Available online at www.sciencedirect.com
ScienceDirect
Clinica Chimica Acta 384 (2007) 163–166
www.elsevier.com/locate/clinchim

Short communication

Relationship between γ-glutamyltransferase, lipids and lipoprotein(a) in the general population

Giuseppe Lippi [a,*], Giovanni Targher [b], Martina Montagnana [a], Gian Luca Salvagno [a], Gian Cesare Guidi [a]

[a] Sezione di Chimica Clinica, Dipartimento di Scienze Morfologico-Biomediche, Università degli Studi di Verona, Italy
[b] Sezione di Endocrinologia e Malattie del Metabolismo, Dipartimento di Scienze Biomediche e Chirurgiche, Università degli Studi di Verona, Italy

Received 16 May 2007; received in revised form 10 June 2007; accepted 10 June 2007
Available online 16 June 2007

Abstract

Background: Population-based epidemiological studies have shown a convincing association between increased γ-glutamyltransferase (GGT) activity and components of the metabolic syndrome, type 2 diabetes, hypertension, ischaemic stroke and myocardial infarction. However, little information is available on the interaction between GGT activity and traditional or emerging markers of cardiovascular risk.
Methods: We performed a retrospective analysis to retrieve results of serum GGT, fasting plasma glucose (FPG), creatinine, LDL-cholesterol, HDL-cholesterol, triglycerides and lipoprotein(a) tests performed on outpatients referred by the general practitioners to our laboratory for routine blood testing during the last 5 years.
Results: The concentrations of most lipid parameters varied with increasing GGT activities. There were graded, positive, associations of GGT concentrations with LDL-cholesterol, triglycerides, atherogenic index of plasma (AIP) and the total to HDL-cholesterol ratio, whereas a negative association was observed with HDL-cholesterol. Lipoprotein(a) concentrations increased in parallel with GGT activity, though such trend did not reach statistical significance. The frequencies of subjects with undesirable values according to the NCEP-ATP III and AHA/ACC thresholds increased across the spectrum of GGT thresholds for all lipids parameters but lipoprotein(a). These associations remained statistically significant even after adjustment for gender, age, FPG and creatinine concentrations. In multiple linear regression analyses GGT activity predicted plasma concentrations of LDL-cholesterol, triglycerides, HDL-cholesterol (negatively), AIP and the total to HDL-cholesterol ratio independently of age, gender, impaired fasting glucose/diabetes and creatinine levels.
Conclusions: The results of this large retrospective study indicate that increased GGT activities are independently associated with a more atherogenic lipid profile in general population.

Keywords: Cholesterol; Lipids; Lipoprotein(a); Triglycerides; γ-glutamyltransferase

1. Introduction

Recent population-based epidemiological studies have shown a convincing association between increased γ-glutamyltransferase (GGT) activity, even within the reference range, and components of the metabolic syndrome. It was also prospectively demonstrated that baseline GGT activity predict development of type 2 diabetes, hypertension, ischaemic stroke and myocardial infarction [1–3]. Moreover, evidence was provided on the interaction between serum GGT levels and individual components of the metabolic syndrome, entailing that people with low-normal serum GGT levels (e.g. <20 U/L) would no longer be considered at high risk of prevalent type 2 diabetes [4]. Nevertheless, little information is available on the interaction between GGT activity, the traditional lipid profile including low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, triglycerides, and emerging markers of cardiovascular risk such as the atherogenic index of plasma (AIP), the total to HDL-cholesterol ratio and lipoprotein(a). Given

* Corresponding author. Sezione di Chimica Clinica, Dipartimento di Scienze Morfologico-Biomediche, Università degli Studi di Verona, Ospedale Policlinico G.B. Rossi, Piazzale Scuro, 10, 37134 - Verona, Italy. Tel.: +39 045 8124516; fax: +39 045 8201889.
E-mail address: ulippi@tin.it (G. Lippi).

0009-8981/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.cca.2007.06.005

the important clinical implications of an interaction between plasma lipids and GGT in predicting the cardiovascular risk, a careful analysis focused on this relationship is needed.

