Videotape, National Center for Health Statistics).

A computed tomography scan of the abdomen was performed at the level of the umbilicus to quantify subcutaneous fat (SCF) area and intra-abdominal fat (IAF) area as described previously (15). Fat area was computed as the area with an attenuation range of −250 to −50 Hounsfield units. IAF and SCF areas were quantified by delineating the border of the peritoneal cavity. These measurements were performed by a single observer using standard GE 8800 computer software. The variability of these measures made by a single observer was 1.5% (15).

Fasting plasma and insulin sensitivity measurements

Subjects underwent a tolbutamide-modified, frequently sampled intravenous glucose tolerance test (FSIGT) to quantify insulin sensitivity as the S_I using Bergman's minimal model of glucose kinetics (16). Three basal blood samples were drawn at 15, 5, and 1 min before the intravenous administration of glucose at time 0. Glucose (11.4 g/m^2 body surface area) was infused over 1 min, and tolbutamide (125 mg/m^2 body surface area) was injected intravenously over 30 s at time 20 min. Blood samples were taken at 32 time points over 240 min after commencement of the glucose injection. Fasting glucose and insulin concentrations were calculated as the average of the three basal samples. Liver function tests were performed on the 3-min sample obtained during the FSIGT.

Alcohol intake

Alcohol intake was assessed using a standardized questionnaire and quantified as self-reported number of drinks per week.

Assays

Glucose was measured in duplicate using the glucose oxidase method. Immunoreactive insulin was measured in duplicate by radioimmunoassay using a modification of the double antibody technique. Samples for liver enzymes were assayed between 5 and 7 years after sampling. GGT was measured using an enzymatic colorimetric method (Modular P; Roche Diagnostics, Indianapolis, IN). AST and ALT were measured using the standardized kinetic method (Modular P). Samples were stored at −70°C before assay.

Calculations and statistics

Statistical analyses were performed using SPSS 12.0 (SPSS, Chicago, IL). For regression analysis, dependent variables were logarithmically transformed where appropriate to satisfy the statistical assumptions of linear regression. Multiple regression analysis was used to determine whether associations between the dependent (liver transaminase levels) and independent variables of interest remained significant after adjustments for other potentially confounding independent variables. Model 1 contained S_I, IAF area, BMI, and age for each sex. Model 2 contained S_I, WHR, BMI, and age for each sex. Comparisons between groups were assessed by ANOVA with Tukey post hoc analysis, Kruskal-Wallis test, *t* test, or Mann-Whitney *U* test as appropriate. Data are presented as means ± SD unless specified. Non-normally distributed data with kurtosis were log transformed before parametric statistical tests were applied. $P < 0.05$ was considered significant.

RESULTS

Demographic, anthropometric, and metabolic characteristics

Characteristics for all subjects are shown in Table 1 ($n = 177$) and subdivided into LIS ($n = 53$), LIR ($n = 60$), and OIR ($n = 56$) subjects and into men ($n = 75$) and women ($n = 102$). In this apparently healthy group of nondiabetic subjects, 66% were insulin resistant (defined as $S_I < 7.0 \times 10^{-5}$ min/[pmol/l]) and 32% were obese (defined as BMI >27.5 kg/m^2). In accordance with the a priori classification, the BMI of the obese group was significantly higher than that of both of the lean groups ($P < 0.0001$) (Table 1). S_I values were 2.3- and 2.8-fold higher in the LIS group than in the LIR and OIR groups, respectively ($P \leq 0.0001$). The mean age of the LIS subjects was slightly lower than that of the insulin-resistant subjects.

LIR subjects were more centrally obese than LIS subjects, as evidenced by higher WHR ($P = 0.009$) and IAF area ($P < 0.0001$), despite a similar BMI in the two groups. LIR subjects were significantly less centrally obese (WHR $P = 0.0005$; IAF area $P < 0.0001$) and more insulin sensitive ($P = 0.0001$) than OIR subjects.

