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Serum γ-glutamyltransferase within its normal concentration range is related to the presence of diabetes and cardiovascular risk factors

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Abstract

Aims Although many studies have reported an association between serum γ-glutamyltransferase (GGT) and cardiovascular risk factors, the mechanism of this relationship has not been clarified.

Methods The medical records of 29 959 subjects (age, median 48, range 14–90 years; 16 706 men, 13 253 women) who visited the Center for Health Promotion at Samsung Medical Center for a medical check-up between January 2001 and December 2003, were investigated. Subjects with hepatic enzyme/GGT concentrations higher than three times the upper limit of the reference range, a positive test for hepatitis C virus antibody, a positive test for hepatitis B virus surface antigen, currently taking anti-diabetic/anti-hypertensive/anti-lipid medication, or a white blood cell (WBC) count higher than 10 000 cells/ml, were excluded. The subjects of each gender were classified into five groups according to their serum GGT concentrations, into quartiles of the normal range of GGT (groups 1, 2, 3 and 4) and into a group with elevated GGT (group 5).

Results As the group number increased (group 1 → 5), the frequencies of all of the following increased: (i) diabetes and impaired fasting glucose (IFG); (ii) hypertension, obesity (body mass index ≥ 27 kg/m^2), dyslipidaemia (LDL-cholesterol ≥ 4.1 mmol/l and/or triglyceride ≥ 2.46 mmol/l, or HDL-cholesterol < 1.16 mmol/l); (iii) metabolic syndrome. Moreover, these significant relationships between GGT concentrations within its normal range and the presence of diabetes/IFG, hypertension, obesity, dyslipidaemia, and metabolic syndrome persisted after adjusting for several clinical and biochemical variables and for the presence of fatty liver based on ultrasonographic findings. Odds ratios (95% CI) for group 4 (highest quartile of normal range of GGT) vs. group 1 (lowest quartile of normal range of GGT); the referent group, were 3.16 (2.15–4.65) for diabetes, 2.24 (1.73–2.90) for IFG, 1.93 (1.59–2.33) for obesity, 1.38 (1.23–1.55) for dyslipidaemia and 2.88 (2.28–3.65) for metabolic syndrome in men. In women, the odds ratios were 2.72 (1.34–5.52), 3.67 (2.26–5.97), 2.10 (1.61–2.74), 1.80 (1.58–2.04) and 3.57 (2.52–5.07), respectively.

Conclusions Our data show that, even within its normal range, serum GGT concentrations are closely associated with the presence of diabetes and cardiovascular risk factors, and that these associations are independent of a fatty liver by ultrasonography.

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Abbreviations ALT, serum alanine aminotransferase; AST, serum aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, serum γ-glutamyl transferase; HDL-C, HDL-cholesterol; IFG, impaired fasting glucose; LDL-C, LDL-cholesterol; NFG, normal glucose tolerance; SBP, systolic blood pressure; WBC, white blood cell

Introduction

Serum γ-glutamyl transferase (GGT) is one of the biliary enzymes and is synthesized in epithelial cells of the intrahepatic duct [1]. In addition to its diagnostic uses as an index of liver dysfunction, and as a biological marker of alcohol intake, serum GGT is of substantial epidemiological significance. Several population studies have shown a strong cross-sectional association between serum GGT concentrations and many cardiovascular risk factors [2–4]. In addition, a number of prospective studies have identified baseline serum GGT concentration as an independent risk marker for the development of both cardiovascular and cerebrovascular disease [5–9]. Excess deposition of fat in the liver, usually termed non-alcoholic fatty liver disease, is strongly associated with elevated serum GGT, obesity, insulin resistance and hyperinsulinaemia [5,10–12]. The Samsung Medical Center is a 1300-bed hospital and one of the largest referral centres in Korea. More than 10 000 subjects visit the Center for Health Promotion at the Samsung Medical Center for an annual medical check-up. Information on lifestyle factors, past medical history, and a family history of diabetes was obtained for all participants by trained nurses. In addition, physical examination, laboratory testing, including serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), GGT, hepatitis C virus antibody and hepatitis B virus surface antigen is conducted routinely. In particular, abdominal ultrasonography is performed in each case according to a standard protocol. Because many factors can affect the relationships between serum GGT concentrations and cardiovascular risk factors, it is essential to adjust for several confounding variables to elucidate the true nature of these associations. In this study, we investigated the relationship between serum GGT concentrations and the frequencies of diabetes, hypertension, dyslipidaemia, obesity and metabolic syndrome, after adjustment for several clinical and biochemical variables and for the presence of fatty liver, based on an ultrasonographic finding.