2. Materials and methods

We performed a retrospective analysis on the database of the Laboratory Information System of the Clinical Chemistry Laboratory of the University Hospital of Verona to retrieve cumulative results of serum GGT, fasting plasma glucose (FPG), creatinine, LDL-cholesterol, HDL-cholesterol, triglycerides and lipoprotein(a) tests which have been performed on all outpatients referred by the general practitioners for routine blood testing during the last 5 years (April 2002-April 2007). Venous blood from outpatients is routinely collected in the morning on fasting subjects. Lipoprotein(a) is measured by the reference nephelometric assays on a Behring Nephelometer-II (Dade Behring GmbH, Marburg, Germany). Serum lipids, lipoproteins, FPG, creatinine and GGT are assayed on the Roche/Hitachi Modular System P (Roche Diagnostics GmbH, Mannheim, Germany). LDL-cholesterol is calculated by the Friedewald's equation [5], whereas the AIP is calculated as log(triglycerides/HDL-cholesterol) [6]. The guidelines from the American Heart Association (AHA) and the American College of Cardiology (ACC) [7] and the US-National Cholesterol Education Programme Adult Treatment Panel III (NCEP-ATP III) [8] were used to calculate the percentages of study participants with undesirable values of FPG and lipids.

Data are expressed as means±SD or proportions. Skewed variables were logarithmically transformed to improve normality prior to analysis and then back-transformed to their natural units for presentation in table. Statistical analyses included the one-way analysis of variance (ANOVA), the chi-squared test with Yates' correction for continuity (for categorical variables), the analysis of covariance (ANCOVA) and the multivariable linear regression analysis. Nonparametric statistical tests were also used, but because the results were identical to those obtained by parametric procedures, only the latter were presented. In ANCOVA analysis the relationships of plasma lipids with GGT concentrations (categorized into three groups: i.e., ≤20, 20–40 and >40 U/l) were tested after adjustment for gender, age, fasting glucose and creatinine concentrations. To further assess the independence of the association of GGT concentrations (considered as a continuous measure) with different plasma lipids, we performed multivariable linear regression analyses. In these multivariable regression models plasma lipids were individually considered as dependent variables (entered as continuous measures), whereas GGT, gender, age, serum creatinine and fasting glucose concentrations were included as covariates. P values <0.05 were considered statistically significant. Statistical analyses were performed using the statistical package SPSS version 12.0 (SPSS, Chicago, IL).

3. Results

Cumulative results for all the parameters included in statistical analyses were retrieved for 1227 outpatients >35 years old (449 females, 37% of total). As shown in Table 1, the concentrations of most lipid parameters remarkably varied with increasing GGT activities. There were graded, positive, associations of GGT concentrations with LDL-cholesterol, triglycerides, AIP and the total to HDL-cholesterol ratio, whereas a negative association was observed with HDL-cholesterol. Similarly, the mean FPG and creatinine concentrations significantly increased across GGT categories. Lipoprotein(a) concentrations increased in parallel with GGT activity, though such trend did not reach a statistical significance. After stratification of patients according to the NCEP-ATP III and AHA/ACC thresholds, the frequencies of those with undesirable values of LDL-cholesterol, triglycerides, HDL-cholesterol, AIP and the total to HDL-cholesterol ratio significantly increased across the spectrum of GGT thresholds. On the contrary, such trend did not achieve a statistical significance for those with undesirable lipoprotein(a) values.

Notably, as also shown in Table 1, the strong associations between serum GGT activity and lipid parameters (except for lipoprotein(a)) remained statistically significant even after adjustment for gender, age, FPG and creatinine concentrations. Almost identical results were observed in multiple linear regression analyses (data not shown). In these analyses, GGT

Table 1
Stratification according to the activity of γ-glutamyltransferase (GGT) of cumulative values for glucose, creatinine and lipids assayed on 1227 consecutive outpatients referred by the general practitioners to our laboratory for routine blood testing over a 5 year-period

