Hepatic Enzymes, the Metabolic Syndrome, and the Risk of Type 2 Diabetes in Older Men

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OBJECTIVE — We have examined the relationship between hepatic enzymes, the metabolic syndrome, insulin resistance, and type 2 diabetes and assessed the potential of hepatic enzyme measurements in determining diabetes risk.

RESEARCH DESIGN AND METHODS — We conducted a prospective study of 3,500 nondiabetic men aged 60–79 years who were followed-up for a mean period of 5 years and in whom there were 100 incident type 2 diabetes cases.

RESULTS — In cross-sectional analyses, alanine aminotransferase (ALT) and γ-glutamyltransferase (GGT) were strongly associated with obesity, insulin resistance, and the metabolic syndrome. Prospectively, the risk of type 2 diabetes significantly increased with increasing levels of ALT and GGT even after adjustment for confounders including BMI (top versus bottom quarter ALT: relative risk 2.72 [95% CI 1.47–5.02]; GGT: 3.68 [1.68–8.04]). Additional adjustment for insulin resistance attenuated the effects, but the relationships with ALT and GGT remained significant (1.91 [1.01–3.60] and 2.69 [1.21–5.97], respectively). Further adjustment for inflammatory markers (C-reactive protein) made minor differences. Among high-risk subjects (obese men or those with the metabolic syndrome), elevated GGT and ALT enhanced the prediction of diabetes risk.

CONCLUSIONS — Elevated levels of ALT and GGT within the normal range are independent predictors of type 2 diabetes in older men and are useful additional measures in identifying those at high risk of diabetes.

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Hepatic dysfunction resulting from the insulin resistance syndrome may contribute to the development of type 2 diabetes (1). Alanine aminotransferase (ALT) is the most specific marker of this hepatic pathology. γ-Glutamyltransferase (GGT) is considered to be a sensitive indicator of liver damage but is not specific (2). Obesity also has major affects on GGT (3). A number of prospective studies (4–11) have shown raised GGT or ALT to predict the development of type 2 diabetes independent of BMI and alcohol intake. In our earlier study, raised GGT level was shown to be an independent risk factor for type 2 diabetes, and we hypothesized that GGT might be a marker for visceral and hepatic fat deposition (steatosis) and, by inference, a marker of hepatic insulin resistance (4). A number of cross-sectional studies (12–13) have since shown relationships between GGT and ALT and the metabolic syndrome and insulin resistance, suggesting that GGT/ALT may serve as a marker for insulin resistance. Moreover, studies (5,9) have suggested that hepatic inflammation may be another possible mechanism by which elevated hepatic enzyme levels are related to diabetes risk. Few studies have examined the role of insulin or inflammation in the link between hepatic enzymes and the risk of diabetes, although elevated ALT has shown to be associated with increased risk of diabetes independent of insulin sensitivity (5,9) and C-reactive protein (10). The National Cholesterol Education Program has proposed a definition of the metabolic syndrome to help identify individuals at risk for both coronary heart disease and type 2 diabetes (14). In this study, we have examined the cross-sectional relationships between hepatic enzymes (ALT and GGT) and the metabolic syndrome (and its components) and insulin resistance (homeostasis model assessment of insulin resistance [HOMA-IR]). We have also prospectively determined the role of these metabolic factors in the relationships between hepatic enzymes and risk of type 2 diabetes and assessed whether these associations are independent of inflammatory markers. In addition, we examine whether hepatic enzymes provide useful complementary markers identifying subjects at high risk of type 2 diabetes and in particular whether they provide further prognostic information in men with the metabolic syndrome.

RESEARCH DESIGN AND METHODS

— The British Regional Heart Study (15) is a prospective study of cardiovascular disease involving 7,735 men aged 40–59 years selected from the age-sex registers of one general practice in each of 24 British towns, who were screened between 1978 and 1980. In 1998–2000, all surviving men, now aged 60–79 years, were invited for a 20th year follow-up examination. Ethics approval was provided by all relevant local research ethics committees. All men provided informed written consent to the investigation, which was carried out in accordance with the Declaration of Helsinki. All men completed a questionnaire (Q20) that included questions on their medical history and lifestyle behavior. The men were asked to fast for a minimum of 6 h, during

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; CRP, C-reactive protein; GGT, γ-glutamyltransferase; HOMA-IR, homeostasis model assessment of insulin resistance.

