MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2014; 20: 706-710
DOI: 10.12659/MSM.890245

Received: 2013.12.26
Accepted: 2014.01.13
Published: 2014.04.30

Serum gamma-glutamyl transferase: A novel biomarker for coronary artery disease

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABC 1 Yu Mao*
DE 2 Xiaolong Qi*
BC 1 Wenjun Xu*
BC 1 Haoming Song*
DF 2 Mingxin Xu
DF 2 Wanrong Ma
AG 1 Lin Zhou

1 Division of Cardiology, Shanghai Tongji Hospital, Shanghai, China
2 Institute of Digestive Disease, Shanghai Tongji Hospital, Shanghai, China

* Equal contribution

Corresponding Author: Lin Zhou, e-mail: linzhoutj@126.com

Source of support: This study was supported by the Shanghai Municipal Bureau of Health Youth Scientific Research Projects (2009Y071); Shanghai Committee of Science and Technology Research Projects (11411951400)

Background: Atherosclerosis is a chronic inflammatory process, in which oxidative stress is the key event. Gamma-glutamyl transferase (GGT) is a cellular production of oxidants. We aimed to elucidate the relationship of serum GGT levels and coronary artery disease (CAD) in a Chinese population.

Material/Methods: A total of 513 adult subjects who had undergone coronary angiography were enrolled in the study. Clinical characteristics, coronary angiography, and serum samples were collected from all the patients and analyzed for the serum GGT, blood lipids, and cardiovascular risk factors.

Results: Subjects with CAD had significantly increased activity of serum GGT (p=0.003). Serum GGT levels exhibited positive correlations with alcohol intake (β=0.177, p<0.001), coronary complexity (β=0.068, p<0.001), and triacylglycerol (β=0.058, p<0.001). High-density lipoprotein cholesterol levels (β=0.157, p=0.008) and age (β=0.004, p=0.002) were negatively correlated with serum GGT in the CAD group. The coronary complexity presented a negative correlation with Ig-apolipoprotein AI (β=−2.517, p=0.001) and positive correlations with smoking (β=0.640, p<0.001), Ig-GGT (β=0.613, p=0.004), Ig high sensitivity-C reactive protein (β=0.320, p<0.001), and hypertension (β=0.286, p<0.026).

Conclusions: The study showed a positive correlation between serum GGT and CAD in a Chinese population. Serum GGT levels may be a potential biomarker for CAD.

MeSH Keywords: **Cardiovascular Diagnostic Technique • Coronary Artery Disease • gamma-Glutamyl Transpeptidase**

Abbreviations: **ALT** – alanine aminotransferase; **ApoAI** – apolipoprotein AI; **ApoB** – apolipoprotein B; **CAD** – coronary artery disease; **GGT** – gamma-glutamyl transferase; **HDL-C** – high-density lipoprotein cholesterol; **HsCRP** – high-sensitivity C reactive protein; **LDL-C** – low-density lipoprotein cholesterol; **Lp(a)** – lipoprotein (a); **TC** – total cholesterol; **TG** – triacylglycerol

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Background

Coronary artery disease (CAD) is a worldwide public health problem with high morbidity and mortality, which involves a chronic inflammatory atherosclerosis process with stable CAD and acute coronary syndromes [1,2]. Various mechanisms are associated with the pathogenesis of CAD in which oxidation and inflammation play significant roles [3]. Serum gamma-glutamyl transferase (GGT) has been widely used as a diagnostic index of liver dysfunction [4]. However, in recent years, a number of epidemiological studies showed that serum GGT was positively associated with cardiovascular mortality, myocardial infarction, stroke, high blood pressure, diabetes, and even cancer [5], suggesting that serum GGT may participate in oxidative and inflammatory reactions. In this study, we aimed to investigate the effect of serum GGT activity on oxidation stress and its diagnostic performance for CAD in a Chinese population.

Material and Methods

Study population

We retrospectively evaluated adult patients who had undergone coronary angiography between 2004 and 2010 in Shanghai Tongji Hospital, China. We excluded patients were with any of the following: 1) severe liver disease or kidney disease; 2) severe infections or heart failure; 3) hyperthyroidism, hypothyroidism, cancer, autoimmune diseases, or chronic connective tissue disease; 4) lipid lowering drugs taken for nearly two months; 5) major surgery, trauma, or burns. A total of 513 subjects were finally enrolled in the study, which consisted of 365 participants with CAD (CAD group) and 148 normal participants (control group). The CAD group was then divided into 3 sub-groups: single-vessel disease (n=114), double-vessel disease (n=121), and triple-vessel disease (n=130). The study protocol was approved by the local ethics committee of Shanghai Tongji Hospital.