As listed in Table 1, fasting glycemia increased with increasing obesity and insulin resistance (LIS vs. LIR and LIR vs. OIR, $P < 0.03$; LIS vs. OIR, $P < 0.0001$), and a similar pattern was seen for triglycerides (LIS vs. LIR $P < 0.006$; LIR vs. OIR, $P < 0.05$; LIS vs. OIR, $P < 0.0001$). Systolic blood pressure was significantly higher in OIR subjects than in LIR and LIS subjects. There was no significant difference in alcohol intake, reported as median number of drinks per week (interquartile range [IQR]) between groups.

Table 1—*Demographics and clinical variables in all subjects, LIS, LIR, OIR, men, and women*

	All	LIS	LIR	OIR	Men	Women
n	177	53	60	56	75	102
Age (years)	52.3 ± 9.9	49.6 ± 8.0	53.8 ± 11.4*	53.2 ±9.6	52.6 ± 10.2	52.0 ± 9.8
Sex (male/female)	75/102	18/35	27/33	25/31	—	—
BMI (kg/m^2)	26.4 ± 4.3	23.4 ± 2.3	24.3 ± 1.8	31.0 ± 3.4*†	26.8 ± 3.5	26.2 ± 4.8
Waist circumference (cm)	87.2 ± 13.2	77.9 ± 8.5	83.7 ± 9.2*	99.3 ± 11.1*†	94.9 ± 10.6‡	81.9 ± 12.2
WHR	0.84 ± 0.09	0.80 ± 0.08	0.83 ± 0.09*	0.89 ± 0.08*†	0.92 ± 0.06‡	0.78 ± 0.06
SCF area (cm^2)	195.8 (135.6)	125.7 (102.7)	179.6 (114.1)*	299.1 (164.1)*†	166.9 (117.3)§	225.9 (162.9)
IAF area (cm^2)	88.4 (84.9)	43.3 (36.4)	76.8 (69.3)*	140.6 (57.9)*†	113.8 (86.9)‡	71.9 (79.1)
Systolic blood pressure (mmHg)	118 ± 12	114 ± 10	117 ± 10	123 ± 12*†	120 ± 11¶	117 ± 12
S_I ($\times 10^{-5}$ min^{-1}/[pmol/l])	5.65 (4.61)	9.35 (3.94)	5.04 (2.54)*	3.59 (2.10)*†	4.93 (4.88)	6.03 (4.18)
Fasting plasma glucose (mmol/l)	5.4 ± 0.4	5.3 ± 0.4	5.4 ± 0.4*	5.6 ± 0.5*†	5.6 ± 0.4‡	5.3 ± 0.4
Triglycerides (mmol/l)	1.4 (0.79)	0.99 (0.72)	1.4 (0.5)*	1.6 (0.75)*†	1.4 (0.82)	1.3 (0.75)
HDL cholesterol (mmol/l)	1.4 ± 0.4	1.5 ± 0.4	1.3 ± 0.4*	1.2 ± 0.4*	1.2 ± 0.3‡	1.5 ± 0.4
Alcohol intake (drinks/week)	1.0 (3.0)	1.0 (2.0)	1.0 (4.0)	1.5 (4.0)	2.0 (7.0)#	1.0 (2.0)

Data are means ± SD or median (IQR). Normal ranges: GGT <51 IU/l, ALT <40 IU/l, and AST <38 IU/l. LIS vs. LIR vs. OIR: ANOVA *$P < 0.05$ vs. LIS; †$P < 0.05$ vs. LIR (eight OIR subjects were excluded from this analysis because of the small number). Men vs. women: *t* test ‡$P < 0.0001$, §$P < 0.005$, ¶$P < 0.05$; Mann Whitney *U* test #$P < 0.05$.