Subjects and methods

Subjects

The medical records of the 29 959 subjects (age, median 48, range 14–90 years; 16 706 men, 13 253 women) who visited our Center for Health Promotion for a medical check-up between 2001 and 2003 were investigated. As routine medical checks are not covered by the Korean medical insurance system, we suspect that most of our study subjects were members of the upper-middle economic class. Subjects meeting any of the following criteria were excluded: hepatic enzyme/GGT concentrations higher than three times the upper limit of the reference range, a positive test for hepatitis C virus antibody, a positive test for hepatitis B virus surface antigen, those currently taking anti-diabetic/anti-hypertensive/anti-lipid medications, or a white blood cell (WBC) count higher than 10 000 cells/ml. Men and women were classified separately into five groups according to their serum GGT concentrations, into quartiles of the normal range of GGT and into an elevated GGT group (Table 1).

Diabetes was defined as fasting plasma glucose ≥ 7.0 mmol/l; hypertension as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg; dyslipidaemia as a serum LDL-cholesterol (LDL-C) ≥ 4.2 mmol/l and/or triglyceride ≥ 2.46 mmol/l and/or HDL-cholesterol (HDL-C) < 1.16 mmol/l; obesity as a body mass index ≥ 27 kg/m^2. Metabolic syndrome was defined as three or more of the following abnormalities: body mass index (BMI) ≥ 25 kg/m^2; triglyceride ≥ 1.7 mmol/l; HDL-cholesterol < 1.04 mmol/l; fasting plasma glucose (FPG) ≥ 6.1 mmol/l; systolic blood pressure (SBP) ≥ 130 mmHg and diastolic blood pressure (DBP) ≥ 85 mmHg [13]. We used body mass index as a parameter of obesity, because data on waist circumference were not available. This study was approved by the Internal Review Board (IRB) of the Samsung Medical Center.

Assay methods

Height and weight were measured with subjects wearing light clothing, but no shoes, in the morning; blood pressure was measured with a mercury sphygmomanometer on the right arm with subjects in a sitting position after a 5-min rest. Body mass index was calculated as weight in kilograms divided by the square of the height in metres. Information on lifestyle factors including alcohol consumption, cigarette smoking and a family history of diabetes were obtained by trained nurses. A family history of diabetes was defined as a mother, father, sister or brother with diagnosed diabetes. Questions about alcohol intake included items about frequency of alcohol consumption per week and type of alcoholic beverage. Weekly alcohol intake was calculated and then converted to daily alcohol consumption. Subjects were classified as non-drinkers or current drinkers when they averaged < 180 or 181 to < 360 g/week of alcohol, respectively. Heavy alcohol drinking was defined as ≥ 360 g/week of alcohol. Blood samples were obtained in the morning after an overnight fast. Plasma glucose was measured in duplicate by the hexokinase method using an autoanalyser

Table 1 Clinical characteristics of study subjects according to the level of serum γ-glutamyl transferase