	GGT categories			P values [a]	P values [b]
	≤20 U/L	20–40 U/L	>40 U/L		
n	717	358	202	–	–
Gender (M/F)	199/518	210/148	110/92	<0.0001	NA
Age	55±17	56±15	60±14	<0.005	NA
Creatinine (mmol/L)	64±17	71±17	72±21	<0.0001	NA
Fasting plasma glucose (mmol/L)	5.0±0.9	5.5±1.3	5.7±1.6	<0.0001	NA
%pts. ≥6.1 mmol/L	3%	10%	13%	<0.0001	NA
LDL-cholesterol (mmol/L)	2.8±0.9	3.0±0.9	3.1±1	<0.0001	<0.0001
% pts. ≥3.37 mmol/L	30%	40%	44%	<0.0001	<0.0001
Triglycerides (mmol/L)	1.0±0.6	1.3±0.7	1.5±1.0	<0.0001	<0.0001
%pts. ≥1.7 mmol/L	11%	32%	35%	<0.0001	<0.0001
HDL-cholesterol (mmol/L)	1.6±0.4	1.4±0.4	1.5±0.5	<0.0001	<0.0001
%pts. ≤1.04 mmol/L	4%	16%	13%	<0.0001	<0.0001
Lipoprotein(a) (mg/L)	128±260	242±267	268±285	0.160	0.250
%pts. ≥300 mg/L	24%	27%	31%	0.185	0.210
Atherogenic index of plasma	−0.23±0.20	−0.02±0.30	−0.01±0.30	<0.0001	<0.0001
%pts. >0	18%	44%	51%	<0.0001	<0.0001
Total to HDL-cholesterol ratio	3.0±0.9	3.7±1.3	3.7±1.2	<0.0001	<0.0001
%pts. ≥3.5	30%	57%	56%	<0.0001	<0.0001

Data are expressed as means±SD or proportions. NA, not applicable.
[a] P values for the trend by one-way ANOVA or chi-squared test (for categorical variables).
[b] P values for the trend by analysis of covariance (ANCOVA) adjusted for age, gender, plasma glucose and creatinine concentrations.

activity strongly predicted plasma concentrations of LDL-cholesterol, triglycerides, HDL-cholesterol (negatively), AIP and the total to HDL-cholesterol ratio independently of age, gender, FPG (or presence of impaired fasting glucose/diabetes) and creatinine levels (standardized beta coefficients for GGT ranging from 0.219 to 0.368; $P<0.0001$).

4. Discussion

It has been highlighted that increased GGT concentrations may predict the incidence of type 2 diabetes, metabolic syndrome, cardiovascular disease as well as death [1–3], suggesting that this enzyme may be regarded not only as index of liver damage and alcohol consumption, but also as a reliable marker of cardiovascular risk [9]. Adjusting for traditional risk factors, a 1-SD increase in GGT levels confers a 13% increase in cardiovascular risk and 26% increased risk of death. Accordingly, individuals in the highest GGT quartile experiences a ~70% increase in the incidence of cardiovascular events [10]. Although such association has been attributed to GGT as a marker of metabolic and cardiovascular risk, little information is currently available on the relationship between GGT concentrations and the lipid profile in the general population, since most of previous epidemiological studies have been principally performed in type 2 diabetic population.

It has been observed that GGT activity is significantly associated with total cholesterol, triglyceride, FPG, homocysteine and systolic blood pressure after controlling for possible confounders such as cigarette smoking, daily alcohol consumption and obesity [9]. GGT activities within the normal range have also been positively associated with triglyceride and total cholesterol irrespective of the drinking or obesity status, suggesting that GGT measurement may have important clinical implications as being more than just a marker of alcohol consumption and obesity-related liver disease [11]. After classifying a cohort of Japanese population into five groups according to GGT concentrations, Kim *et al.* observed that the frequencies of undesirable values for LDL-cholesterol and/or triglyceride increased in parallel with the GGT activity after adjustment for a variety of potential confounders [12]. Overall, the main findings of our study – which was performed on a large cohort of general population – essentially agree with this conclusion, since the mean concentration and the frequency of undesirable values according to the AHA and NCEP-ATP III criteria increased steadily across the spectrum of GGT thresholds for LDL-cholesterol, triglycerides, AIP, HDL-cholesterol and the total to HDL-cholesterol ratio. These results remained essentially unchanged even after adjusting for gender, age, FPG and creatinine concentrations, all of which being potentially important correlates of GGT. In addition, in our multivariate analyses, higher concentrations of GGT strongly predicted most of lipid parameters independently of potential confounders. At variance with earlier studies, we have also investigated the potential influence of GGT activity on serum lipoprotein(a). Although both the mean concentration and the prevalence of undesirable values of this lipoprotein tended to be higher across the GGT thresholds, such trend did not reach statistical significance. However, this is not surprising in that the concentration of this atherogenic lipoprotein particle varies over 1000-fold between individuals and it is determined primarily by quantitative and qualitative polymorphisms at the apolipoprotein(a) locus [13], which globally account for up to 98% of lipoprotein(a) variance in the general population [14].