Effect of sex on liver enzymes

There was no sex-based difference in age or BMI (Table 1). As expected, men had higher WHR ($P < 0.0001$) and IAF area ($P < 0.001$) than women, whereas women had more SCF area ($P < 0.005$) than men (Table 1). Fasting glucose was higher in men ($P < 0.001$), but S_I did not differ between men and women ($P = 0.1$) (Table 1). All liver transferase levels, reported as median (IQR) were significantly higher in men compared with women: GGT 17 (14) vs. 10 (6) IU/l, ALT 16 (10) vs. 11 (6) IU/l, and AST 21 (7) vs. 17.5 (5) IU/l ($P < 0.0001$ for each).

Effect of obesity and insulin sensitivity on liver enzymes

Because transaminase levels were significantly higher in men than in women, the effect of obesity and insulin sensitivity on transaminase levels was analyzed separately for each sex. In men, GGT levels were significantly higher in insulin-resistant subjects (LIR and OIR) compared with LIS subjects (Fig. 1*A*). GGT levels did not differ between LIR and OIR subjects ($P = 0.6$). In women, GGT levels were also significantly higher in the OIR group than in the LIS group and tended to be higher in the LIR than in the LIS group ($P = 0.09$) (Fig. 1*A*). ALT and AST levels did not differ significantly among the LIS, LIR, and OIR groups in either men or women (Figs. 1*B* and *C*).

Relationship between liver enzymes, body anthropometrics, insulin sensitivity, and sex

GGT was negatively associated with S_I and positively associated with IAF area, SCF area, WHR, and BMI (Table 2) after adjustment for age and sex. Waist circumference and alcohol consumption were not associated with GGT levels. ALT and AST were not associated with any of the variables and were thus not included in the multiple regression models.

Multiple linear regression analyses stratified by sex were performed with GGT as the dependent variable. In men, only S_I remained significantly associated with GGT levels independent of IAF area and WHR (models 1 and 2 in Table 3), age, and BMI. In contrast, in women, IAF area and WHR (models 1 and 2 in table 3) were significantly associated with GGT levels, but S_I was not.

CONCLUSIONS — We examined the relationship between body fat distribution, insulin sensitivity, and liver enzymes in a cohort of 177 nondiabetic subjects of whom >97% had GGT levels within the normal range. It is well recognized that body fat distribution and insulin sensitivity are associated (17,18), and in this cohort of apparently healthy individuals, we found that GGT was negatively associated with insulin sensitivity in men, whereas in women GGT was associated with central obesity. In common with other studies (19), we found that men had higher GGT levels and increased central adiposity than women, and these differences may explain the different results in men and women. ALT and AST were not associated with insulin sensitivity or body fat measures in our study.

The association between elevated liver transaminase levels and insulin resistance in the context of NAFLD is well established (20). In the Tübingen Family Study, GGT was associated with insulin sensitivity and glucose tolerance in both men and women. In addition, in this same study GGT was positively correlated with hepatic lipid content measured by magnetic resonance spectroscopy (21). ALT has previously been shown to be inversely related to insulin sensitivity, determined by the euglycemic clamp, and it has also been shown to have this same relationship with endothelial function in subjects with type 2 diabetes (22). Recently, the role of liver transaminases in predicting the development of type 2 diabetes has been examined in two large studies. In a study of 906 subjects, Hanley et al. (6) found that ALT and, to a lesser extent, AST were associated with the development of diabetes; however, they did not examine whether GGT predicted the development of hyperglycemia. In another study of 5,974 nondiabetic subjects, Sattar et al. (23) found that ALT levels within the normal range predicted incident diabetes. In the Mexico City Diabetes Study, GGT was shown to be an independent risk factor for the development of impaired glucose tolerance and diabetes (24), whereas Vozarova et al. (25) found that only ALT predicted progression to diabetes in Pima Indians.