All subjects were asked to provide information about cardiovascular risk factors such as hypertension or diabetes mellitus, smoking, and details regarding medication administration received before the admission. Hypertension was defined as a systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg in resting state, or self-reported use of an antihypertensive drug [6]. Subjects were considered to have diabetes if they had been informed of the diagnosis by a physician, were taking oral anti-hyperglycemic agents or insulin, or were receiving diet therapy, and those who presented with fasting serum glucose of more than 7.0 mmol/L or above on 2 measurements during hospitalization [7]. Subjects were considered as smokers if they smoked at the time of admission or reported cessation <6 months before [8]. Subjects were considered as excessive drinkers if men drank >40 g alcohol per day and women >20 g [9].

Biochemical analysis

A venous blood specimen (5 mL) was collected at 6:00 a.m. to 7:00 a.m. 1 day before angiography, after an overnight fast. Serum was separated by centrifugation at 1500 × g for 15 min. All laboratory analysis were performed at the department of Chemical Pathology and standard techniques were used to evaluate triacylglycerol, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein, apolipoprotein AI, apolipoprotein B, lipoprotein (a) and alanine aminotransferase, and high-sensitivity C-reactive protein levels. Serum GGT levels were measured spectrophotometrically with the American Beckman DXC800 automatic biochemical analyzer. Reference range for GGT was 0-40 U/L.

Coronary angiography

After preoperative preparation, coronary angiography was performed by vascular medicine physicians through the femoral artery or radial artery, using the Judkins method, with 2 projections for the left coronary artery and 4 projections for the right coronary artery, adding extra projections if necessary. Evaluation criteria were according to ACC/AHA Guidelines for Coronary Angiography [10]. Angiographic results were judged by 2 senior physician specialists observing images together according to: the degree of coronary artery stenosis (by comparing the area of narrowing to an adjacent normal segment), percentage reduction of normal vessels, and lesion diameter ≥50% of the normal vessel diameter. When angiographic results involved left anterior descending artery, left circumflex artery, or right coronary artery, branches were divided into single, double, or triple vessel disease. When the left main coronary artery was involved, left anterior descending and left circumflex artery were also calculated.

Statistical analysis

All data was analyzed by SPSS 14.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation. The differences between normally distributed numeric variables were evaluated by Student's *t*-test or one-way ANOVA, while non-normally distributed variables were analyzed by Mann-Whitney U test or Kruskal-Wallis variance analysis, as appropriate. Chi-square test was employed for the comparison of categorical variables. Multivariate analysis used multivariate stepwise regression. $P<0.05$ was considered as statistical significance.

Results

According to coronary angiography, 114 subjects (22.2%) were diagnosed with single-vessel disease, 121 subjects (23.6%)

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Table 1. Baseline characteristics of clinic, angiography and laboratory.

	Coronary complexity				P value
	0 (n=148)	1 (n=114)	2 (n=121)	3 (n=130)	
Male	63 (42.6%)	96 (84.2%)	94 (77.7%)	99 (76.2%)	<0.001
Age	56.0±9.14	57.5±12.1	60.6±12.0	64.1±12.1	0.423
Hypertension (%)	22 (24.86%)	50 (20.16%)	70 (28.22%)	128 (51.63%)	<0.001
Diabetes (%)	20 (13.5%)	23 (20.2%)	29 (24.0%)	44 (33.8%)	<0.001
Alcohol intake (%)	22 (14.9%)	29 (25.4%)	20 (16.5%)	19 (14.6%)	0.090
Smoking (%)	35 (23.6%)	61 (53.5%)	71 (58.7%)	76 (58.5%)	<0.001
TC (mmol/L)	4.71±0.89	4.61±0.93	4.73±1.12	4.66±1.24	0.823
TG (mmol/L)	1.66±1.12	1.60±0.95	1.85±1.49	1.79±1.30	0.392
LDL-C (mmol/L)	2.89±0.75	2.94±0.85	3.01±0.99	3.02±0.99	0.549
HDL-C (mmol/L)	1.09±0.30	1.01±0.33	0.97±0.31	0.92±0.26	<0.001
ApoAI (mg/L)	1.30 (1.15~1.44)	1.14 (1.03~1.3)	1.16 (1.0~1.34)	1.14 (1.03~1.33)	<0.001
ApoB (mg/L)	0.82 (0.69~0.99)	0.88 (0.76~1.0)	0.83 (0.69~1.04)	0.83 (0.71~1.02)	0.058
Lp(a) (mg/L)	160 (101~322)	187 (91~332)	187 (65~302)	167 (58~304)	0.548
HsCRP (mg/L)	2.05 (1~8)	8 (1.65~29)	7 (2~25.9)	8.85 (3.7~23.8)	<0.001
ALT (U/L)	18.5 (13.8~27.3)	32.5 (18~57.5)	34.5 (18.3~54.5)	32 (23~50)	<0.001
GGT (U/L)	22 (15~37)	23 (16~49)	24 (17~47)	30 (20~41.5)	0.003

