Relationship of Serum γ-Glutamyltransferase to Atherogenic Dyslipidemia and Glycemic Control in Type 2 Diabetes

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We evaluated possible interactions between BMI and serum γ-glutamyltransferase (GGT) concentration and their effects on the prevalence of poor glycemic control and common comorbidities of diabetes. We assessed whether the association of BMI with poor glycemic control, hypertension, atherogenic dyslipidemia (i.e., high triglycerides and/or low high-density lipoprotein (HDL) cholesterol), hypercholesterolemia, and hyperuricemia differed according to serum GGT concentration in a cohort of 3,633 type 2 diabetic individuals. The associations of BMI with different outcome measures were significant, but the associations varied remarkably by GGT concentration. As GGT concentration increased, the association of BMI with atherogenic dyslipidemia and glycemic control strengthened (P = 0.01 and 0.004 for interactions, respectively); in contrast, the association of BMI with hypertension, hypercholesterolemia, and hyperuricemia did not change substantially across GGT quartiles. For example, within the lowest GGT quartile, BMI was not associated with atherogenic dyslipidemia or poor glycemic control, whereas in the highest GGT quartile, the prevalence rates ranged from 62.3 to 74.7% for dyslipidemia and from 75.3 to 83% for poor glycemic control. The results remained unchanged after adjustment for sex, age, alcohol consumption, diabetes duration, and diabetes treatment. In conclusion, our findings show that BMI was associated with atherogenic dyslipidemia and poor glycemic control only when serum GGT activity was in its high-normal range. These findings suggest that obesity itself may not be a sufficient risk factor for atherogenic dyslipidemia or poor glycemic control in people with type 2 diabetes.

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INTRODUCTION

Recent population-based studies have shown a strong association of serum γ-glutamyltransferase (GGT) activity, even within the reference range, with incident cardiovascular events independently of obesity and other traditional risk factors (1–5). A possible, direct, contribution of GGT to atherosclerosis progression is supported by the growing evidence that human atherosclerotic plaques have GGT enzyme activity (6–9). Given the known function of GGT, these data are consistent with a role for oxidative stress in the atherosclerotic process (6–9). It is also suggested that mild elevations of serum GGT activity and other serum liver enzymes have clinical and epidemiological significance as biomarkers of nonalcoholic fatty liver disease and related liver dysfunction (10,11).

Recently, a strong association of above-median serum GGT activity and obesity with the risk of type 2 diabetes has been reported in a nationally representative cohort of US adults (12). The study found that obesity is associated with an increased prevalence of diabetes only among individuals with high-normal serum GGT concentrations, and not among those with low-normal serum GGT concentrations, suggesting that obesity itself may not be a sufficient risk factor for diabetes and that the clinical determination of GGT concentrations can be useful for identifying individuals at high risk for type 2 diabetes. These findings are supported by an earlier prospective cohort study of 20,158 Finnish men and women that demonstrated that obesity is more strongly associated with incident type 2 diabetes in both adult men and women with median or higher GGT concentrations than in subjects with lower than median GGT concentrations (13).

Given the potential scientific and clinical importance of an interaction between obesity and serum GGT concentrations in predicting type 2 diabetes, we evaluated possible interactions between BMI and serum GGT activity in predicting poor glycemic control and other common comorbidities of type 2 diabetes. We assessed whether the association of BMI with hypertension, atherogenic dyslipidemia, hypercholesterolemia, hyperuricemia, and poor glycemic control varied significantly according to serum GGT activity in a large cohort of type 2 diabetic individuals.

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METHODS AND PROCEDURES

Study participants were enrolled in the Verona Diabetes Study, a prospective observational study designed primarily to evaluate associations between type 2 diabetes and the incidence of cardiovascular complications (14). In this analysis, we included the entire cohort (n = 3,633) of adult outpatients with type 2 diabetes (2,014 men and 1,619 women with a mean age of 68 years) who regularly attended our diabetes clinic during the period January to December 2006 and for whom we had complete data for the analysis. We excluded 791 participants with missing data for serum liver enzymes, lipids, uric acid, cigarette smoking, or alcohol consumption.