Although GGT has been widely used as a marker of alcohol consumption, Lee et al. (9) have shown that GGT levels are also associated with an increased risk of development of type 2 diabetes independent of alcohol intake. In another study of >4,000 subjects, although an association

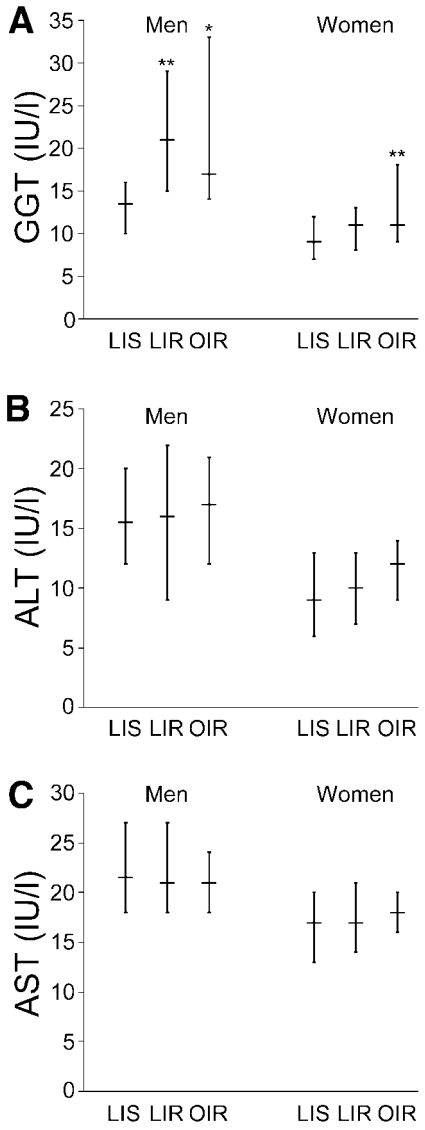

Figure 1—*GGT* (A)*, ALT* (B)*, and AST* (C) *levels in men* (left) *(LIS,* n = *18; LIR,* n = *27; and OIR,* n = *25) and women* (right) *(LIS,* n = *35; LIR,* n = *33; and OIR,* n = *31). Data are median (IQR).* *P < *0.05 vs. LIS;* **P < *0.01 vs. LIS.*

between the incidence of diabetes and ALT levels was found, this was most strongly observed in the abnormal range of ALT and was weaker than the association with GGT levels (26). Others have found a strong, independent, and graded association between GGT levels and type 2 diabetes but not ALT or AST levels (7,8,27). However, to our knowledge, no previous study has examined the relationship between GGT, IAF area, and insulin sensitivity in nondiabetic subjects.

The recent emergence of the potential protective role of GGT against oxidative stress may explain the inverse association between GGT levels and insulin sensitivity we found here. The basis of the proposed link between GGT and oxidative stress is that glutathione is a major intracellular defense against free radicals and peroxides. However, as intact glutathione cannot be taken up by cells, the intracellular synthesis of glutathione depends on the metabolism of extracellular glutathione by GGT to release cysteine, which is then transported into the cell and used as a substrate for the de novo intracellular synthesis of glutathione (28). In vitro studies have demonstrated a protective effect of GGT against oxidative stress and cell death (29). Thus, increased GGT expression may initially represent an adaptive protective response to persistent oxidative stress. This would be consistent with the recent in vivo finding of a positive association between GGT and C-reactive protein levels (30). GGT levels have also been shown to predict future levels of inflammatory markers including C-reactive protein, fibrinogen, and F2-isoprostanes (a biomarker of lipid peroxidation) (10).

Yki-Jarvinen's group has shown that fatty liver is associated with fasting insulin as a surrogate measure of insulin sensitivity independently of IAF and SCF areas. In their study ALT was more strongly correlated with liver fat than GGT (31). We found that in men, GGT but not ALT or AST was associated with insulin sensitivity independently of body fat measures. As we quantified insulin sensitivity directly, we believe that our data raise the possibility that GGT may be a more sensitive marker of the liver's response to insulin sensitivity than ALT and AST. The finding that, even across the normal range, GGT levels are related to insulin sensitivity is of clinical relevance in the light of the emerging possible therapeutic role of the peroxisome proliferator–activated receptor-γ agonists in the treatment of NASH. Promrat et al. (32) demonstrated an improvement in transaminases and amelioration of insulin resistance in subjects with NASH after 48 weeks of treatment with pioglitazone. Lifestyle changes with weight loss and increased exercise have also been shown to improve liver enzymes and histological findings in subjects with NAFLD (4). Our data raise the possibility that increasing GGT levels (even within the normal range) in the context of insulin resistance may be an indication for lifestyle changes with the aim of weight loss or treatment with peroxisome proliferator–activated receptor-γ agonists.