	Men					Women				
Serum GGT (IU/ml)	2–20 (*n* = 3632)	21–26 (*n* = 2850)	27–35 (*n* = 3215)	36–50 (*n* = 3056)	51–150 (*n* = 3953)	2–11 (*n* = 3359)	12–14 (*n* = 3289)	15–19 (*n* = 3223)	20–50 (*n* = 2975)	51–150 (*n* = 407)
Age (years)	48.8 ± 11.7	49.1 ± 10.5	49.0 ± 9.8	48.3 ± 9.2	47.1 ± 8.5	45.1 ± 9.1	47.3 ± 9.5	48.7 ± 9.5	50.3 ± 9.3	51.7 ± 9.3
Alcohol drinking (%)	63.8	81.3	83.3	86.2	92.8	27.4	26.5	30.8	32.2	30
Heavy alcohol drinking (%)	41.3	50.5	59.8	67.5	79.4	4.8	5.3	8.5	10.3	11.3
Current smoking (%)	28.9	34.7	36.1	42.4	50.0	0.9	3.7	5.2	6.5	7.9
BMI (kg/m^2)	23.0 ± 2.5	23.9 ± 2.4	24.4 ± 2.4	24.9 ± 2.6	25.3 ± 2.6	21.9 ± 2.4	22.4 ± 2.6	22.9 ± 2.8	23.7 ± 3.1	24.2 ± 3.1
BMI ≥ 27 kg/m^2 (%)	5.2	9.0	13.0	20.0	23.8	2.5	5.0	7.9	14.4	16.8
Body fat percentage	16.5 ± 4.6	21.0 ± 4.9	21.9 ± 4.3	22.8 ± 4.4	23.5 ± 4.6	27.1 ± 4.8	28.2 ± 5.1	29.2 ± 5.3	30.6 ± 5.6	31.7 ± 5.7
FPG (mmol/l)	5.07 ± 0.62	5.23 ± 0.93	5.33 ± 0.99	5.42 ± 1.02	5.53 ± 1.08	4.84 ± 0.50	4.95 ± 0.51	5.04 ± 0.67	5.19 ± 0.83	5.40 ± 1.14
IFG (%)/diabetes (%)	2.7/1.0	4.0/2.4	6.8/3.1	7.7/4.5	10.8/5.7	0.7/0.3	2.1/0.4	3.2/1.0	5.2/2.8	7.9/4.9
SBP (mmHg)	116.7 ± 16.2	117.8 ± 15.9	119.7 ± 15.9	120.3 ± 16.0	122.5 ± 16.5	109.3 ± 15.2	112.9 ± 24.6	113.3 ± 17.2	116.4 ± 18.0	117.8 ± 18.0
DBP (mmHg)	72.9 ± 10.7	74.2 ± 10.5	75.9 ± 10.6	76.2 ± 10.7	77.9 ± 11.1	66.6 ± 10.6	68.2 ± 11.0	68.6 ± 11.3	70.0 ± 11.3	71.1 ± 12.4
Hypertension (%)	9.3	9.3	10.7	12.2	15.0	4.5	7.5	8.6	11.6	14.0
LDL-C (mmol/l)	3.28 ± 0.77	3.45 ± 0.78	3.58 ± 0.80	3.63 ± 0.81	3.63 ± 0.87	3.10 ± 0.77	3.29 ± 0.84	3.45 ± 0.89	3.61 ± 0.92	3.67 ± 0.93
Triglyceride (mmol/l)	1.14 ± 0.56	1.36 ± 0.68	1.55 ± 0.81	1.74 ± 0.93	2.07 ± 1.22	0.92 ± 0.45	1.03 ± 0.54	1.15 ± 0.63	1.34 ± 0.76	1.63 ± 1.04
HDL-C (mmol/l)	1.33 ± 0.32	1.30 ± 0.32	1.28 ± 0.31	1.27 ± 0.29	1.27 ± 0.30	1.55 ± 0.34	1.55 ± 0.36	1.51 ± 0.36	1.47 ± 0.36	1.47 ± 0.36
DyslipidAemia (%)	43.4	51.8	60.2	65.6	71.7	21.7	30.4	37.6	48.6	53.9
WBC (cell/ml)	5732 ± 1348	5949 ± 1365	6023 ± 1360	6234 ± 1375	6358 ± 1405	5193 ± 1302	5334 ± 1243	5518 ± 1369	5678 ± 1390	5903 ± 1465
AST (IU/ml)	20.2 ± 5.4	21.4 ± 5.6	22.9 ± 6.5	24.9 ± 7.7	28.5 ± 9.4	18.0 ± 4.8	18.8 ± 4.7	20.0 ± 5.3	23.0 ± 8.2	30.6 ± 13.9
ALT (IU/ml)	20.4 ± 8.1	24.1 ± 10.1	28.2 ± 12.6	33.5 ± 16.9	41.1 ± 20.2	14.4 ± 5.2	16.2 ± 6.2	18.8 ± 7.9	25.2 ± 13.7	39.5 ± 21.7
GGT (IU/ml)	16.3 ± 3.0	23.5 ± 1.7	30.7 ± 2.6	42.3 ± 4.3	78.1 ± 24.4	9.6 ± 1.5	13.0 ± 0.8	16.7 ± 1.4	27.6 ± 7.5	74.3 ± 22.3
Family history of diabetes (%)	8.8	9.8	11.3	13.1	13.6	12.9	12.6	12.5	15.4	17.2
College or university graduation (%)	58.3	58.6	57.2	58.8	57.1	60.6	57.9	59.3	57.3	62.3
Household income ≥ 40 000 $US/year (%)	54.9	54.0	55.4	54.4	53.9	56.2	54.2	54.9	56.7	55.0
Fatty liver in ultrasonography (%)	22.1	35.2	47.7	57.3	60.0	7.9	14.0	23.8	36.5	46.6
Metabolic syndrome (%)	2.8	6.1	10.1	14.9	20.1	1.2	2.9	5.8	11.2	16.9

Data are means ± SD or percentage.

