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Association of serum gamma-glutamyltransferase (GGT) and diabetes with triglycerides-to-HDL cholesterol ratio in Japanese subjects: The Nagasaki Study

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Background: Although we reported in a previous study that diabetes with a high serum triglycerides to high-density lipoprotein cholesterol (TG-HDL) ratio constitutes a risk for atherosclerosis, associations in terms of TG-HDL ratio between diabetes and gamma-glutamyltransferase (GGT), which is also known as an independent risk factor for atherosclerosis, have not yet been clarified. The purpose of this study was to test the hypothesis that a positive association between GGT and diabetes may be confined to high TG-HDL.

Methods: This was a cross-sectional study of 2,302 Japanese subjects who were undergoing a general health check in 2014. All subjects were divided into TG-HDL level tertiles and serum GGT and diabetes status were investigated.

Results: Of 207 diabetes patients identified in this study, 94 had high TG-HDL, 63 intermediate TG-HDL, and 50 low TG-HDL. Independent of classical cardiovascular risk factors, serum GGT showed a positive association with diabetes in patients with high TG-HDL, but not in patients with intermediate and low TG-HDL diabetes. The multivariable adjusted odds ratios (OR) and 95% coincidence intervals (95%CI) of diabetes for 1 standard deviation (SD) increment of GGT were 1.64 (95%CI: 1.16-2.31) for high TG-HDL, 1.46 (95%CI: 0.95-2.26) for intermediate TG-HDL, and 1.04 (95%CI: 0.60-1.79) for low TG-HDL diabetes.

Conclusion: Serum GGT is positively associated with diabetes in patients with high TG-HDL but not with intermediate or low TG-HDL diabetes. This finding may prove to be an efficient tool for estimating atherosclerotic risk in diabetes patients.

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Key words: GGT, diabetes, triglycerides-HDL

Introduction

Serum gamma-glutamyl transferase (GGT) was reported to be positively associated with atherosclerosis [1-3] and diabetes incidence [4]. On the other hand, our previous study reported that categorizing diabetes based on TG-HDL ratio might be a beneficial tool for the estimation of atherosclerotic risk as well as renal dysfunction risk, which is also strongly associated with atherosclerosis [5], with significant risk noted for high TG-HDL diabetes but not for intermediate and low TG-HDL diabetes [6] [7], However, no studies have reported on the association between serum GGT levels and diabetes in terms of the TG-HDL ratio.

We therefore investigated the association in terms of TG-

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HDL level between serum GGT levels and diabetes among Japanese men and women who had participated in a survey on a cardiovascular risk in 2014.

Methods

Study population

The survey population included 3,438 subjects aged 40 to 95 years, all of whom were residents of Goto City and Saza town. A total of 1,136 individuals with missing data (including 8 individual without smoking status, 1 individuals without BMI data and 1,127 individuals without serum data) were excluded, leaving 2,302 subjects (812 men and 1,490 women) enrolled in this study.

The mean age of the study population was 66.4 years (± 10.1 SD; range 40-95). Trained interviewers obtained information on smoking status, drinking status, medical history, use of agents for antihypertensive agents, lipid lowering agents and those for diabetes mellitus.

Anthropometric measurements

Body weight and height were measured with an automatic body composition analyzer (BF-220; Tanita, Tokyo, Japan) at the time of drawing blood. Systolic and diastolic blood pressure was recorded at rest.

Biochemical measurements

Fasting blood samples were collected in a siliconized tube and serum was isolated by centrifugation after blood coagulation. Serum triglycerides, serum HDL cholesterol, serum aspartate aminotransferase (AST), serum γ-glutamyltranspeptidase (GGT), HbA1C and serum creatinine were measured using standard laboratory procedures. Glomerular filtration rate (GFR) was estimated using an established method with three variations recently proposed by a working group of the Japanese Chronic Kidney Disease initiative [8]. According to this adaptation, GFR (mL/min/1.73 m2) = 194 × (serum creatinine (enzyme method))-1.094 × (age)-0.287 (× 0.739 for women). Presence of diabetes was defined as HbA1c (NGSP) $\geq$ 6.5%, and/or initiation of glucose-lowering medication or insulin therapy [9]. We further defined subtypes of diabetes by calculating tertiles of TG-HDL for all participants, as in our previous study [5].