The advantages of our analysis are that we examined a large number of subjects in whom insulin sensitivity had been determined by the FSIGT, and all of whom had fat distribution measured using computed tomography scans. However, the lack of any direct measure of hepatic fat is a drawback. Another potential limitation is that because alcohol intake was assessed by self-reported questionnaire, consumption may have been underestimated. Although liver en-

Table 2—*Linear regression analyses for liver transferases adjusted for age and sex*

	GGT		ALT		AST	
	r	*P*	*r*	*P*	*r*	*P*
S_I	**−0.26**	**<0.0001**	−0.07	0.326	0.02	0.754
IAF area	**0.22**	**0.003**	0.12	0.127	0.02	0.844
WHR	**0.25**	**0.001**	0.15	0.054	0.08	0.292
BMI	**0.17**	**0.027**	0.14	0.066	0.02	0.766
SCF area	**0.16**	**0.036**	0.10	0.192	0.01	0.916
Waist circumference	0.04	0.569	0.07	0.403	0.05	0.501
Alcohol consumption	0.09	0.220	−0.03	0.688	-0.12	0.118

Data in bold are significant.

Table 3—*Multiple regression models with GGT as the dependent variable*

	Men		Women	
	Partial *r*	*P*	Partial *r*	*P*
Model 1				
S_I	**−0.29**	**0.014**	−0.08	0.449
IAF area	−0.15	0.206	**0.29**	**0.004**
BMI	0.15	0.210	−0.15	0.137
Age	0.01	0.921	−0.01	0.955
Model 2				
S_I	**−0.32**	**0.010**	−0.15	0.162
WHR	0.06	0.647	**0.29**	**0.005**
BMI	−0.06	0.660	−0.13	0.198
Age	−0.02	0.896	0.02	0.821

Data in bold are significant.

zyme measurements were made on a sample taken just after glucose administration, we doubt this affected our findings, as nutrient intake has been shown not to affect liver enzyme levels (33). The transferase levels were uniformly lower than would be expected in a normal population, which may be due to the fact that transaminase levels tend to decrease slightly (about 8%) with time, even when stored at −80°C (34,35). However, all samples were handled in the same manner. Although the absolute levels may have been affected, all samples should have been affected to the same degree, and therefore it is likely that although the absolute values may be lower, relative differences would have been robust and maintained.

In summary, GGT but not ALT or AST levels are inversely related to insulin sensitivity independently of central obesity in nondiabetic men. In contrast, in women GGT levels were positively associated with IAF area and WHR but were not associated with insulin sensitivity. If GGT is a marker of hepatic fat accumulation, this sex difference suggests that body fat distribution may be a more important player in the development of hepatic steatosis in women than in men. This finding suggests that GGT is a more sensitive marker of insulin resistance, at least in men, but whether this liver enzyme will prove useful to guide treatment decisions related to insulin resistance awaits further research.

Acknowledgments— This work was supported by the Medical Research Service of the Veterans Affairs; the American Egg Board; National Institutes of Health Grants DK-02654, DK-17047, DK-35747, DK-35816, HL-30086, HL-07028, RR-37, and RR-16066; the U.S. Department of Agriculture; the McMillen Family Trust; and an American Diabetes Association Distinguished Clinical Scientist Award to S.E.K.

We thank the subjects, Diane Collins, and the nursing staff of the General Clinical Research Center at University of Washington.