ALT, serum alanine aminotransferase; AST, serum aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FPG fasting plasma glucose; GGT, serum γ-glutamyl transferase; HDL-C, HDL-cholesterol; IFG, impaired fasting glucose; LDL-C, LDL-cholesterol; SBP, systolic blood pressure; WBC, white blood cell.

Definitions: heavy alcohol drinking as an alcohol intake ≥ 360 g/week; hypertension as an SBP ≥ 140 mmHg and/or a DBP ≥ 90 mmHg; dyslipidaemia as an LDL-C ≥ 4.1 mmol/l and/or triglyceride ≥ 2.46 mmol/l and/or HDL-C < 1.16 mmol/l.

Metabolic syndrome was defined as having three or more of the following abnormalities: BMI ≥ 25 kg/m^2; triglyceride ≥ 1.7 mmol/l; HDL-C < 1.04 mmol/l; FPG ≥ 6.1 mmol/l; SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg.

(Hitachi, Tokyo, Japan), which had an interassay coefficient of variation of 1.6%. Standard liver testing, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides were measured using an autoanalyser (Hitachi, Tokyo, Japan), as were white blood cell counts (Sysmex, Kobe, Japan). HBsAg was measured using a commercially available immunoradiometric assay (Riakey, Koyang, Korea), and anti-HCV was also tested by immunoradiometric assay (Riakey, Koyang, Korea). Per cent of body fat was measured by bioelectrical impedence analysis (In Body 3.0, Biospace, Seoul, Korea).

Three grades were defined for fatty infiltration of liver: grade 1 (mild), slight diffuse increase in the fine echoes in the hepatic parenchyma with normal visualization of the diaphragm and intrahepatic vessel borders; grade 2 (moderate), moderate diffuse increase in the fine echoes with slightly impaired visualization of the diaphragm and intrahepatic vessels; and grade 3 (severe), marked increase in the fine echoes with poor or no visualization of the diaphragm, intrahepatic vessels, and posterior portion of the right lobe of the liver [14]. In this study, any degree of fatty infiltration including mild, moderate and severe infiltrations were considered as fatty liver. A total of 27 radiologists (medical doctors who were expert on abdominal untrasonography) performed full standard abdominal ultrasonography. There was no difference in the frequencies of fatty liver according to the radiologist ($\chi^2 = 22.3$).

Statistics

Data are expressed as means ± 1 SD. ANOVA or χ^2 tests were used to compare group variables. Logistic regression analyses were used to obtain odds ratio for diabetes, impaired fasting glucose, hypertension, dyslipidaemia, obesity and metabolic syndrome after adjusting for several clinical and biochemical variables and the presence of fatty liver. Statistical analyses were performed using the SPSS/PC+ software program (SPSS Inc., Chicago, IL, USA). Differences were considered statistically significant at a level of $P < 0.05$.

Results

The clinical characteristics of the study subjects according to serum γ-glutamyl transferase are presented in Table 1. Univariate analyses showed that the following increased in frequency with increasing GGT: heavy alcohol drinking, current smoking, family history of diabetes, obesity, impaired fasting glucose, diabetes, hypertension, dyslipidaemia, fatty liver and metabolic syndrome in both genders. Serum white blood cell count, serum alanine aminotransferase and serum aspartate aminotransferase increased with increasing GGT in both genders. There was no significant difference in income and educational background with increasing serum GGT. In the logistic regression analyses between the lowest quartile of the normal range of GGT (group 1) and the highest quartile (group 4), age, WBC, ALT, AST, the presence of family history of diabetes, smoking history, alcohol consumption, abnormal fasting glucose, dyslipidaemia, obesity and fatty liver independently predicted serum GGT, in both genders (Table 2). Hypertension was a significant predictor of serum GGT in women only.

