

# Liver Enzymes, the Metabolic Syndrome, and Incident Diabetes

## The Mexico City Diabetes Study

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**OBJECTIVE** — To test the hypothesis that enzymes conventionally associated with liver dysfunction (aspartate aminotransferase, alanine aminotransferase,  $\gamma$ -glutamyltransferase [GGT], and alkaline phosphatase) may predict diabetes.

**RESEARCH DESIGN AND METHODS** — From a population-based diabetes survey, we selected 1,441 men and women in whom serum enzyme levels were  $\leq 3$  SDs of the mean population value, alcohol intake was  $< 250$  g/week, and hepatitis B and C virus testing was negative. At follow-up (7 years), 94 subjects developed diabetes and 93 impaired glucose tolerance (IGT).

**RESULTS** — At baseline, all four enzymes were related to most of the features of the metabolic syndrome. After controlling for sex, age, adiposity/fat distribution, alcohol intake, serum lipids, and blood pressure, higher alanine aminotransferase and GGT values were significantly ( $P < 0.01$ ) associated with both IGT and diabetes, whereas alkaline phosphatase was associated with diabetes only ( $P = 0.0004$ ) and aspartate aminotransferase with IGT only ( $P = 0.0001$ ). Raised GGT alone was associated with all the features of the metabolic syndrome. Raised GGT was a significant predictor of either IGT or diabetes (odds ratio 1.62 [95% CI 1.08–2.42] top quartile vs. lower quartiles,  $P < 0.02$ ) after controlling for sex, age, adiposity/fat distribution, alcohol consumption, fasting plasma insulin and proinsulin levels, and 2-h postglucose plasma glucose concentrations.

**CONCLUSIONS** — Although mild elevations in liver enzymes are associated with features of the metabolic syndrome, only raised GGT is an independent predictor of deterioration of glucose tolerance to IGT or diabetes. As GGT signals oxidative stress, the association with diabetes may reflect both hepatic steatosis and enhanced oxidative stress.

*Diabetes Care* 28:1757–1762, 2005

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Received for publication 23 September 2004 and accepted in revised form 14 April 2005.

**Abbreviations:** ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT,  $\gamma$ -glutamyltransferase; NAFLD, nonalcoholic fatty liver disease; NGT, normal glucose tolerance.

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

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A syndrome characterized by liver steatosis, lobular hepatitis, and chronically elevated serum alanine aminotransferase (ALT) concentrations—termed nonalcoholic fatty liver disease (NAFLD), or nonalcoholic steatohepatitis (NASH), depending on the degree of parenchymal inflammation—has been identified in patients with negligible alcohol intake (1,2). These patients are often obese and dyslipidemic (3–6). In cross-sectional studies, NAFLD is associated with insulin resistance irrespective of BMI, fat distribution, and glucose tolerance (1,7,8). On these grounds, it has been suggested that hyperinsulinemia and insulin resistance may play a role in the pathogenesis of NAFLD (1) and that NAFLD is a feature of the metabolic syndrome (9).

In a prospective study in Pima Indians, serum ALT concentrations were related to both hepatic insulin resistance and later decline in hepatic insulin sensitivity (10). In contrast, aspartate aminotransferase (AST) and  $\gamma$ -glutamyltransferase (GGT) concentrations were unrelated to changes in hepatic insulin action (10). Based on previous findings (1,2), Vozarova et al. (10) suggested that a raised ALT reflects fatty changes in the liver and that this abnormality antedates the development of type 2 diabetes.

Although GGT is a less specific marker of liver function, higher GGT levels have also been linked with obesity, physical inactivity, hypertension, dyslipidemia, and hyperinsulinemia, implying that elevated GGT belongs in the cluster of the metabolic syndrome (11–17). More recently, a prospective cohort study of nondiabetic men found that serum GGT, but not AST or alkaline phosphatase (ALP), levels were an independent predictor of incident type 2 diabetes (17). Information on the association of liver enzymes with prevalent or incident IGT is lacking.