References

1. Browning JD, Horton JD: Molecular mediators of hepatic steatosis and liver injury. *J Clin Invest* 114:147–152, 2004
2. Hilden M, Christoffersen P, Juhl E, Dalgaard JB: Liver histology in a 'normal' population—examinations of 503 consecutive fatal traffic casualties. *Scand J Gastroenterol* 12:593–597, 1977
3. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH: Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 40:1387–1395, 2004
4. Utzschneider KM, Kahn SE: Review: The role of insulin resistance in nonalcoholic fatty liver disease. *J Clin Endocrinol Metab* 91:4753–4761, 2006
5. Daniel S, Ben-Menachem T, Vasudevan G, Ma CK, Blumenkehl M: Prospective evaluation of unexplained chronic liver transaminase abnormalities in asymptomatic and symptomatic patients. *Am J Gastroenterol* 94:3010–3014, 1999
6. Hanley AJ, Williams K, Festa A, Wagenknecht LE, D'Agostino RB Jr, Kempf J, Zinman B, Haffner SM: Elevations in markers of liver injury and risk of type 2 diabetes: the Insulin Resistance Atherosclerosis Study. *Diabetes* 53:2623–2632, 2004
7. Perry IJ, Wannamethee SG, Shaper AG: Prospective study of serum γ-glutamyltransferase and risk of NIDDM. *Diabetes Care* 21:732–737, 1998
8. Nakanishi N, Nishina K, Li W, Sato M, Suzuki K, Tatara K: Serum γ-glutamyltransferase and development of impaired fasting glucose or type 2 diabetes in middle-aged Japanese men. *J Intern Med* 254: 287–295, 2003
9. Lee DH, Silventoinen K, Jacobs DR Jr, Jousilahti P, Tuomileto J: γ-Glutamyltransferase, obesity, and the risk of type 2 diabetes: observational cohort study among 20,158 middle-aged men and women. *J Clin Endocrinol Metab* 89:5410–5414, 2004
10. Lee DH, Jacobs DR Jr, Gross M, Kiefe CI, Roseman J, Lewis CE, Steffes M: γ-Glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Clin Chem* 49:1358–1366, 2003
11. Wannamethee G, Ebrahim S, Shaper AG: γ-Glutamyltransferase: determinants and association with mortality from ischemic heart disease and all causes. *Am J Epidemiol* 142:699–708, 1995
12. Kissebah AH: Intra-abdominal fat: is it a major factor in developing diabetes and coronary artery disease? *Diabetes Res Clin Pract* 30:25–30, 1996
13. Knopp RH, Retzlaff B, Fish B, Walden C, Wallick S, Anderson M, Aikawa K, Kahn SE: Effects of insulin resistance and obesity on lipoproteins and sensitivity to egg feeding. *Arterioscler Thromb Vasc Biol* 23: 1437–1443, 2003
14. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP, Porte D Jr: Quantification of the relationship between insulin sensitivity and β-cell function in human subjects: evidence for a hyperbolic function. *Diabetes* 42:1663–1672, 1993
15. Shuman WP, Morris LL, Leonetti DL, Wahl PW, Moceri VM, Moss AA, Fujimoto WY: Abnormal body fat distribution detected by computed tomography in diabetic men. *Invest Radiol* 21:483–487, 1986
16. Bergman R, Ider Y, Bowden C, Cobelli C: Quantitative estimation of insulin sensitivity. *Am J Physiol* 236:E667–E677, 1979
17. Cnop M, Landchild MJ, Vidal J, Havel PJ, Knowles NG, Carr DR, Wang F, Hull RL, Boyko EJ, Retzlaff BM, Walden CE, Knopp RH, Kahn SE: The concurrent accumulation of intra-abdominal and subcutaneous fat explains the association between insulin resistance and plasma leptin concentrations : distinct metabolic effects of two fat compartments. *Diabetes* 51:1005–1015, 2002
18. Despres JP, Lemieux I: Abdominal obesity and metabolic syndrome. *Nature* 444:881–887, 2006
19. Nilssen O, Forde OH, Brenn T: The Tromso Study: distribution and population determinants of γ-glutamyltransferase. *Am J Epidemiol* 132:318–326, 1990
20. Machado M, Cortez-Pinto H: Non-alcoholic fatty liver disease and insulin resistance. *Eur J Gastroenterol Hepatol* 17:823–826, 2005
21. Thamer C, Tschritter O, Haap M, Shirkavand F, Machann J, Fritsche A, Schick F, Haring H, Stumvoll M: Elevated serum GGT concentrations predict reduced insulin sensitivity and increased intrahepatic lipids. *Horm Metab Res* 37:246–251, 2005
22. Schindhelm RK, Diamant M, Bakker SJ, van Dijk RA, Scheffer PG, Teerlink T, Kostense PJ, Heine RJ: Liver alanine aminotransferase, insulin resistance and endothelial dysfunction in normotriglyceridaemic subjects with type 2 diabetes mellitus. *Eur J Clin Invest* 35:369–374, 2005
23. Sattar N, Scherbakova O, Ford I, O'Reilly DS, Stanley A, Forrest E, Macfarlane PW, Packard CJ, Cobbe SM, Shepherd J: Elevated alanine aminotransferase predicts new-onset type 2 diabetes independently of classical risk factors, metabolic syndrome, and C-reactive protein in the West of Scotland Coronary Prevention Study. *Diabetes* 53:2855–2860, 2004
24. Nannipieri M, Gonzales C, Baldi S, Posadas R, Williams K, Haffner SM, Stern MP, Ferrannini E: Liver enzymes, the metabolic syndrome, and incident diabetes: the Mexico City Diabetes Study. *Diabetes Care* 28:1757–1762, 2005
25. Vozarova B, Stefan N, Lindsay RS, Saremi A, Pratley RE, Bogardus C, Tataranni PA: High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. *Diabetes* 51:1889–1895, 2002