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

which they were instructed to drink only water and to attend for measurement at a prespecified time between 0800 and 1800. They then provided a blood sample, collected using the Sarstedt Monovette system. A total of 4,252 men (77% of survivors) attended for examination. Blood measurements were available in 4,045 men after they completed the Q20. Of these, 3,475 men (86%) fasted for at least 6 h, and 2,140 men were measured after an overnight fast.

Cardiovascular risk factors

Details of measurement and classification methods for smoking status, physical activity, BMI, social class, alcohol intake, blood pressure, and blood lipids in this cohort have been described (15–18). Men were asked to recall a doctor diagnosis of coronary heart disease (myocardial infarction or angina), stroke, and diabetes. Plasma glucose was measured by a glucose oxidase method using a Falcor 600 automated analyser. Serum insulin was measured using an enzyme-linked immunosorbent assay, which does not cross-react with proinsulin. Triglycerides, blood glucose, and insulin concentrations were adjusted for the effects of fasting duration and time of day (18). C-reactive protein (CRP) was assayed by ultrasensitive nephelometry (Dade Behring, Milton Keynes, U.K.). Hepatic enzymes including GGT, ALT, and aspartate transaminase (AST) were measured using a Hitachi 747 automated analyser. Hepatic enzyme levels showed no diurnal variation and were unrelated to fasting duration.

Insulin resistance and the metabolic syndrome

Insulin resistance was estimated according to the HOMA-IR (the product of fasting glucose [mmol/l] and insulin [units/ml] divided by the constant 22.5) (19). The metabolic syndrome was defined based on National Cholesterol Education Program definitions (15) as having three or more of the following: *1*) high glucose (fasting plasma glucose ≥110 mg/dl; 6.1 mmol/l), *2*) high triglycerides (≥150 mg/dl; 1.7 mmol/l), *3*) low HDL cholesterol (<40 mg/dl; 1.04 mmol/l, *4*) hypertension (blood pressure of at least 135/85 mmHg or on antihypertensive treatment), and *5*) waist circumference >102 cm.

Follow-up

All men have been followed-up for all-cause mortality, cardiovascular morbidity, and development of a diagnosis of type 2 diabetes from initial examination to June 2004, and follow-up has been achieved for 99% of the cohort (20). This analysis is based on follow-up from rescreening in 1998–2000, a mean follow-up period of 5 years (4–6 years). Information on death was collected through the established "tagging" procedures provided by the National Health Service central registers. Information on new cases of diabetes was obtained by regular two-yearly reviews of the patients' notes (including hospital and clinic correspondence) through to the end of the study period and from repeated personal questionnaires to surviving subjects after initial examination.

Statistical methods

The distributions of GGT and ALT were skewed, log transformation was used, and geometric means and interquartile ranges were presented. The men were divided into four equal quarters on the basis of ALT or GGT distributions. In Table 1, linear regression analysis was used to test for trend across the four groups fitting quantitative variables (1–4) for the four groups. Cox's proportional hazards model was used to assess the multivariate-adjusted relative risk for each quarter compared with the reference group (lowest quarter). In the adjustment, smoking (never, long-term ex-smokers [>15 years], recent ex-smokers [≤15 years], and current smokers), social class (seven groups), physical activity (four groups), alcohol intake (five groups), preexisting coronary heart disease (yes/no), and stroke (yes/no) were fitted as categorical variables. BMI, HOMA-IR, CRP, and white cell count were fitted as continuous variables. In Table 2, tests for trend were carried out fitting ALT and GGT in their original continuous form. Elevated GGT/ALT was defined as the top quarter of the distribution. All analyses were carried out using SAS version 8.2 (SAS Institute, Cary, NC).

Study subjects

Men with a doctor diagnosis of diabetes, men diagnosed with diabetes in year of reexamination, and those with a fasting glucose of ≥7 mmol/l (World Health Organization criteria) were considered to have prevalent diabetes and were excluded (n = 484). We further excluded men with levels three times above the reference range for either ALT (>120 IU/l) or GGT (>150 IU/l), as these men were likely to have established liver damage (n = 51), and a further ten men with no data on liver enzymes. Thus, analysis is based on 3,500 men with blood measurements. Almost all these men (97.4%; n = 3,408) were white Caucasian, 0.4% were of other ethnic origin (n = 16), and in 76 men (2.2%) the ethnicity was unknown.