Patients were considered to have arterial hypertension if their blood pressure values were ≥140/90 mm Hg or they were taking antihypertensive agents; to have atherogenic dyslipidemia if they had high triglycerides (≥1.7 mmol/l) and/or low high-density lipoprotein (HDL) cholesterol (≤1.04 mmol/l) or they were taking lipid-lowering agents; to have hypercholesterolemia if they had high LDL cholesterol (≥4.13 mmol/l) or they were taking lipid-lowering agents; to have poor glycemic control if they had hemoglobin A1c ≥6.5%; and to have hyperuricemia if they had high uric acid (≥0.416 mmol/l in males and ≥0.386 in females) or they were taking allopurinol.

BMI was calculated by dividing weight in kilograms by the square of height in meters. Blood pressure was measured in triplicate with a standard mercury manometer. Information on daily alcohol consumption, smoking status, and current use of medications was obtained from all participants by questionnaire and/or by reviewing the clinical hospital records. Alcohol consumption was assessed on the basis of the self-reported number of drinks consumed per day. The following volumes of alcoholic beverages were considered one drink: 330 ml beer (containing ~5% alcohol), 150 ml wine (containing ~12% alcohol), and 40 ml strong alcohol (containing ~50% alcohol). Most participants were abstainers (n = 2,209; 60% of total) or drank minimally (alcohol consumption <20 g/day; 30% of total); only ~10% of participants drank moderately (from 20 to 90 g/day). Information on waist circumference, plasma inflammatory markers, leisure time physical activity, and coffee consumption among these participants was not extensively available.

Venous blood was drawn in the morning after an overnight fast. Serum liver enzymes, glucose, lipids, and other biochemical blood measurements were determined using standard laboratory procedures (DAX 96; Bayer Diagnostics, Milan, Italy). LDL cholesterol was calculated using the Friedewald equation. Hemoglobin A1c (HbA1c) was measured using a high-performance liquid chromatography analyzer (Bio-Rad Diamat, Milan, Italy); the upper limit of normal for the laboratory was 5.8%. Most participants had serum liver enzymes within the reference ranges in our laboratory, which for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities were 5–45 U/l, and for GGT activity was 5–55 U/l.

Statistical analysis

Data are means ± s.d. or proportions. Skewed variables were logarithmically transformed to improve normality before analysis. Statistical analyses included the one-way ANOVA and the χ^2-test (for categorical variables).

The participants were categorized into quartiles of serum GGT (<19, 19–29, 30–52, and >52 U/l for men, and <12, 12–19, 20–31, and >31 U/l for women) and into quartiles of BMI (<25.3, 25.3–28.2, 28.3–31.4, and >31.4 kg/m^2).

We used multiple logistic regression analysis to examine the relationships with poor glycemic control (yes/no), hypertension (yes/no), atherogenic dyslipidemia (yes/no), hypercholesterolemia (yes/no), or hyperuricemia (yes/no) included as dependent variables, predicted from the quartiles of BMI within the four quartiles of serum GGT activity (as categorized above). Adjusting variables were age, sex, alcohol consumption, diabetes duration, and diabetes treatment

Table 1 Baseline characteristics of participants grouped according to GGT quartile