In the present study, we determined the pattern of association of all four enzymes (AST, ALT, ALP, and GGT) with

Table 1—Baseline clinical and metabolic characteristics by glucose tolerance status

	NGT	IGT	Type 2 diabetes
n	1,080	153	208
Sex (M/F)	439/641	50/103	70/138
Age (years)	46 ± 8	48 ± 8*	52 ± 8†
BMI (kg/m <sup>2</sup> )	27.7 ± 4.1	29.4 ± 4.2*	28.6 ± 4.5*
Waist circumference (cm)	96 ± 12	99 ± 11*	100 ± 14†
Systolic blood pressure (mmHg)	115 ± 16	123 ± 18*	126 ± 23*
Diastolic blood pressure (mmHg)	72 ± 10	75 ± 11*	75 ± 10*
Alcohol consumption (g/week)	18 ± 41	13 ± 35	8 ± 29†
Triglycerides (mmol/l)	1.90 (1.30)	2.38 (1.79)*	2.44 (1.77)*
Total cholesterol (mmol/l)	4.89 ± 1.11	5.21 ± 1.18*	5.37 ± 1.24*
HDL cholesterol (mmol/l)	0.87 ± 0.24	0.85 ± 0.24	0.87 ± 0.24
Fasting glucose (mmol/l)	4.6 ± 0.6	5.2 ± 0.7*	10.2 ± 4.7†
2-h glucose (mmol/l)	5.3 ± 1.3	8.9 ± 0.9*	15.0 ± 5.8†
Fasting insulin (pmol/l)	66 (54)	89 (69)*	95 (110)†
2-h insulin (pmol/l)	360 (395)	810 (624)*	520 (732)†
Fasting proinsulin (pmol/l)	7.8 (6.0)	12.1 (11.4)*	19.5 (22.9)†

Data are means ± SD or, for non-normally distributed variables, median (interquartile range). \* $P < 0.05$  or less for IGT or type 2 diabetes vs. NGT; † $P < 0.05$  or less for type 2 diabetes vs. IGT or NGT by Bonferroni-Dunn test.

the features of the metabolic syndrome in a population-based study of type 2 diabetes and cardiovascular risk factors. In addition, using data from a follow-up examination in this population, we examined the ability of liver enzymes to predict either IGT or type 2 diabetes (or both) over 7 years.

## RESEARCH DESIGN AND METHODS

Data were collected as part of the Mexico City Diabetes Study (18), a population-based survey of diabetes and cardiovascular risk factors. Among the 15,532 inhabitants of low-income neighborhoods, 3,505 eligible individuals (35- to 64-year-old men and nonpregnant women) were identified. Of these, 2,278 subjects completed baseline medical examinations at the clinic. In 1997, a follow-up examination was begun. IGT and type 2 diabetes were classified at baseline and follow-up according to American Diabetes Association criteria (19). Subjects who gave a history of diabetes and who at the time of their clinical examination were taking either insulin or oral antidiabetic agents were also considered to have type 2 diabetes regardless of their plasma glucose values. Diabetic subjects who were not taking insulin were considered to have type 2 diabetes; insulin-taking diabetic subjects whose age of onset was  $\geq 40$  years or whose BMI was  $> 30$  kg/m<sup>2</sup> were also considered to have

type 2 diabetes. The remaining insulin-taking diabetic subjects were considered to have type 1 diabetes or to be unclassifiable and were excluded from the analyses. The present analysis is based on data from 1,589 subjects in whom liver enzymes were measured. Of these, subjects who tested positive for hepatitis B or C infection, those whose serum enzyme levels exceeded 3 SDs above the mean of the entire population (i.e., AST  $> 43$  units/l, ALT  $> 28$  units/l, GGT  $> 205$  units/l), and those whose alcohol consumption, as assessed by detailed history, exceeded 250 g/week were excluded. The present analysis therefore includes 1,441 subjects, of whom 1,406 completed the follow-up examination.

The protocol was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio and the American British Cowdray Hospital in Mexico City. All the subjects gave informed consent.

## Anthropometric measurements

Height, weight, waist and hip circumferences, and systolic and diastolic blood pressure were measured as described elsewhere (18). At baseline and follow-up, all participants were asked to fast for at least 12 h before the examination. Blood samples were obtained in both the fasting state and 2 h after a standardized 75-g oral glucose load. Serum samples

were centrifuged, divided into aliquots, and stored at  $-70^{\circ}\text{C}$  until assayed.

## Biochemical measurements

Fasting concentrations of serum insulin, proinsulin, plasma glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, and plasma glucose and insulin concentrations 2 h after an oral glucose load were determined as described elsewhere (20). Serum AST, ALT, GGT, and ALP levels were measured by an enzymatic method (Syncron CX 4; Beckman Instruments, Fullerton, CA) at the baseline visit after an overnight fast.