This study was approved by the Ethics Committee for Human Use of Nagasaki University (project registration number: 14051404). All participants provided written, informed consent.

Statistical analysis

Sex-and age-adjusted clinical characteristics in this study based on GGT levels were expressed. TG-HDL categories were established according to tertiles of TG-HDL values for all subjects. Logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) of diabetes with TG-HDL and Log GGT levels, since GGT had a skewed distribution; and logarithmic transportation was performed for the association between GGT and diabetes.

Two different approaches were used for making adjustments for confounding factors. First, the data were adjusted only for sex and age. Second, we included other possible confounding factors, namely smoking status (never smoker, former smoker, current smoker), alcohol consumption [non-drinker, current light to moderate drinker (1-6 times/week), current heavy drinker (every day)], systolic blood pressure (mmHg), antihypertensive medication use (no, yes), history of cardiovascular disease (no, yes), AST (IU/L), lipid lowing-agents(medication) (no, yes), estimated GFR and menopausal status (pre-menopausal women, postmenopausal women).

All statistical analyses were performed with the SAS system for Windows (version 9.4; SAS Inc., Cary, NC). All p-values for statistical tests were two-tailed, and values of <0.05 were regarded as statistically significant.

Results

Of 2,302 subjects aged 40-95 years, 207 diabetes patients were identified, with 94 patients having high TG-HDL (high TG-HDL diabetes), 63 patients having intermediate TG-HDL (intermediate TG-HDL diabetes), and 50 patients having low TG-HDL (low TG-HDL diabetes).

Clinical characteristics of the study population are summarized in Table1. Systolic blood pressure, diastolic blood pressure, antihypertensive medication use, BMI, current drinker, current smoker, TG, TG-HDL ratio, AST, ALT, and glucose lowering medication were positively associated with GGT level.

Table 2 shows Odd ratios (OR) and 95% confidence intervals (CI) of diabetes in relation to GGT level. Independent of classical cardiovascular risk factors, GGT level was found to be significantly associated with diabetes.

Analysis of the association between GGT levels and diabetes categorized by TG-HDL levels revealed a significant positive association for high TG-HDL diabetes, whereas no significant associations were observed for intermediate- and low TG-HDL diabetes (Table 3).

Table 1. Sex-and age-adjusted distribution of characteristics by tertile of serum γ-glutamyltranspeptidase (GGT) level

	GGT tertiles			
	T1 (low)	T2	T3 (high)	p
No. at risk	750	787	765	
Age, years	68.3 ± 11.0	67.0 ± 9.8	64.1 ± 9.2	
Men, %	35.6	34.4	35.8	
Systolic blood pressure, mmHg	132	134	137	<0.001
Diastolic blood pressure, mmHg	78	79	81	<0.001
Antihypertensive medication use, %	28.7	36.3	44.6	<0.001
Body mass index, kg/m^2	22.3	22.8	23.6	<0.001
Current drinker, %	44.8	55.8	63.7	<0.001
Current smoker, %	7.2	9.9	12.2	0.003
History of cardiovascular disease, %	11.6	11.4	14.6	0.100
Serum triglycerides (TG), mg/dl	95	106	130	<0.001
Serum HDL-cholesterol (HDL), mg/dl	60	60	62	0.192
TG-to-HDL ratio	1.75	2.00	2.46	<0.001
HbA1c, %	5.6	5.7	5.8	<0.001
Lipid lowing medication	17.2	18.6	23.9	0.012
Serum aspartate aminotransferase (AST), IU/L	21	22	28	<0.001
Serum alanine aminotransferase (ALT), IU/L	16	19	28	<0.001
Glcose-lowering medication, %	4.8	5.0	7.5	0.048
Serum creatinine, mg/dl	0.76	0.77	0.75	0.335
Glomerular Filtration Rate (GFR), ml/min/1.73m^2	68.7	69.5	69.5	0.410
Postmenopausal women, %*	81.6	86.7	88.3	0.002

Age: mean ± standrd deviation. Serum γ-glutamyltranspeptidase (GGT) level tertiles were <24 IU/L, 24-41 IU/L, and >41 IU/L for men, and <16IU/L, 16-23IU/L, and >23 IU/L for women.* Data was calculated only among women.