	Quartile of GGT				
	Q1	Q2	Q3	Q4	*P* for trend
N	852	898	958	925	
Gender (% male)	57.0	54.0	56.0	55.0	0.647
Age (years)	70.0 ± 10	69.2 ± 10	67.5 ± 11	67.1 ± 10	<0.001
Duration of diabetes (years)	15.5 ± 11	14.3 ± 11	12.2 ± 10	12 ± 10	<0.001
BMI (kg/m^2)	27.8 ± 4.7	28.2 ± 4.6	29.2 ± 5.1	29.7 ± 6.3	<0.001
Oral hypoglycemic drugs (%)	55.3	57.7	60.8	56.2	0.244
Insulin only (%)	25.8	23.7	20.3	26.1	0.346
Current smokers (%)	19.5	16.7	20.0	16.7	0.843
Systolic blood pressure (mm Hg)	142 ± 20	141 ± 20	140 ± 20	142 ± 20	0.123
Diastolic blood pressure (mm Hg)	80 ± 9	80 ± 10	81 ± 10	81 ± 10	0.231
Hemoglobin A1c (%)	7.2 ± 1.1	7.3 ± 1.3	7.4 ± 1.3	7.5 ± 1.4	<0.001
Triglycerides (mmol/l)	1.3 ± 0.7	1.5 ± 1.1	1.6 ± 1.3	1.9 ± 1.2	<0.001
HDL cholesterol (mmol/l)	1.4 ± 0.4	1.4 ± 0.3	1.4 ± 0.4	1.4 ± 0.4	0.239
LDL cholesterol (mmol/l)	2.9 ± 0.8	3.0 ± 0.8	3.0 ± 0.8	3.0 ± 0.8	0.587
Uric acid (mmol/l)	0.30 ± 0.12	0.31 ± 0.12	0.32 ± 0.13	0.32 ± 0.09	0.452
AST (U/l)	19 ± 7	20 ± 6	23 ± 10	34 ± 36	<0.001
ALT (U/l)	20 ± 12	22 ± 10	28 ± 17	39 ± 35	<0.001
GGT (U/l)	11 ± 4	20 ± 5	32 ± 9	98 ± 94	<0.001

Cohort size: n = 3,633. Data are expressed as means ± s.d. or percentages. Significance was evaluated using one-way ANOVA (for continuous variables) and the χ^2-test (for categorical measures). The cutoff points for γ-glutamyltransferase (GGT) quartiles were <19, 19–29, 30–52, and >52 U/l for men and <12, 12–19, 20–31, and >31 U/l for women.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

(i.e., diet, oral hypoglycemic drugs, or insulin). In light of the well-known association between alcohol drinking and liver injury, we repeated the analyses described above after excluding participants who were light-to-moderate drinkers. Values of P <0.05 were considered statistically significant.

The Verona University ethics committee approved the study protocol. All participants gave their informed consent.

RESULTS

Of the 3,633 adult participants in the study, 79.2% had hypertension (defined as blood pressure ≥140/90 mm Hg or on treatment), 64% had atherogenic dyslipidemia (triglycerides ≥1.7 mmol/l and/or HDL cholesterol ≤1.04 mmol/l or on treatment), 51% had hypercholesterolemia (LDL-C ≥4.13 mmol/l or on treatment), 12.4% had hyperuricemia (≥0.416 mmol/l in men and ≥0.386 mmol/l in women or on treatment), and 75% had poor glycemic control (HbA1c ≥6.5%). When we used a less stringent criterion for diagnosing poor glycemic control, 57.3% of participants had HbA1c values ≥7%. Most participants were overweight or obese (~77% had BMI ≥25 kg/m^2).

The main clinical and biochemical characteristics of participants, stratified by GGT quartiles, are shown in **Table 1**. BMI, HbA1c, and serum triglycerides steadily increased across GGT quartiles. Conversely, age and duration of diabetes decreased with increasing serum GGT concentration. Smoking status, gender, treatment of diabetes, blood pressure, and HDL cholesterol, LDL cholesterol, and uric acid concentrations were not significantly different across GGT quartiles. As expected, both serum ALT and AST concentrations increased progressively across GGT quartiles, although the vast majority of participants had serum liver enzymes within the reference ranges (8.8% of participants had ALT >45 U/l, 4.2% had AST >45 U/l, and 26.8% had GGT >55 U/l).