RESULTS

— During the mean follow-up period of 5 years (range 4–6 years) there were 100 incident cases of diabetes in the 3,500 nondiabetic men. The correlation coefficient between GGT and ALT was r = 0.39, between AST and GGT r = 0.36, and between ALT and AST r = 0.65. GGT and ALT levels were significantly higher in those who developed diabetes (geometric mean [interquartile range] GGT: 37.0 IU/l [24–52] vs. 27.4 IU/l [19–37]; ALT: 19.3 IU/l [14–25] vs. 15.3 IU/l [12–20], both $P < 0.0001$).

Table 1 shows the baseline characteristics by quarters of the GGT and ALT distributions. GGT and ALT were significantly associated with both BMI and waist circumference. With the exception of HDL cholesterol, all the metabolic risk factors and inflammatory markers significantly increased with increasing GGT levels (Table 1). ALT was significantly associated with HOMA-IR, triglycerides, HDL cholesterol, and, to a lesser extent, with glucose but showed significant inverse relationships with inflammatory markers. These associations seen between the hepatic enzymes and the metabolic risk factors and inflammatory markers remained significant even after further adjustment for BMI (data not shown). HOMA-IR was significantly associated with GGT and ALT within all BMI groups. The prevalence of the metabolic syndrome increased significantly with increasing GGT and ALT. GGT and ALT increased significantly with increasing number of metabolic abnormalities ($P <$ 0.0001). Mean (geometric) GGT for those with 0,1,2,3, and ≥4 abnormalities were 24.0, 25.0, 28.6, 30.6, and 34.5 units/l, respectively, and for ALT the corresponding means were 13.7, 14.3, 15.5, 16.7, and 18.7 units/l, respectively.

Incidence rates and relative risks of type 2 diabetes by the four groups of ALT and GGT, using those in the lowest quarter as the reference group, are shown in Table 2. GGT and ALT were significantly predictive of type 2 diabetes even after adjustment for age, social class, physical activity, smoking status, alcohol intake,

Table 1—*GGT, ALT, and cardiovascular and metabolic risk factors and inflammatory markers in older British men*

GGT (IU/l)	Quarters				*P* value (trend across groups)
	1 (low) (<18)	2 (19–25.9)	3 (26–36.9)	4 (high) (≥37)	
Mean age	69.2	68.8	68.5	68.1	<0.0001
Mean waist circumference (cm)	94	96	98	98	<0.0001
Mean BMI	25.5	26.6	27.2	27.3	<0.0001
Percent current smokers	13.2	12.6	13.3	13.3	0.84
Percent inactive	31.7	30.3	34.7	34.3	0.09
Percent heavy drinkers	1.3	2.2	3.3	7.2	<0.0001
Percent manual social class	54.4	49.8	54.9	55.8	0.20
Percent myocardial infarction	17.3	16.7	19.2	20.1	0.07
Percent stroke	3.8	4.1	5.4	6.5	0.005
Percent use of statins	5.9	5.1	7.9	8.5	0.005
Metabolic and inflammatory markers					
Mean systolic blood pressure (mmHg)	147	146	148	151	0.0003
Mean HDL cholesterol (mmol/l)	1.36	1.33	1.32	1.33	0.08
Mean triglycerides (mmol/l)	1.35	1.52	1.67	1.86	<0.0001
Mean glucose (mmol/l)	5.53	5.53	5.58	5.58	0.0005
Mean HOMA-IR	0.48	0.66	0.78	0.78	<0.0001
Mean CRP (mg/l)	1.22	1.54	1.88	2.20	<0.0001
Mean white cell count (10^9/l)	6.55	6.75	6.89	7.03	<0.0001
Percent metabolic syndrome	17.4	24.6	32.8	37.6	<0.0001
ALT (IU/l)	1 (<12)	2 (13–15.9)	3 (16–20.9)	4 (≥ 21)	*P* value (trend across groups)
Mean age	70.7	68.9	67.7	66.8	<0.0001
Mean waist circumference	94	96	97	99	<0.0001
Mean BMI	25.6	26.5	27.0	27.7	<0.0001
Percent current smokers	17.9	13.1	10.7	9.3	<0.0001
Percent inactive	38.0	30.0	31.9	29.5	0.0003
Percent heavy drinkers	2.7	2.7	3.9	4.7	0.009
Percent manual social class	55.5	55.6	52.3	50.9	0.02
Percent myocardial infarction	21.1	17.9	16.4	17.0	0.01
Percent stroke	6.3	4.8	4.2	4.0	0.01
Percen use of statins	6.1	6.3	8.4	6.9	0.23
Metabolic and inflammatory markers					
Mean systolic blood pressure (mmHg)	149	147	147	149	0.67
Mean HDL cholesterol (mmol/l)	1.36	1.35	1.34	1.28	<0.0001
Mean triglycerides (mmol/l)	1.40	1.52	1.63	1.84	<0.0001
Mean glucose (mmol/l)	5.53	5.53	5.53	5.58	0.002
Mean HOMA-IR	0.50	0.61	0.71	0.91	<0.0001
Mean CRP (mg/l)	1.90	1.63	1.51	1.60	0.0004
Mean white cell count (10^9/l)	6.96	6.69	6.89	7.03	0.02
Percent metabolic syndrome	20.1	26.7	27.2	39.4	<0.0001