In conclusion, results of this large retrospective study indicate that increased GGT activities are independently associated with a more atherogenic lipid profile in general population. Such an association may be at least partially explained by enhanced oxidative stress, liver steatosis and insulin resistance, which may be important underlying mechanisms by which raised GGT levels might adversely affect lipoprotein metabolism. We are aware of some limitations in this study. First, the cross-sectional design of this study precludes the establishment of causal or temporal relations among lipids and GGT. Prospective studies will be required to sort out the time sequence of events. Another possible limitation is that we cannot definitively exclude that the strong associations between GGT and lipid parameters could be partly explained by some unmeasured anthropometric/demographical variables such as body mass index, concomitant pharmacological treatment and, especially, alcohol consumption, which would also explain the higher prevalence of male subjects in the top tertile of GGT activity. However, it is also to mention that GGT concentrations are associated with lipid abnormalities independently of drinking and obesity status [11]. Thus, irrespective of potential unmeasured effects of lifestyle factors, obesity or other associated comorbidities, we have observed a marked interaction between GGT, even within its normal range, and lipid parameters in the general population, suggesting the possibility that determination of GGT may help in cardiovascular risk prediction with important management implications, provided that laboratory, clinical and other diagnostic data are available. Similarly, if longer term prospective studies will substantiate this findings, the identification of people with raised GGT activity would highlight a subgroup of individuals to be targeted with more intensive lipid-lowering therapy for lowering the risk of cardiovascular events.

References

[1] Perry IJ, Wannamethee SG, Shaper AG. Prospective study of serum gamma-glutamyltransferase and risk of NIDDM. Diabetes Care 1998;21:732–7.
[2] Lee DH, Ha MH, Kim JH, et al. Gamma-glutamyltransferase and diabetes — a 4 year follow-up study. Diabetologia 2003;46:359–64.
[3] Pompella A, Emdin M, Passino C, Paolicchi A. The significance of serum gamma-glutamyltransferase in cardiovascular diseases. Clin Chem Lab Med 2004;42:1085–91.
[4] Lim JS, Lee DH, Park JY, Jin SH, Jacobs Jr DR. 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, doi:10.1373/clinchem.2006.079814 [published 3 May].
[5] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.
[6] Dobiasova M. Atherogenic index of plasma [log(triglycerides/HDL-cholesterol)]: theoretical and practical implications. Clin Chem 2004;50:1113–5.
[7] Grundy SM, Pasternak R, Greenland P, Smith Jr S, Fuster V. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. Circulation 1999;100:1481–92.

[8] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
[9] Sakuta H, Suzuki T, Yasuda H, Ito T. Gamma-glutamyl transferase and metabolic risk factors for cardiovascular disease. Intern Med 2005;44: 538–41.
[10] Lee DS, Evans JC, Robins SJ, et al. Gamma glutamyl-transferase and metabolic syndrome, cardiovascular disease, and mortality risk: the Framingham Heart Study. Arterioscler Thromb Vasc Biol 2007;27: 127–33.
[11] Lim JS, Kim YJ, Chun BY, Yang JH, Lee DH, Kam S. The association between serum GGT level within normal range and risk factors of cardiovascular diseases. J Prev Med Pub Health 2005;38:101–6.
[12] Kim DJ, Noh JH, Cho NH, et al. Serum gamma-glutamyltransferase within its normal concentration range is related to the presence of diabetes and cardiovascular risk factors. Diabet Med 2005;22:1134–40.
[13] Lippi G, Guidi G. Lipoprotein(a): an emerging cardiovascular risk factor. Crit Rev Clin Lab Sci 2003;40:1–42.
[14] DeMeester CA, Bu X, Gray RJ, Lusis AJ, Rotter JI. Genetic variation in lipoprotein (a) levels in families enriched for coronary artery disease is determined almost entirely by the apolipoprotein (a) gene locus. Am J Hum Genet 1995;56:287–93.