ALT – alanine aminotransferase; ApoAI – apolipoprotein AI – ApoB, apolipoprotein B; GGT – gamma-glutamyl transferase; HDL-C – high-density lipoprotein cholesterol; HsCRP – high sensitivity C reactive protein; LDL-C – low-density lipoprotein cholesterol; Lp(a) – lipoprotein (a); TC – total cholesterol; TG – triacylglycerol.

with double-vessel disease, 130 subjects (25.3%) with triple-vessel disease, and 148 subjects (28.8%) were normal. Clinical, angiography, and laboratory baseline characteristics are summarized in Table 1. Subjects with triple-vessel disease in he tCAD group had statistically significantly higher prevalence ($p<0.001$) of diabetes, hypertension, and smoking compared with double-vessel, single-vessel, and control groups. Lesions associated with the left anterior descending artery were the most common, followed by right coronary and circumflex artery. Left main coronary artery was the rarest, with only 7 cases.

Serum GGT levels had statistical significance ($p=0.003$) in the triple-vessel disease group when compared with the other groups, demonstrating an increase from single-vessel disease as 23 (16–49) to triple-vessel disease as 30 (20–41.5). In addition, serum HDL-C, apolipoprotein AI, high-sensitivity C reactive protein, hypertension, and diabetes were also significantly higher ($p<0.001$) in the triple-vessel group. There was no significant difference ($p>0.05$) in each group concerning serum total cholesterol, triacylglycerol, low-density lipoprotein cholesterol, apolipoprotein B, lipoprotein (a) level, and alcohol intake (Table 1).

According to the multiple regression analysis, IgGGT was positively correlated with alcohol intake ($\beta=0.177$, $p<0.001$), the coronary complexity ($\beta=0.068$, $p<0.001$), and TG ($\beta=0.058$, $p<0.001$), in which alcohol intake and coronary complexity had high correlation coefficients. However, HDL-C levels ($\beta=0.157$, $p=0.008$) and age ($\beta=0.004$, $p=0.002$) were negatively correlated with IgGGT in the CAD group (Table 2).

With coronary complexity as the dependent variable, multiple-regression analysis revealed that it had a negative correlation with Ig-apolipoprotein AI ($\beta=-2.517$, $p=0.001$), and positive correlations with smoking ($\beta=0.640$, $p<0.001$), IgGGT ($\beta=0.613$, $p=0.004$), Ig high-sensitivity C reactive protein ($\beta=0.320$, $p<0.001$), and hypertension ($\beta=0.286$, $p<0.026$). There was a weak correlation between coronary complexity and age ($\beta=0.037$, $p<0.001$) (Table 3).

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Table 2. Multivariate analysis between GGT and other factors.

Characters	β	SE	Standard β	t	Sig
HDL-C	–0.157	0.059	–0.153	–2.671	0.008
TG	0.058	0.013	0.254	4.571	<0.001
Alcohol intake	0.177	0.046	0.216	3.852	<0.001
Coronary complexity	0.068	0.015	0.269	4.591	<0.001
Age	–0.004	0.001	–0.183	–3.066	0.002

GGT – gamma-glutamyl transferase; HDL-C – high-density lipoprotein cholesterol; TG – triacylglycerol.