26. Lee DH, Ha MH, Kim JH, Christiani DC, Gross MD, Steffes M, Blomhoff R, Jacobs DR Jr: γ-Glutamyltransferase and diabetes—a 4 year follow-up study. *Diabetologia* 46:359–364, 2003
27. Andre P, Balkau B, Born C, Royer B, Wilpart E, Charles MA, Eschwege E: Hepatic markers and development of type 2 diabetes in middle aged men and women: a three-year follow-up study: the D.E.S.I.R. Study (Data from an Epidemiological Study on the Insulin Resistance Syndrome). *Diabetes Metab* 31:542–550, 2005
28. Pastore A, Federici G, Bertini E, Piemonte F: Analysis of glutathione: implication in redox and detoxification. *Clin Chim Acta* 333:19–39, 2003
29. Karp DR, Shimooku K, Lipsky PE: Expression of γ-glutamyl transpeptidase protects Ramos B cells from oxidation-induced cell death. *J Biol Chem* 276:3798–3804, 2001
30. Lee DH, Jacobs DR Jr: Association between serum γ-glutamyltransferase and C-reactive protein. *Atherosclerosis* 178: 327–330, 2005
31. Westerbacka J, Corner A, Tiikkainen M, Tamminen M, Vehkavaara S, Hakkinen AM, Fredriksson J, Yki-Jarvinen H: Women and men have similar amounts of liver and intra-abdominal fat, despite more subcutaneous fat in women: implications for sex differences in markers of cardiovascular risk. *Diabetologia* 47: 1360–1369, 2004
32. Promrat K, Lutchman G, Uwaifo GI, Freedman RJ, Soza A, Heller T, Doo E, Ghany M, Premkumar A, Park Y, Liang TJ, Yanovski JA, Kleiner DE, Hoofnagle JH: A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. *Hepatology* 39:188–196, 2004
33. Siest G, Schiele F, Galteau MM, Panek E, Steinmetz J, Fagnani F, Gueguen R: Aspartate aminotransferase and alanine aminotransferase activities in plasma: statistical distributions, individual variations, and reference values. *Clin Chem* 21:1077–1087, 1975
34. Williams KM, Williams AE, Kline LM, Dodd RY: Stability of serum alanine aminotransferase activity. *Transfusion* 27:431–433, 1987
35. Clark JM, Brancati FL, Diehl AM: The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol* 98:960–967, 2003