Table 2 Odds ratios (95% CI) in the highest quartile of the normal range of GGT with the lowest quartile as the referent group

	Men		Women	
	Odds ratios (95% CI)	*P*	Odds ratios (95% CI)	*P*
Age	1.01 (1.00–1.02)	< 0.05	1.03 (1.02–1.04)	< 0.001
WBC	1.16 (1.11–1.22)	< 0.001	1.18 (1.12–1.24)	< 0.001
AST	1.01 (0.99–1.02)	NS	0.96 (0.95–0.98)	< 0.001
ALT	1.11 (1.09–1.12)	< 0.001	1.22 (1.03–1.50)	< 0.001
Family history of diabetes	1.33 (1.08–1.63)	< 0.01	1.24 (1.03–1.50)	< 0.05
Smoking history	*P* for trend	< 0.001	*P* for trend	< 0.01
Ex-smoker	1.21 (1.02–1.43)	< 0.05	1.20 (0.90–1.60)	NS
Current smoker	2.14 (1.79–2.55)	< 0.001	1.75 (1.29–2.37)	< 0.001
Alcohol history	*P* for trend	< 0.001	*P* for trend	< 0.001
< 180 g/week	1.04 (0.82–1.33)	NS	1.49 (1.25–1.79)	< 0.001
181–360 g/week	1.53 (1.20–1.94)	< 0.01	2.18 (1.67–2.83)	< 0.001
≥ 360 g/week	4.82 (4.01–5.79)	< 0.001	4.28 (3.33–5.51)	< 0.001
Abnormal fasting glucose	*P* for trend	< 0.001	*P* for trend	< 0.001
Impaired fasting glucose	2.20 (1.62–2.99)	< 0.001	3.70 (2.19–6.27)	< 0.001
Diabetes	2.96 (1.91–4.60)	< 0.001	2.49 (1.16–5.36)	< 0.05
Hypertension	1.09 (0.89–1.34)	NS	1.37 (1.05–1.77)	< 0.05
LDL-cholesterol ≥ 4.1 mmol/l	1.78 (1.51–2.09)	< 0.001	1.98 (1.66–2.36)	< 0.001
Triglyceride = 2.24 mmol/l	2.68 (2.26–3.18)	< 0.001	1.91 (1.50–2.43)	< 0.001
HDL-cholesterol < 1.16 mmol/l	1.33 (1.15–1.54)	< 0.001	0.92 (0.76–1.120	NS
BMI ≥ 27 kg/m^2	1.72 (1.38–2.14)	< 0.001	2.06 (1.53–2.76)	< 0.001
Fatty liver	2.11 (1.83–2.43)	< 0.001	2.00 (1.65–2.41)	< 0.001

Age, WBC, AST and ALT were continuous variables. Diabetes, fasting plasma glucose (FPG) ≥ 7.0 mmol/l; impaired fasting glucose (IFG), FPG ≥ 6.1 mmol/l. Subjects with GGT (2–20) in men and those with GGT (2–11) in women were the referent group, respectively. Range of GGT in the highest quartile of men was 36–50 and that of women was 20–50 IU/ml, respectively. Hypertension was defined as an systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg.

Table 3 Odds ratios (95% CI) for diabetes and impaired fasting glucose according to serum γ-glutamyl transferase concentrations

Men			Women		
GGT (IU/ml)	Diabetes	IFG	GGT (IU/ml)	Diabetes	IFG
21–26	1.96 (1.31–2.95)*	1.35 (1.02–1.78)**	12–14	0.96 (0.42–2.19)†	2.42 (1.47–3.99)*
27–35	2.30 (1.56–3.40)	2.12 (1.65–2.73)	15–19	1.48 (0.71–3.12)†	3.06 (1.89–4.96)
36–50	3.16 (2.15–4.65)	2.24 (1.73–2.90)	20–50	2.72 (1.34–5.52)*	3.67 (2.26–5.97)
51–150	3.82 (2.58–5.67)	3.16 (2.43–4.09)	51–150	2.72 (1.11–6.69)**	4.31 (2.29–8.12)