The associations of BMI with different outcome measures were significant, but the associations varied remarkably by

Table 2 Prevalence of hypertension, atherogenic dyslipidemia, hypercholesterolemia, poor glycemic control, and hyperuricemia by BMI quartile after stratification by GGT quartile in type 2 diabetic patients

	Quartile of BMI (kg/m^2)				
Quartile of GGT	<25.3	25.3–28.2	28.3–31.4	>31.4	*P*
Q1					
Hypertension	70.0	80.0	81.5	87.7	<0.001
Atherogenic dyslipidemia	54.2	57.7	57.6	62.3	0.639
Hypercholesterolemia	50.9	50.2	50.0	48.7	0.978
Poor glycemic control	75.1	70.5	67.2	75.3	0.281
Hyperuricemia	8.8	8.6	15.1	17.5	0.101
Q2					
Hypertension	70.9	73.6	81.5	83.5	0.003
Atherogenic dyslipidemia	58.2	62.8	64.9	69.1	0.599
Hypercholesterolemia	49.8	54.8	49.3	53.1	0.587
Poor glycemic control	75.9	79.8	81.4	74.0	0.137
Hyperuricemia	6.8	11.6	9.0	17.5	0.001
Q3					
Hypertension	75.1	78.2	82.3	86.7	0.002
Atherogenic dyslipidemia	57.9	70.3	66.7	65.7	0.05
Hypercholesterolemia	56.4	58.4	55.1	47.7	0.09
Poor glycemic control	74.6	73.2	79.8	83.0	0.164
Hyperuricemia	7.7	8.7	13.7	19.2	<0.001
Q4					
Hypertension	74.3	77.9	79.9	86.5	<0.001
Atherogenic dyslipidemia	62.3	66.4	70.5	74.7	0.01
Hypercholesterolemia	49.7	43.9	49.4	49.5	0.55
Poor glycemic control	64.2	71.8	72.8	83.0	0.004
Hyperuricemia	13.1	11.5	15.2	15.9	0.121

Cohort size: n = 3,633. Data are expressed as percentages. The cutoff points for γ-glutamyltransferase (GGT) quartiles were <19, 19–29, 30–52, and >52 U/l for men and <12, 12–19, 20–31, and >31 U/l for women. Hypertension was defined as blood pressure ≥140/90 mm Hg or on treatment. Atherogenic dyslipidemia was defined as triglycerides ≥1.7 mmol/l and/or high-density lipoprotein cholesterol (HDL-C) ≤1.04 mmol/l or on treatment. Hypercholesterolemia was defined as low-density lipoprotein cholesterol (LDL-C) ≥4.13 mmol/l or on treatment. Poor glycemic control was defined as hemoglobin A1c ≥6.5%. Hyperuricemia was defined as uric acid ≥0.416 mmol/l in men and ≥0.386 mmol/l in women or on treatment.

P values for trends in each quartile of GGT have been adjusted for age, sex, diabetes duration, diabetes treatment and alcohol consumption using multiple logistic regression analysis.

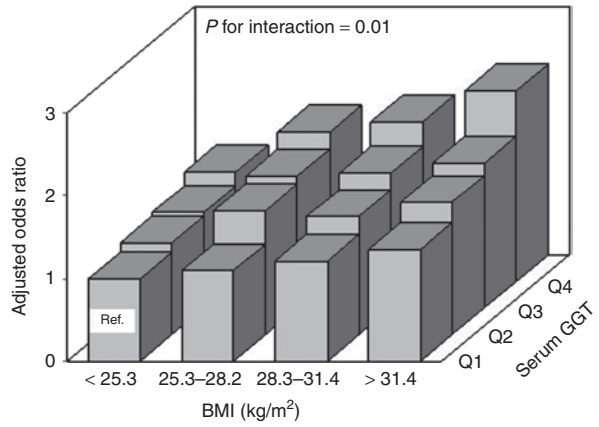

Figure 1 Adjusted odds ratios of prevalent atherogenic dyslipidemia by quartiles of BMI and serum γ-glutamyltransferase (GGT) activity in 3,633 type 2 diabetic patients. Odds ratios were adjusted for age, sex, alcohol consumption, diabetes duration, and diabetes treatment.