## Statistical analysis

Data are presented as means ± SD; median and interquartile ranges are given for variables with skewed distribution (plasma insulin, serum triglycerides, and liver enzymes). Categorical variables were compared by the  $\chi^2$  test, continuous variables were analyzed by one-way ANOVA, and post hoc comparisons were performed with the Bonferroni-Dunn test. Simultaneous association with two categorical variables was carried out by two-way ANOVA; an interaction term was always computed. Multivariate analysis was performed by using general linear models including both continuous and categorical variables. Logistic regression was carried out by standard methods; results are expressed as the odds ratio (OR) with 95% CIs. For all these analyses, variables with non-normal distribution were log transformed.

**RESULTS**— The baseline clinical characteristics of the subjects grouped by diabetic status are reported in Table 1. Both type 2 diabetic (14% of the cohort) and IGT subjects (11%) were older and heavier than subjects with normal glucose tolerance (NGT) and had significantly higher waist circumference, systolic and diastolic blood pressure levels, serum triglyceride, total cholesterol, fasting and 2-h postglucose plasma glucose and insulin concentrations, and fasting serum proinsulin levels. Fasting and postglucose hyperglycemia and hyperinsulinemia and fasting hyperproinsulinemia were more pronounced in type 2 diabetes than IGT.

AST and ALT were tightly interrelated ( $r = 0.70$ ,  $P < 0.0001$ ), whereas all other interenzyme correlations were weaker (with  $r$  values ranging from 0.28 to 0.40,  $P < 0.0001$  for all). Upon stratifying en-

Table 2—Multiple regression analysis of serum liver enzymes

	AST	ALT	GGT	ALP
Sex (M/F)	0.4 (NS)	5.3 (0.02)	82.1 (0.0001)	2.7 (NS)
Age	0.1 (NS)	6.2 (0.01)	1.1 (NS)	46.1 (0.0001)
BMI	1.1 (NS)	0.8 (NS)	2.3 (NS)	5.1 (0.02)
Waist	0.4 (NS)	0.4 (NS)	0.8 (NS)	9.8 (0.002)
Triglycerides	10.4 (0.001)	17.4 (0.0001)	54.5 (0.000)	16.8 (0.0001)
HDL cholesterol	0.1 (NS)	0.3 (NS)	7.9 (0.005)	0.1 (NS)
Total cholesterol	5.4 (0.02)	17.6 (0.0001)	0.25 (NS)	0.4 (NS)
Fasting insulin	0.6 (NS)	3.7 (0.05)	28.6 (0.0001)	0.1 (NS)
Alcohol consumption	0.7 (NS)	0.1 (NS)	25.0 (0.0001)	1.3 (NS)
Systolic blood pressure	0.2 (NS)	0.1 (NS)	3.4 (0.06)	0.4 (NS)
Diastolic blood pressure	3.2 (NS)	3.7 (0.05)	0.1 (NS)	1.2 (NS)
Baseline diabetic status				
IGT vs. NGT	18.7 (0.0001)	29.0 (0.0001)	13.0 (0.0003)	2.3 (NS)
Diabetes vs. NGT	0.1 (NS)	8.3 (0.004)	14.7 (0.0001)	12.4 (0.0004)

Data are *F* ratios and their significance level.

zyme levels by sex and age quartiles, ALT and GGT concentrations were higher in men than in women ( $P = 0.01$  and  $P < 0.0001$ , respectively). All four enzymes increased with age in women, and only ALP did so in men (all  $P < 0.01$ ). When enzyme data were stratified by baseline diabetic status and obesity (using the median BMI of the population,  $27.6 \text{ kg/m}^2$ ,

as the cutoff), higher ALT, AST, and GGT concentrations were associated with obesity (each  $P < 0.001$ ), and all four enzymes were higher in IGT and type 2 diabetes than in subjects with NGT (all  $P < 0.0001$ ).