preexisting coronary heart disease, stroke, use of statins, and BMI (*column B*). Exclusion of heavy drinkers (five or more drinks per day) ($n = 129$) made little difference to the relationships seen in Table 2. We repeated the analyses in Table 2, adjusting for waist circumference instead of BMI, and similar results were obtained. No significant association was seen between AST and diabetes. The adjusted relative risks for the four quarters were 1.00, 0.91 (95% CI 0.47–1.76), 1.41 (0.77–2.58), and 1.52 (0.83–2.77).

Hepatic enzymes, obesity, and diabetes

The presence of elevated hepatic enzymes (top quarter, ≥37 IU/l) was associated with increased risk of diabetes in both obese (BMI ≥30 kg/m^2) and nonobese men. In nonobese men, the cumulative incidence of diabetes for men with elevated GGT (≥37 IU/l) and those with levels <37 IU/l were 1.5 and 2.8%, and in obese men, the corresponding incidences were 7.7 and 10.7%. The incidence in nonobese men with elevated ALT (>20 IU/l) was 1.6% compared with 2.6% in those with levels <20 IU/l, and in obese men the corresponding incidences were 6 and 13.1%. Among nonobese men, the relative risks of diabetes associated with elevated GGT and ALT were 2.02 (95% CI 1.15–3.57) and 1.84 (1.03–3.30) after adjustment for age, social class, physical activity, alcohol, smoking, and preexisting cardiovascular disease. Among obese men, the corresponding relative risks for GGT and ALT were 1.54 (0.82–2.10) and 2.02 (1.15–3.57), respectively.

Table 2—*Adjusted relative risk of type 2 diabetes by quarters of GGT and ALT*

		Adjusted relative risk of type 2 diabetes		
	Incidence % (no. of cases)	A	B	C
GGT (IU/l) (*n* men)				
≤18 (866)	1.0 (9)	1.00	1.00	1.00
19–25 (920)	2.2 (20)	2.09 (0.95–4.59)	2.14 (0.95–4.93)	1.83 (0.80–4.20)
26–36 (847)	3.8 (32)	3.72 (1.78–7.80)	3.14 (1.43–6.86)	2.42 (1.10–5.34)
≥37 (867)	4.5 (39)	4.52 (2.19–9.33)	3.68 (1.68–8.04)	2.69 (1.21–5.97)
Trend	—	$P < 0.0001$	$P < 0.0001$	$P = 0.01$
ALT (IU/l)				
≤12 (1,072)	1.4 (16)	1.00	1.00	1.00
13–15 (790)	2.4 (19)	1.59 (0.81–3.09)	1.31 (0.65–2.61)	1.20 (0.60–2.42)
16–20 (742)	2.8 (21)	1.93 (1.00–3.73)	1.60 (0.82–3.15)	1.54 (0.78–3.00)
≥21 (896)	5.0 (44)	3.44 (1.91–6.21)	2.72 (1.47–5.06)	1.91 (1.01–3.60)
Trend	—	$P < 0.0001$	$P = 0.0006$	$P = 0.11$

Data are relative risk (95% CI). A = age-adjusted; B = adjusted for age, social class, physical activity, smoking status, alcohol intake, preexisting coronary heart disease or stroke, use of statins, and BMI; C = adjusted for above and HOMA-IR.

Insulin resistance (HOMA-IR) and inflammation

We further examined the relationship between hepatic enzymes and diabetes adjusting for HOMA-IR. Such adjustment (Table 2, *column C*) reduced the risk further, but GGT remained significantly associated with type 2 diabetes. The trend with increasing ALT was no longer significant, although elevated ALT still showed significantly elevated risk. Further adjustment for CRP and white cell count made little difference to the relationships seen in Table 2. For GGT, the adjusted relative risks for the four quarters were 1.00, 1.82 (95% CI 0.79–4.16), 2.32 (1.05–5.12), and 2.51 (1.13–5.60). For ALT the corresponding relative risks were 1.00, 1.22 (0.60–2.46), 1.55 (0.79–3.04), and 1.97 (1.04–3.73).