Diabetes, fasting plasma glucose (FPG) ≥ 7.0 mmol/l; impaired fasting glucose (IFG), FPG ≥ 6.1 mmol/l. Subjects with GGT (2–20) in men and those with GGT (2–11) in women were the referent group, respectively. Subjects with impaired fasting glucose were excluded to calculate the odds ratio for diabetes, and those with diabetes were excluded for impaired fasting glucose.
*$P < 0.01$, **$P < 0.05$, †not significant. All other odds ratio were $P < 0.001$. All odds ratio were obtained after adjustment for age, family history of diabetes, smoking history, alcohol history, body mass index, body fat per cent, white blood cell counts, aspartate aminotransferase, alanine aminotransferase, systolic and diastolic blood pressure, serum LDL-cholesterol, HDL-cholesterol, triglyceride, the presence of fatty liver based on ultrasonographic finding and radiologist who performed ultrasonogram.

Table 4 Odds ratios (95% CI) for dyslipidaemia, obesity and hypertension according to serum γ-glutamyl transferase concentrations

GGT (IU/ml)	Dyslipidaemia	Obesity	Hypertension
Men			
21–26	1.09 (0.98–1.21)†	1.29 (1.05–1.58)**	0.88 (0.74–1.05)†
27–35	1.32 (1.18–1.47)	1.48 (1.22–1.80)	0.95 (0.80–1.13)†
36–50	1.38 (1.23–1.55)	1.93 (1.59–2.33)	1.05 (0.88–1.25)†
51–150	1.65 (1.46–1.86)	1.93 (1.59–2.35)	1.26 (1.05–1.50)**
Women			
12–14	1.27 (1.13–1.43)	1.42 (1.08–1.87)**	1.29 (1.04–1.61)**
15–19	1.45 (1.29–1.63)	1.64 (1.26–2.14)	1.22 (0.98–1.51)†
20–50	1.80 (1.58–2.04)	2.10 (1.61–2.74)	1.33 (1.06–1.68)**
51–150	1.72 (1.34–2.22)	1.62 (1.07–2.43)**	1.35 (0.91–2.00)†

Obesity was defined as body mass index ≥ 27 kg/m^2, dyslipidaemia as an LDL-C ≥ 4.1 mmol/l and/or triglyceride ≥ 2.46 mmol/l and/or HDL-C < 1.16 mmol/l, and hypertension as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg. Subjects with GGT (2–20) in men and those with GGT (2–11) in women were the referent group, respectively.
*$P < 0.01$, **$P < 0.05$, †not significant. All other odds ratio were $P < 0.001$. Odds ratios for dyslipidaemia; adjusted for age, body mass index, body fat per cent, smoking history, alcohol history, white blood cell counts, aspartate aminotransferase, alanine aminotransferase, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, the presence of fatty liver by untrasonography and radiologist who performed ultrasonogram. Odds ratios for obesity; adjusted for age, smoking history, alcohol history, white blood cell count, aspartate aminotransferase, alanine aminotransferase, systolic blood pressure, diastolic blood pressure, LDL-C, triglyceride, HDL-C, fasting plasma glucose, the presence of fatty liver by ultrasonography and radiologist who performed ultrasonogram. Odds ratios for hypertension; adjusted for age, smoking history, alcohol history, body mass index, body fat per cent, white blood cell count, aspartate aminotransferase, alanine aminotransferase, LDL-C, triglyceride, HDL-C, fasting plasma glucose, the presence of fatty liver by ultrasonography and radiologist who performed ultrasonogram.

Table 3 shows that a higher concentration of serum GGT, even within its normal range, is a risk factor for diabetes and impaired fasting glucose, and that these relationships are independent of age, gender, a family history of diabetes, smoking history, alcohol history, body mass index, white blood cell count, liver enzyme, blood pressure, lipid profile or the presence of fatty liver. Table 4 presents odds ratios for obesity and dyslipidaemia according to serum GGT concentrations and shows that an elevated serum GGT concentration is an independent risk factor for obesity and dyslipidaemia. However, the relationship between hypertension and serum GGT was not consistent (Table 4). Odds ratios (95% CI) for the metabolic syndrome in the highest quartile of normal range of GGT compared with the lowest quartile of normal range of GGT; the referent group were 2.88 (2.28–3.65) in men and 3.57 (2.52–5.07) in women (Table 5).