In the univariate analysis, enzyme levels were associated with most of the anthropometric and metabolic variables

(especially GGT vs. serum triglycerides,  $r = 0.37$ , and AST vs. 2-h plasma insulin levels,  $r = 0.25$ , both  $P < 0.001$ ). In multivariate models controlling for sex, age, BMI, waist circumference, alcohol intake, fasting plasma insulin, triglycerides, total and HDL cholesterol, and blood pressure, ALT and GGT concentrations were independently associated with both prevalent IGT and prevalent type 2 diabetes. ALP was only associated with prevalent type 2 diabetes, whereas AST values were higher in association with prevalent IGT only. Moreover, serum triglyceride levels showed independent associations with all four enzymes. Of note, GGT was positively related to most variables of the metabolic syndrome, including fasting plasma insulin concentrations, whereas ALP was the only one that showed an independent association with BMI and waist circumference (Table 2).

Among 1,233 subjects free of diabetes at baseline, 94 subjects developed type 2 diabetes over 7 years; over the same time period, of 1,080 subjects who had NGT at baseline, 93 developed IGT. Figure 1 shows enzyme levels in persistent NGT subjects, IGT converters, and type 2 dia-

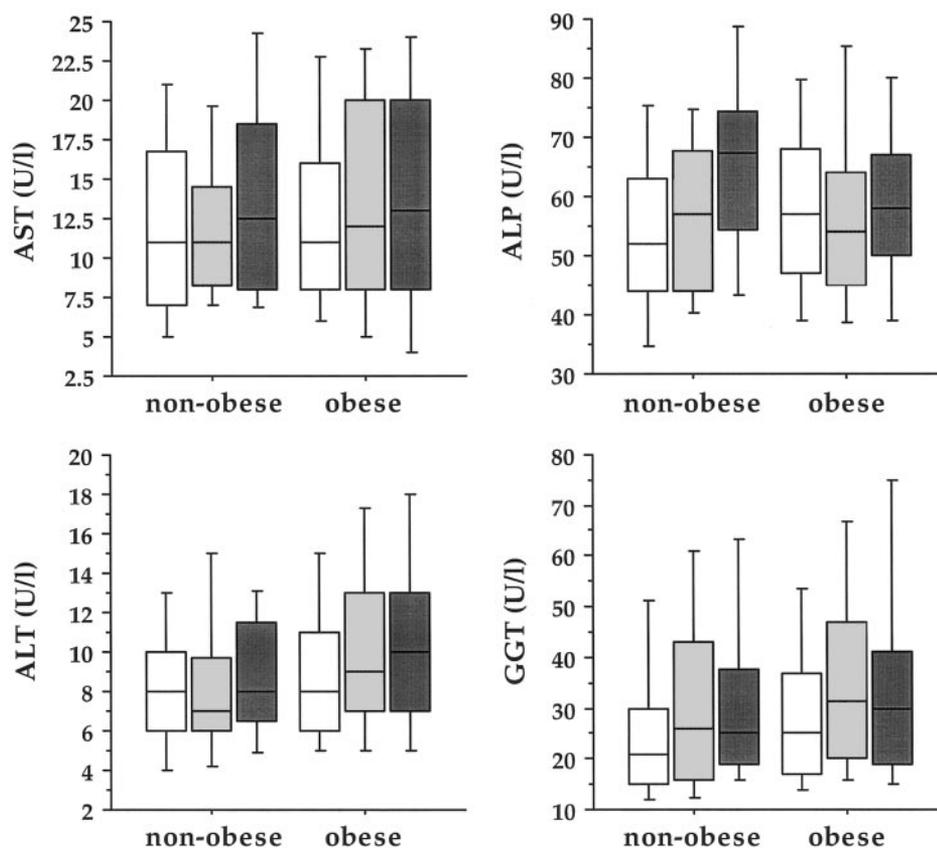


Figure 1—Baseline serum enzyme levels in persistent NGT (□), IGT converters (▨), and type 2 diabetes converters (■) by obesity status (BMI  $< 27.6 \text{ kg/m}^2$ ).