The metabolic syndrome, elevated hepatic enzymes, and type 2 diabetes

The metabolic syndrome was present in >70% of diabetic case subjects. Men with the metabolic syndrome showed a more than fourfold increase in the risk of type 2 diabetes compared with those without the metabolic syndrome, even when BMI levels were taken into account (Table 3). Elevated GGT and ALT were associated with increased incidence of diabetes in men with the metabolic syndrome (Table 3). The number of diabetic cases in men without the metabolic syndrome was small and less association was seen. Table 3 shows the combined effects of the metabolic syndrome and elevated GGT and ALT (top quarter) on diabetes risk with adjustment including and excluding BMI. Among men with the metabolic syndrome, after adjustment for BMI levels, elevated GGT was associated with a 1.76 (95% CI 1.03–2.99)-fold increase in risk compared with those without elevated GGT, and for ALT the corresponding relative risk was 1.80 (1.03–3.12).

Overnight fasting

Although all analyses were adjusted for time of day and fasting duration, we also examined the relationships restricted to subjects who fasted overnight ($n = 1,909$; 51 case subjects). Although numbers were small, the pattern of relationships was similar. Elevated GGT was associated with over a threefold increase in risk of diabetes compared with men in the bottom quarter after adjustment for factors included in *column B* (Table 2) (adjusted relative risk 3.43 [95% CI 1.12–10.50]; test for trend $P = 0.002$). Further adjustment for HOMA-IR attenuated the rela-

Table 3—*Metabolic syndrome, elevated GGT and ALT, and adjusted relative risk of type 2 diabetes*

	Number of men (cases)	Incidence (%)	Adjusted relative risk*	Adjusted relative risk†
Metabolic syndrome				
No	2,519 (29)	1.2	1.00	1.00
Yes	981 (71)	7.4	5.56 (3.58–8.63)	4.14 (2.56–6.70)
No, GGT <37	1,978 (22)	1.1	1.00	1.00
No, GGT ≥37	541 (7)	2.3	1.19 (0.51–2.81)	0.98 (0.39–2.43)
Yes, GGT <37	655 (39)	5.9	4.74 (2.79–8.06)	3.41 (1.94–5.99)
Yes, GGT ≥37	326 (32)	9.8	7.96 (4.55–13.93)	5.64 (3.11–10.23)
No, ALT <20	1,976 (20)	1	1.00	1.00
No, ALT ≥20	543 (9)	1.7	1.71 (0.77–3.80)	1.76 (0.79–3.91)
Yes, ALT <20	628 (36)	5.7	4.91 (2.82–8.56)	3.86 (2.14–6.96)
Yes, ALT ≥20	353 (35)	9.9	9.31 (5.26–16.50)	6.88 (3.69–12.80)

Data are relative risk (95% CI) or *n* (%). *Adjusted for age, social class, physical activity, smoking status, alcohol intake, preexisting coronary heart disease, stroke, and use of statins. †Adjusted for above and BMI.

tionship, but there still remained over a twofold increase in risk (adjusted relative risk 2.19 [0.69–6.94]). Although this difference was not statistically significant because of the small numbers involved, the test for trend was significant ($P = 0.04$). For ALT, the corresponding adjusted relative risks were 2.53 (1.05–6.10) and 1.45 (0.57–3.69).

CONCLUSIONS — In this study of older men aged 60–79 years, we have shown elevated ALT/GGT within the "normal" range to be significantly predictive of type 2 diabetes independent of obesity and alcohol intake. Elevated GGT was associated with an almost fourfold increase in risk compared with a nearly threefold increase for elevated ALT. The increased risks were seen in both nonobese and obese men (BMI $\geq$30 kg/m^2) and in men with the metabolic syndrome. In contrast, significant associations with AST and type 2 diabetes were not seen in multivariate analysis. These observations confirm our earlier findings carried out in middle-aged men (4) and those of other studies (5–11) and extend previous reports by assessing the influence of insulin resistance and inflammation on the relationship between GGT and ALT and diabetes.