Table 2. Odds ratios (OR) and 95% confidence intervals (CI) for diabetes in relation to γ-glutamyltranspeptidase (GGT) levels

	GGT tertiles				1SD increment of Log GGT*
	T1 (low)	T2	T3 (high)	P for trend	
No. at risk	750	787	765		
No. of cases (percentages)	50 (6.7)	63 (8.0)	94 (12.3)		
Sex- and age-adjusted OR	1.00	1.27 (0.86-1.87)	2.13 (1.47-3.08)	<0.001	1.69 (1.36-2.08)
Multivariable OR	1.00	1.12 (0.75-1.67)	1.58 (1.05-2.37)	0.023	1.45 (1.12-1.87)

Multivariable OR: adjusted further for systolic blood pressure, antihypertensive medication use, history of cardiovascular disease, body mass index, smoking, alcohol intake, lipid lowing-agents(medication), serum aspartate aminotransferase (AST), glomerular filtration rate (GFR), and menopausal status. GGT level tertiles were <24 IU/L, 24-41 IU/L, and >41 IU/L for men, and <16IU/L , 16-23IU/L, and >23 IU/L for women.
*1 standard deviation for GGT was 57 IU/L for men and 27 IU/L for women.

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) for diabetes subtypes in relation to γ-glutamyltranspeptidase (GGT) levels

	GGT tertiles				1SD increment of Log GGT*
	T1 (low)	T2	T3 (high)	P for trend	
No. at risk	750	787	765		
Low TG-HDL diabetes					
No. of cases (percentage)	15 (2.0)	16 (2.0)	16 (2.1)		
Sex-and age-adjusted OR	1.00	1.04 (0.51-2.12)	1.07 (0.52-2.22)	0.848	0.99 (0.62-1.58)
Multivariable OR	1.00	1.02 (0.49-2.14)	1.078(0.49-2.37)	0.857	1.034 (0.60-1.79)
Intermediate TG-HDL diabetes					
No. of cases (percentage)	19 (2.5)	21 (2.7)	27 (3.5)		
Sex- and age-adjusted OR	1.00	1.14 (0.61-2.15)	1.65 (0.89-3.05)	0.108	1.48 (1.03-2.13)
Multivariable OR	1.00	1.07(0.56-2.05)	1.48(0.75-2.92)	0.253	1.46 (0.95-2.26)
High TG-HDL diabetes					
No. of cases (percentage)	16 (2.1)	26 (3.3)	51 (6.7)		
Sex- and age-adjusted OR	1.00	1.60 (0.85-3.01)	3.42 (1.91-6.11)	<0.001	2.13 (1.60-2.84)
Multivariable OR	1.00	1.33(0.70-2.54)	2.10 (1.13-3.92)	0.014	1.64 (1.16-2.31)

Multivariable OR: adjusted further for systolic blood pressure, antihypertensive medication use, history of cardiovascular disease, body mass index, smoking, alcohol intake, lipid lowing-agents(medication), serum aspartate aminotransferase (AST), glomerular filtration rate (GFR), and menopausal status. GGT level tertiles were <24 IU/L, 24-41 IU/L, and >41 IU/L for men, and <16IU/L , 16-23IU/L, and >23 IU/L for women.
*1 standard deviation for GGT was 57 IU/L for men and 27 IU/L for women.

Discussion

Serum GGT is positively associated with high TG-HDL diabetes but not with intermediate TG-HDL and low TG-HDL diabetes. These findings suggest serum GGT as an efficient tool to estimate atherosclerotic risk in diabetes patients.

A previous study comprised of 1,441 men and women followed up for 7 years reported elevated GGT as a significant predictor of either impaired glucose tolerance or diabetes (OR 1.62 (1.08–2.42) top quartile vs. lower quartiles, $P < 0.02$) after controlling for sex, age, adiposity/fat distribution, alcohol consumption, fasting plasma insulin, proinsulin levels, and 2 hours post-standardized 75g oral glucose load glucose level [10].