Table 3—Predictivity of liver enzymes for the development of IGT or diabetes

	Diabetes		IGT	
	OR (95% CI)	P	OR (95% CI)	P
Sex (F)	0.42 (0.25–0.69)	0.0007	1.37 (0.79–2.36)	NS
Age (years)	1.00 (0.98–1.04)	NS	1.03 (0.99–1.06)	NS
BMI (kg/m <sup>2</sup> )	1.17 (1.07–1.28)	0.0008	1.09 (0.99–1.19)	NS
Waist (cm)	0.98 (0.95–1.02)	NS	0.98 (0.95–1.02)	NS
Fasting plasma insulin (ln[pmol/ml])	1.34 (0.91–2.00)	NS	1.69 (1.16–2.47)	0.006
Alcohol (ln[g/week])	0.82 (0.70–0.96)	0.01	1.03 (0.89–1.20)	NS
AST (top quartile)	1.67 (1.06–2.64)	0.028	—	—
GGT (top quartile)	—	—	2.07 (1.29–3.33)	0.003

betes converters separately for nonobese and obese subjects. Each of AST, ALT, and GGT singly predicted incident diabetes, with ORs of 1.9 (95% CI 1.2–3.0), 1.6 (1.1–1.5), and 1.8 (1.2–2.8), respectively, for the top quartile versus the lower three quartiles of enzyme levels. When the model was adjusted for sex, age, BMI, waist circumference, alcohol consumption, and fasting insulin concentration, only AST remained significantly related to incident diabetes (Table 3). Only GGT singly predicted incident IGT (OR 2.16 [1.39–3.37]), and this association remained significant when running a complete model (as in Table 3).

When the end points of IGT and type 2 diabetes were combined, GGT was the only enzyme to retain independent predictivity in the multivariate model in Table 3, with an OR of 2.05 (95% CI 1.39–3.03), which remained fully significant (1.62 [1.08–2.42],  $P < 0.02$ ) when further controlling for plasma proinsulin and 2-h glucose levels, i.e., two strong predictors of deterioration of glucose tolerance in this population (Fig. 2).

**CONCLUSIONS**— The present study examined the role of four liver enzymes as markers of metabolic syndrome and predictors of diabetes. Increased serum enzyme concentrations are conventionally interpreted as a marker of alcohol abuse and/or liver damage (21). We therefore only included subjects who were free of evidence of hepatitis B or C virus infection or active liver damage and further adjusted the results for alcohol consumption. The major findings were that 1) each enzyme was associated with multiple features of metabolic syndrome when examined in univariate analysis; 2) in multivariate analysis, ALT, ALP, and

GGT were associated with prevalent type 2 diabetes (AST with prevalent IGT); 3) GGT was the enzyme clustering with the largest number of features of metabolic syndrome (including male sex, dyslipidemia, hyperinsulinemia, and IGT or type 2 diabetes); and 4) GGT was a predictor of incident IGT/type 2 diabetes at follow-up, independently of anthropometric characteristics, and plasma glucose and proinsulin concentrations.

Concentrations of serum aminotransferase close to the upper limit of the normal range, but still within the normal range (in the absence of hepatitis virus infection or heavy alcohol consumption), have been related to NAFLD, or nonalcoholic steato-hepatitis (22,23). These conditions have been associated with insulin resistance (particularly hepatic), obesity,

central fat distribution, glucose intolerance, dyslipidemia, and higher blood pressure (1,8,9), i.e., with one or more features of, or the full-blown, metabolic syndrome (9). While the current results generally support this notion, the observed pattern of associations suggests a more complex picture. Thus, only ALP was independently associated with obesity and central adiposity, whereas only high serum triglycerides were associated with raised levels of each of the four enzymes, and GGT was the sole marker for the full metabolic syndrome after adjusting for anthropometric variables and alcohol consumption. Previous cross-sectional studies have reported an association between diabetes and ALT and GGT concentrations independently of obesity (24–26). The separate association of liver enzymes with IGT rather than type 2 diabetes has received less attention.

A general problem is the extent to which fatty liver changes (and their pathophysiological correlates, hyperglycemia, dyslipidemia, etc.) are reflected in raised concentrations of one or the other circulating enzyme. On the one hand, the hepato-cellular processes causing ALT/AST versus GGT or ALP to be released in increased amounts into the circulation are not well understood. For example, alcohol use has been positively associated with raised serum ALT and AST in several population studies (24–27), yet in the present study, we did not find any inde-