While most studies (4,6–11) show an association between GGT and diabetes independent of obesity and alcohol, the association between ALT and diabetes within the "normal" range have been less consistent (5,7–10). Studies showing no relationships between elevated ALT and diabetes have tended to come from Korea or Japan. This difference between studies could reflect the ethnic differences in the populations studied. The present cohort comprised an unmixed population of white Caucasian men, and, as mean BMI levels are considerably lower among the Koreans and Japanese studied (7,8), this suggests that ethnic differences in levels of visceral fat (which probably plays a major role in the relationship between ALT and diabetes) may account for the differing outcome in various studies. In the present study, risk of diabetes increased substantially in men in the third quarter of the GGT distribution, whereas for ALT risk was sharply increased only at a higher threshold (top quarter). The cases of diabetes identified are all new cases of diabetes. We have no information that allows us to discriminate formally between different types. However, the great majority of these new cases of adult-onset diabetes would be expected to be type 2 diabetes rather than latent autoimmune diabetes of adults or other idiopathic varieties of diabetes.

Insulin resistance

Although GGT has been regarded as a marker of excessive alcohol consumption and liver disease, neither of these factors explains the relationship between GGT and diabetes seen within the normal range. Elevated hepatic enzyme has been interpreted as a marker for visceral fat, hepatic steatosis, and hepatic insulin resistance (4) and, more recently, as a possible marker of inflammation (5,9). Emerging evidence has shown a strong association between GGT/ALT and many factors associated with insulin resistance and the metabolic syndrome (3,8,10,12, 13), as was seen in this study.

Several possible mechanisms have been proposed to explain how hepatic enzymes increase the risk of the metabolic syndrome and diabetes. GGT and ALT levels even within the normal range correlates with increasing hepatic fat (21). It has been suggested that the elevation of hepatic enzymes could be an expression of excess deposition of fat in the liver as exemplified by nonalcoholic fatty liver, which is closely related to obesity and visceral fat deposition and now regarded as a feature of the insulin resistance syndrome (1). However, there still remained a two- to almost threefold increase in risk of diabetes associated with raised ALT and GGT after adjustment for insulin resistance (HOMA-IR). In the few studies that have considered the role of insulin resistance, ALT has shown to be associated with development of diabetes independent of direct measures of insulin sensitivity and secretion (5,9).

Inflammation

Fat accumulation in the liver can stimulate cytokine production, and it has been found that inflammatory cytokines such as tumor necrosis factor-α and interleukin-6 can influence fatty acid metabolism in the liver and predispose to formation of fatty liver (22). Thus, another possible mechanism is that elevated liver enzymes may reflect inflammation, which in turn impairs insulin signaling in both the liver and other organs (5). Inflammation has been associated with the development of diabetes (23–24). In this study, markers of inflammation were positively correlated with GGT but inversely correlated with ALT. The lack of positive association between ALT and CRP is consistent with other population studies (10,25). Evidence for a positive association between ALT and inflammation has come from studies examining subjects with abnormally high levels of ALT (26), which might reflect nonalcoholic steatohepatitis that can lead to liver inflammation (22). It has also been suggested that GGT might be an early marker of oxidative stress (7,25). Inflammation is one manifestation of oxidative stress, and the pathways that generate the mediators of inflammation such as adhesion molecules and interleukins are all induced by oxidative stress (27). This may explain the association between inflammation and GGT and not ALT within the normal range. However, adjustment for markers of inflammation made minor differences to the relationships between liver enzymes and diabetes risk. Thus, GGT might also be involved in the pathogenesis of diabetes through other mechanisms related to oxidative stress (28).

In the present study of men aged 60–79 years, the metabolic syndrome was common in those with elevated hepatic enzymes (GGT/ALT). GGT and, to a lesser extent, ALT showed a significant graded and independent association with risk of developing type 2 diabetes even after adjustment for obesity, inflammatory markers, and insulin resistance. ALT and GGT are simple measurements available in routine clinical practice. Our study was carried out in a predominantly white Caucasian male population, and we cannot generalize our findings to women or other ethnic groups, although GGT has also shown to be a significant predictor of type 2 diabetes in women (11). However, the presence of raised hepatic enzymes may help identify an individual who is likely to have insulin resistance and features of the metabolic syndrome and who is at particularly high risk. Our study supports the suggestion that even a modest degree of nonalcoholic fatty liver is important in the pathogenesis of diabetes and that hepatic enzymes may be useful additional measures in identifying men at high risk of diabetes.

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