GGT activity (**Table 2**). As serum GGT activity increased, the association of BMI with atherogenic dyslipidemia and poor glycemic control strengthened ($P = 0.01$ and 0.004 for interactions, respectively; see also **Figure 1** for atherogenic dyslipidemia). In contrast, the association of BMI with hypertension, hypercholesterolemia, and hyperuricemia did not substantially change across GGT categories. For example, within the lowest quartile of serum GGT, BMI was not associated with atherogenic dyslipidemia or poor glycemic control, in contrast to the highest quartile of GGT, where the prevalence rates ranged from 62.3 to 74.7% for atherogenic dyslipidemia, and from 75.3 to 83% for poor glycemic control. Notably, these results remained significant even after adjustment for sex, age, alcohol consumption, diabetes duration, and diabetes treatment. Further adjustment for statin use did not materially alter the results (data not shown). **Figure 1** shows the multiple-adjusted odds ratios of prevalent atherogenic dyslipidemia by quartiles of BMI and GGT in the entire sample of participants.

Almost identical results were found when participants who were light-to-moderate drinkers were excluded from the statistical analysis (data not shown).

The results did not change substantially when a less stringent criterion for diagnosing poor glycemic control (i.e., HbA1c ≥7%) was used or when the analysis was restricted to those with good glycemic control (HbA1c <6.5%). In this subgroup of participants ($n = 908$), BMI was associated with atherogenic dyslipidemia only among those with high-normal GGT, and not in those with low-normal GGT. In contrast, the association of BMI with hypertension, hyperuricemia, and hypercholesterolemia did not substantially change across GGT categories (data not shown).

When we repeated the main analyses with the quartiles of ALT rather than GGT, the results were essentially the same as those presented in **Table 2**. As serum ALT increased, the association of BMI with atherogenic dyslipidemia and poor glycemic control strengthened ($P = 0.002$ and 0.053 for interactions, respectively); in contrast, the association of BMI with hypertension, hyperuricemia, and hypercholesterolemia did not change substantially across ALT categories (data not shown).

DISCUSSION

To the best of our knowledge, this is the first study to examine possible interactions between serum GGT and BMI and their effects on the prevalence of atherogenic dyslipidemia, hypercholesterolemia, hypertension, hyperuricemia, and poor glycemic control in a large outpatient cohort of type 2 diabetic individuals.

The main finding of this study is that in people with type 2 diabetes, BMI was significantly associated with poor glycemic control and atherogenic dyslipidemia only among those with high-normal serum GGT activity, and not in those with low-normal serum GGT activity. In contrast, the association of BMI with hypertension, hyperuricemia, and hypercholesterolemia did not change substantially across GGT quartiles. Importantly, the interaction between serum GGT activity and BMI remained strongly predictive of atherogenic dyslipidemia and poor glycemic control even after adjustment for important confounders such as age, sex, diabetes duration, diabetes treatment, and alcohol consumption. Because self-reporting of alcohol consumption may be unreliable and often underestimates the true risk, we repeated the statistical analyses after excluding those participants who were light-to-moderate drinkers. Notably, the main results were unchanged.

Overall, our findings, although only correlative in nature, complement previously published observations (12,13) suggesting that the association of BMI with the risk of type 2 diabetes varied remarkably with serum GGT activity in both sexes.

The strong association of serum GGT activity with some diabetes-related metabolic disorders, such as atherogenic dyslipidemia and poor glycemic control, may be explained by underlying, not mutually exclusive, biological mechanisms such as fatty liver, insulin resistance, and enhanced oxidative stress (6–11,15–19).