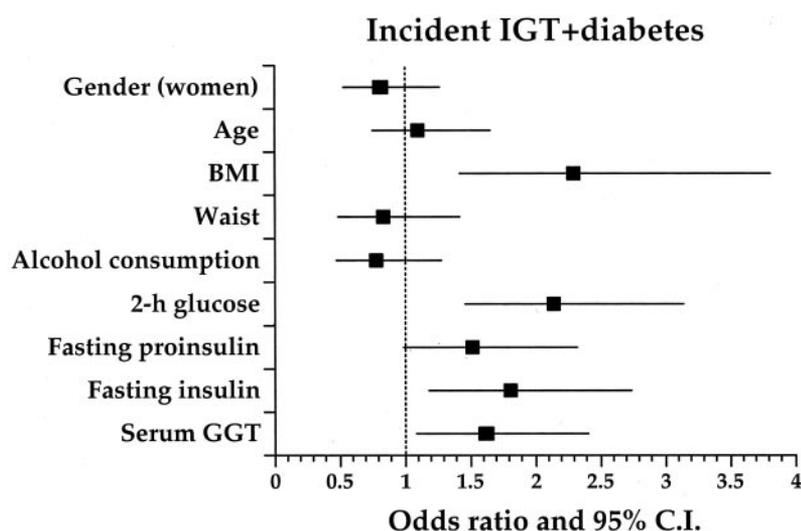


Figure 2—Predictors of a combined outcome (IGT plus type 2 diabetes) in the Mexico City Diabetes Study. For each of the independent variables, the solid square is the OR (and the horizontal line the 95% CI) for the top quartile versus the other three quartiles of the distribution of that variable.

pendent association between ALT or AST levels and alcohol consumption within the range 0–250 g/week of alcohol consumption (Table 2). On the other hand, different enzymes have been measured in different studies (6,17,24–27), rarely all four of them have been part of the screening, and adjustment for confounders has been variable (17,28). Even in the same database, AST is associated with prevalent IGT only (Table 2) but predicts diabetes and not IGT (Table 3). Thus, the variability of the available observations may be explained both in terms of insufficient understanding of the biology of these enzymes and incomplete capture of their correlates and confounders.

A conservative interpretation of the cross-sectional data of the present study is that raised GGT (within 3 SDs of the mean population value) is a bona fide component of the metabolic syndrome independent of sex, age, adiposity, and alcohol consumption. The very strong independent association with serum triglycerides suggests that GGT and hypertriglyceridemia may be biochemical markers for a fatty liver with the attendant increased export of triglyceride-rich lipoproteins. In line with this finding, our prospective data show that GGT is the only enzyme associated with incident IGT or diabetes, even after controlling for the main predictors of deteriorating glucose tolerance (Fig. 2). The interpretation of this finding is that liver steatosis and hepatic insulin resistance are a harbinger of deteriorating glucose tolerance. Two recent prospective studies have shown a strong predictive power of GGT for incident type 2 diabetes: one of the studies only included men, and type 2 diabetes was doctor reported (17); in the other study, diabetes was based on fasting glucose levels only and incident diabetes was not adjusted for glucose levels (29). The current data thus consolidate the preeminence of GGT as an independent predictor of metabolic outcome. At variance are the findings of Ohlsson et al. (30) in a prospective study of Swedish men and those of Vozarova et al. (10) in Pima Indians, who found ALT, but not GGT, to be a risk factor for the development of diabetes. The latter study, however, did not adjust the association for baseline plasma glucose concentration, a strong and consistent predictor of diabetes. A recent report of the Insulin Resistance Atherosclerosis Study confirmed an independent predictivity of

both AST and ALT for incident diabetes (31).

An attractive hypothesis is that GGT may relate to diabetes because it is a marker of oxidative stress. GGT has a pivotal role in the maintenance of intracellular defenses through its mediation of extracellular glutathione transport into most types of cells (32). Increases in GGT activity in response to oxidative stress may serve to facilitate transport of glutathione into cells. In addition, although GGT has been regarded as a marker of liver disease, it shows a high activity in the kidney and in several other organs (33). Thus, increased serum GGT concentrations may identify subjects with a generalized increase in oxidative stress (34). Moreover, recent studies (35) indicated that, under physiological conditions in the presence of  $\text{Fe}^{3+}$  and  $\text{Cu}^{2+}$ , GGT is directly involved in the generation of reactive oxygen species. This increased reactive oxygen species generation could exceed the capacity of the antioxidant system and induce or perpetuate oxidative stress to cells. Because oxidative stress with the attendant low-grade inflammation is implicated in a number of pathological conditions, including aging, atherosclerosis, and diabetes (36), one could speculate that chronic mild elevations in GGT may predispose to diabetes by mediating/inducing oxidative stress. Future investigation will decide the merit of this hypothesis.

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