Table 3. Multivariate analysis between coronary complexity and other factors.

Characters	β	SE	Standard β	t	Sig
Age	0.037	0.005	0.387	7.170	<0.001
Smoking	0.640	0.126	0.276	5.087	<0.001
lg-HsCRP	0.320	0.091	0.185	3.531	<0.001
lg-ApoA1	–2.517	0.733	–0.179	–3.432	0.001
lg-GGT	0.613	0.208	0.155	2.940	0.004
Hypertension	0.286	0.128	0.115	2.233	0.026

ApoAI – apolipoprotein AI; GGT – gamma-glutamyl transferase; HsCRP – high sensitivity C reactive protein.

Discussion

It is increasingly believed that atherosclerosis is a chronic inflammatory process, the key event of which is oxidative stress resulting from the imbalance between reactive oxygen species and the antioxidant defense system [11]. Reactive oxygen species can inhibit prostacyclin synthetase activity, promote the synthesis of thromboxaneA2, and lead to platelet aggregation and even thrombosis [12]. While increasing lipid peroxidation, reactive oxygen species can cause red blood cells to produce plasma protein cross-linking and increased blood viscosity. However, it results in the injury of endothelial cells and attenuation of lipid infiltration [11]. As a result, the endothelial cells are activated, leading to the release of endothelin and adhesion molecules. In addition, activated monocytes can induce the expression of cytokines, such as tumor necrosis factor and interleukin. Subsequently, macrophages and endothelial cells are induced into the intrarenal arterial wall and oxidize low-density lipoproteins recognized by macrophage scavenger receptors [13]. Eventually, atherosclerosis is induced due to the lipid accumulation and foam cell formation from smooth muscle cells.

GGT is an enzyme on the surface of the cellular membrane, which is responsible for the extracellular catabolism of glutathione of the anti-oxidation mechanism. It has been always associated with alcohol intake or liver dysfunction [4]. Biologically, GGT divides the gamma-glutamyl part from glutathione. Then, the glutamyl fragment is transferred into amino acid; either a dipeptide or glutathione. Therefore, GGT supplies cellular glutathione resynthesis [14]. Meanwhile, the cysteinylglycine moiety on the cellular membrane or in the extracellular space can act as a strongly reduced agent of iron, with the development of the super-oxide ion and hydrogen peroxide. The oxidization of low-density lipoprotein cholesterol particles may occur, which may participate in the formation of inflammatory atheroma within the vascular endothelial wall [15]. Therefore, serum GGT may take part in atherosclerotic plaque progression and rupture. As a result, studies indicated that serum GGT level might be a potential biomarker of atheromatous plaque in humans [16].

Recent studies showed that serum GGT has a strong association with cardiovascular risk factors [5]. According to a prospective study of 6997 subjects (aged 40–59 years) with no history of CAD or diabetes mellitus in 24 British towns, researchers performed a 24-year followed-up and concluded that the elevated GGT (≥22 U/L) was significantly related with the increased risk of fatal CAD events and mortality, which was independent of the established CAD risk factors [17]. In our study, serum GGT levels were related to alcohol intake, coronary lesion count, triacylglycerol, HDL-C, and age in the CAD

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group. Alcohol intake and HDL-C levels present high correlation coefficients. However, there is no significant difference in alcohol consumption among the 4 groups in the correlation between coronary complexity and serum GGT levels.

It has been demonstrated that HDL-C possesses significant antioxidant activity, primarily mediated via the inhibition of the ox-low-density lipoprotein with a subsequent reduction of the cellular uptake by the monocyte macrophage system [18]. In addition, HDL-C could prevent atherosclerosis via effects on platelet function, endothelial function, coagulation parameters, inflammation, and interactions with triglyceride-rich lipoprotein. However, the specific mechanisms by which GGT performs the oxidation process of ox-low-density lipoprotein cholesterol need further investigation. In the study, serum GGT levels were higher in triple-vessel disease, double-vessel disease, and diffuse pathology patients.

The study is limited in that it was a retrospective analysis without histopathology investigation. The relationship between GGT and pathological mechanisms of CAD should be further studied. In addition, the study lacked the follow-up analysis of cardiovascular event and mortality.

Conclusions

Our study results suggest that serum GGT has a positive correlation with CAD in the Chinese population, which may act as a novel biomarker for CAD.

Competing interests

None declared.

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