The present study also showed a positive association between serum GGT and diabetes comparable with the previous study. The multivariable OR of the highest tertile vs. lowest tertile was 1.54 (1.02-2.32). We found further evidence that the positive association was confined to the high TG-HDL diabetes group.

A previous study of 3,412 Japanese men reported a relation between GGT and increased levels of arterial stiffness as evaluated by brachial-ankle pulse wave velocity (PWV). Conventional risk factor adjusted log GGT was significantly associated with PWV (β=0.060, $p<0.001$) [2]. Association between GGT level and diabetes might therefore be strongly influenced by the risk of atherosclerosis.

On the other hand, our previous study of 1,344 Japanese men reported high TG-HDL diabetes (but not intermediate and low TG-HDL diabetes) as a risk factor for atherosclerosis (diagnosed as carotid intima-media thickness ≥1.1 mm) and increased arterial stiffness (diagnosed as cardio-ankle vascular index ≥8.0) [6]. Therefore, GGT was positively associated with high TG-HDL diabetes, which is risk factor for atherosclerosis, while no significant association was observed for intermediate and low TG-HDL diabetes, which are much less significant atherosclerotic risk factors. Since renal function is well known to be associated with atherosclerosis [5], we also evaluated the GFR values for each of the diabetes categories. In this study, we additionally measured GFR, which is related to arteriosclerosis. The high TG-HDL ratio group had a significantly lower GFR than the low TG-HDL group (high TG-HDL 68.4 ml/min/1.73m2, and low TG-HDL 76.0 ml/min/1.73m2($p < 0.001$)). These results also support the above mentioned associations.

Although the mechanisms for these associations were not elucidated, higher TG-HDL was found to correlate with insulin resistance among the general population [11], among overweight individuals [12,13], and among type 2 diabetes patients [14]. Therefore, diabetes classification according to tertile TG-HDL level (Shimizu's diabetes classification) is based on the assumption that high TG-HDL is mainly caused by insulin resistance with less compensatory β-cell function, while low TG-HDL is mainly caused by absolute β-cell dysfunction [6]. In addition to these mechanisms, GGT measurement can be a sensitive method for early diagnosis and a predictor of insulin resistance in the general population [15], and may also be a predictor of diabetes incidence [4]. The association between GGT and diabetes categorized by TG-HDL might therefore be affected by the state of insulin resistance.

We reported in previous study that our previous diabetes classification is efficient tool to evaluate the risk of atherosclerosis [5] and CKD [6]. And this diabetes classification might not only indicates insulin resistance [11] but also indicates the activity of low grade inflammation [16] and hematopoietic activity [17]. On the other hands, GTP is also known factor that is associated with inflammation and arterial stiffness [2]. Perspective of our present study is that, further investigation with longitudinal study became efficient tool to clarify the background mechanism of those factors.

Potential limitations of this study warrant consideration. First, GGT levels are well known to be influenced by drinking status [18]; however, additional information on the drinking status of the subjects was unavailable, and a high and low prevalence of male and female drinkers, respectively, among the general Japanese population has been reported [19,20]. Gender differences may therefore influence the association between GGT level and diabetes categorized by TG-HDL level. However, the limited number of study subjects in this study prevents meaningful gender-specific conclusions to be drawn. Nonetheless, our additional analyses showed essentially the same correlations for both men and women with regard to the association between GGT level and diabetes categorized by TG-HDL. The age-adjusted ORs of 1SD increments of GGT for low and high TG-HDL diabetes were 0.75 (95%CI: 0.37-1.51) and 1.36 (95%CI: 1.12-1.65) for men, and 1.09 (95%CI: 0.85-1.40) and 1.18 (95%CI: 1.03-1.36) for women. Second, since data on exercise were not available, we were not able to make adjustments with regard to the influence of exercise. Additionally, no data on family history of diabetes, fasting glucose, and total cholesterol was available and therefore could not be evaluated. Finally, since this study was cross-sectional, causal relationships were not able to be established.

Conclusion

The positive association between GGT and diabetes is confined to high TG-HDL. This finding might be applied as efficient tool to estimate atherosclerotic risk in patients with diabetes.

Competing interests

The authors declare that they have no conflict of interest.

Human and animal rights and informed consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics Committee for Human Use of Nagasaki University obtained ethical approval.

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