Patients with fatty liver are more insulin resistant and have higher plasma triglycerides and lower HDL cholesterol than those without fatty liver (10,11,15,20). Moreover, markers of hepatic fat content, such as serum GGT activity and other liver enzymes, have been shown in large prospective studies to predict the incidence of type 2 diabetes, insulin resistance, and cardiovascular disease independently of obesity (1–5,16–20). Thus, insulin resistance in humans does not seem to depend on obesity, as severe insulin resistance also characterizes patients lacking subcutaneous fat, such as those with lipodystrophy (21). A close linear relationship has been found between liver fat content and direct measures of hepatic insulin resistance independent of obesity (21). Thus, fatty liver might help to explain why some, but not all, obese individuals have insulin resistance and why even lean individuals may be insulin resistant and thereby at risk of developing diabetes-related metabolic disorders. There is now growing evidence to suggest that GGT is not only a marker of fatty liver but also a marker of oxidative stress (6–9). It is possible that the occurrence of GGT-mediated redox reactions plays a direct role in the pathogenesis of atherogenic

dyslipidemia and poor glycemic control, independently of the presence of fatty liver, possibly through the induction of chronic inflammation and insulin resistance (22).

Our study has several strengths, including the large cohort size, the complete nature of the dataset, and the ability to adjust for important potential confounders. Despite the comprehensive nature of the dataset, there are some important limitations, however. First, the cross-sectional design of our study precludes the establishment of causal or temporal relationships between BMI and serum GGT activity in the prediction of diabetes-related metabolic abnormalities. Second, the diagnosis of fatty liver was based on serum liver enzymes but not confirmed by ultrasound imaging or liver biopsy. Finally, information on potential causes of liver enzymes elevation such as viral hepatitis was not available in this study. However, nonalcoholic fatty liver disease is the commonest cause of chronic liver disease in people with type 2 diabetes (~70–75% of type 2 diabetic patients may have some form of nonalcoholic fatty liver disease) (10,23), whereas chronic viral hepatitis is extremely rare in Italian type 2 diabetic individuals (<2%) (23). In addition, when we limited the analysis to subjects with serum ALT and GGT activity within the reference ranges (as nonalcoholic fatty liver disease is associated with more modest elevations of serum liver enzymes than other causes of chronic liver disease) (11), the results were essentially the same as those presented.

In conclusion, our findings indicate that in type 2 diabetic patients, the association of obesity with the prevalence of atherogenic dyslipidemia and poor glycemic control varied remarkably with serum GGT activity. BMI was associated with atherogenic dyslipidemia and poor glycemic control only when serum GGT activity was in its high-normal range. In patients with low-normal serum GGT activity, BMI was not associated with atherogenic dyslipidemia and poor glycemic control. Our findings raise the possibility that obesity itself may not be a sufficient risk factor for atherogenic dyslipidemia or poor glycemic control in type 2 diabetes. Future prospective cohort studies are, obviously, required to confirm whether the interaction between BMI and serum GGT is useful for identifying a high-risk subpopulation of type 2 diabetic patients.

DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

1. Jousilahti P, Rastenyte D, Tuomilehto J. Serum gamma-glutamyltransferase, self-reported alcohol drinking, and the risk of stroke. *Stroke* 2000;31:1851–1855.
2. Lee DS, Evans JC, Robins SJ *et al*. Gamma-glutamyltransferase and metabolic syndrome, cardiovascular disease, and mortality risk: the Framingham Heart Study. *Arterioscler Thromb Vasc Biol* 2007;27:127–133.
3. Ruttmann E, Brant LJ, Concin H *et al*. Gamma-glutamyltransferase as a risk factor for cardiovascular disease mortality: an epidemiological investigation in a cohort of 163,944 Austrian adults. *Circulation* 2005;112:2130–2137.
4. Lee DH, Silventoinen K, Hu G *et al*. Serum gamma-glutamyltransferase predicts non-fatal myocardial infarction and fatal coronary heart disease among 28,838 middle-aged men and women. *Eur Heart J* 2006;27:2170–2176.
5. Schindhelm RK, Dekker JM, Nijpels G *et al*. Alanine aminotransferase predicts coronary heart disease events: a 10-year follow-up of the Hoorn Study. *Atherosclerosis* 2007;191:391–396.
6. Lee DH, Blomhoff R, Jacobs DR Jr. Is serum gamma glutamyltransferase a marker of oxidative stress? *Free Radic Res* 2004;38:535–539.
7. Paolicchi A, Emdin M, Ghliozeni E *et al*. Images in cardiovascular medicine: human atherosclerotic plaques contain gamma-glutamyl transpeptidase enzyme activity. *Circulation* 2004;109:1440.
8. Emdin M, Passino C, Pompella A, Paolicchi A. Gamma-glutamyltransferase as a cardiovascular risk factor. *Eur Heart J* 2006;27:2145–2146.
9. Franzini M, Corti A, Martinelli B *et al*. Gamma-glutamyltransferase activity in human atherosclerotic plaques. Biochemical similarities with the circulating enzyme. *Atherosclerosis*. 2008; e-pub ahead of print 11 April 2008.
10. Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med* 2002;346:1221–1231.
11. de Alwis NM, Day CP. Non-alcoholic fatty liver disease: the mist gradually clears. *J Hepatol* 2008;48(Suppl 1):S104–S112.
12. Lim JS, Lee DH, Park JY, Jin SH, Jacobs DR Jr. A strong interaction between serum gamma-glutamyltransferase and obesity on the risk of prevalent type 2 diabetes: results from the Third National Health and Nutrition Examination Survey. *Clin Chem* 2007;53:1092–1098.
13. Lee DH, Silventoinen K, Jacobs Dr Jr, Jousilahti P, Tuomilehto J. Gamma-glutamyltransferase, obesity, and the risk of type 2 diabetes: observational cohort study among 20,158 middle-aged men and women. *J Clin Endocrinol Metab* 2004;89:5410–5414.
14. Muggeo M, Zoppini G, Bonora E *et al*. Fasting plasma glucose variability predicts 10-year survival of type 2 diabetic patients: the Verona Diabetes Study. *Diabetes Care* 2000;23:45–50.
15. Browning JD, Szczepaniak LS, Dobbins R *et al*. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004;40:1387–1395.
16. Thamer C, Tschritter O, Haap M *et al*. Elevated serum GGT concentrations predict reduced insulin sensitivity and increased intra-hepatic lipids. *Horm Metab Res* 2005;37:246–251.
17. Hanley AJ, Williams K, Festa A *et al*. Liver markers and development of the metabolic syndrome. The Insulin Resistance Atherosclerosis Study. *Diabetes* 2005;54:3140–3147.
18. Nannipieri M, Gonzales C, Baldi S *et al*. Liver enzymes, the metabolic syndrome, and incident diabetes: the Mexico City diabetes study. *Diabetes Care* 2005;28:1757–1762.
19. Targher G. Nonalcoholic fatty liver disease, the metabolic syndrome and the risk of cardiovascular disease: the plot thickens. *Diabet Med* 2007;24:1–6.
20. Targher G, Bertolini L, Poli F *et al*. Nonalcoholic fatty liver disease and risk of future cardiovascular events among type 2 diabetic patients. *Diabetes* 2005;54:3541–3546.
21. Yki-Jarvinen H, Westerbacka J. The fatty liver and insulin resistance. *Curr Mol Med* 2005;5:287–295.
22. Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. *Circulation* 2005;111:1448–1454.
23. Targher G, Bertolini L, Padovani R *et al*. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. *Diabetes Care* 2007;30:1212–1218.