Discussion

Our analysis demonstrates that the serum GGT concentration, even within its normal range, is closely related to the presence of components of the metabolic syndrome. Although several studies have already revealed these associations, these have usually involved a relatively small numbers of subjects and the

Table 5 Odds ratios (95% CI) for metabolic syndrome according to serum γ-glutamyl transferase concentrations

Men			Women		
GGT (IU/ml)	Model 1	Model 2	GGT (IU/ml)	Model 1	Model 2
21–26	1.99 (1.55–2.56)	1.69 (1.31–2.18)	12–14	1.89 (1.30–2.74)*	1.67 (1.15–2.44)*
27–35	3.03 (2.40–3.83)	2.32 (1.83–2.94)	15–19	3.19 (2.25–4.51)	2.53 (1.78–3.60)
36–50	4.01 (3.18–5.05)	2.88 (2.28–3.65)	20–50	4.90 (3.48–6.91)	3.57 (2.52–5.07)
51–150	4.74 (3.76–5.98)	3.57 (2.82–4.51)	51–150	4.87 (3.10–7.65)	3.76 (2.37–5.99)

Metabolic syndrome was defined as having three or more of the following abnormalities: body mass index ≥ 25 kg/m^2; triglyceride ≥ 1.7 mmo/l; HDL-cholesterol < 1.04 mmol/l; fasting plasma glucose ≥ 6.1 mmol/l; systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg. Subjects with GGT (2–20) in men and those with GGT (2–11) in women were the referent group, respectively.
*P < 0.01. All other odds ratios were P < 0.001.
Model 1, adjusted for age, gender, smoking history, alcohol history, white blood cell counts, aspartate aminotransferase and alanine aminotransferase.
Model 2, adjusted for the presence of fatty liver based on ultrasonographic finding, radiologist who performed the ultrasonogram and the variables of model 1.

exclusion criteria used were insufficient. In some studies, subjects with hepatitis C virus antibody and/or hepatitis B virus surface antigen were not excluded. In particular, we found that serum GGT concentration increase, even within its normal range, is a risk factor for diabetes, dyslipidaemia, obesity and metabolic syndrome, independent of the presence of fatty liver by ultrasonography.

The mechanism of the relationship between insulin resistance and GGT elevation has not been clarified, although hepatic steatosis or hepatic insulin resistance, caused by visceral obesity, may be the first possible mechanism [12,15–18]. However, dose–response relations between GGT concentration and the presence of diabetes, or with cardiovascular risk factors, were observed among subjects within a normal ALT range, which usually increases in cases of hepatic steatosis [7]. Also, in the present study, significant associations were found between GGT concentration and the presence of diabetes and with cardiovascular risk factors in subjects with serum ALT within the normal range. These findings suggest that hepatic steatosis and hepatic insulin resistance are not the only mechanisms that explain these relations, although a low normal ALT value does not guarantee freedom from underlying steatohepatitis. Imaging studies, including ultrasonography, cannot be used to determine accurately the severity of liver damage without a liver biopsy. However, the significant association between serum GGT concentration and the presence of the metabolic syndrome, even after adjusting for the presence of fatty liver, suggests that another mechanism governs the relation between serum GGT concentration and metabolic syndrome.

Because oxidative stress can play a role in the pathophysiology of cardiovascular diseases, and GGT has a pivotal role in maintaining intracellular glutathione transport into most types of cells [19–21], oxidative stress provides a second possible mechanism. Increased GGT activity may be a response to oxidative stress, one which can increase the transport of glutathione precursors into cells. In addition, GGT leaks into serum possibly as a result of normal cell turnover and cellular stress. Subclinical inflammation, which could represent a third underlying mechanism [22,23], may be another possible cause. In the present study, the white blood cell count was a significantly related to serum GGT concentration, after adjusting for age, gender, alcohol history, smoking history, body mass index, blood pressure, lipid profile, serum AST, serum ALT, fasting plasma glucose and the presence of fatty liver ($\beta = 0.028$, $R^2 = 0.477$, $P < 0.001$).

The most important limitation of our study is that this is a cross-sectional study so that causation cannot be inferred. In addition, all variables were only measured once, and therefore prevalence rates of hypertension, impaired fasting glucose/diabetes and the metabolic syndrome may be inflated.

In conclusion, we believe that our data suggest that the serum GGT concentration may be a marker for diabetes and cardiovascular risk factors, independent of its well-known associated variables and of fatty liver by ultrasonography. Further investigation of the mechanisms underlying these associations is warranted.

Competing interests

None declared.

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