Gamma-glutamyl transferase predicts future stroke: A Study of Civil Servants in Southern China

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Abstract

Although gamma-glutamyltransferase (GGT) is widely recognized as an alternative biomarker for drinking, its independent role in vascular disease has only recently emerged. However, its role in stroke remains unclear. The purpose of this study was to clarify a population cohort by randomly selecting civil servants in Guangdong Province. We analyzed qualified individuals from this cohort. The Cox proportional hazard model was used to study the relationship between GGT and stroke. Of the 32,275 eligible participants, 400 had a stroke. GGT is an independent factor associated with increased risk of stroke after adjusting for alcohol consumption and stroke risk (hazard ratio (HR), 1.57/1.3/.1.4 for Q2/Q3/Q4). Although the effects of gender, age, and alcohol have changed, the risk of total stroke and stroke is still significant with high GGT levels in all subgroups.

Keywords

GGT, stroke, risk factor, south of China.

1. Introduction

Gamma-glutamyltransferase (GGT) is a glycoprotein widely distributed in the plasma membrane of various cell and organ tissues. Although the most well-known is a marker of liver disease or excessive drinking,[1, 2] GGT has also been reported to be associated with cardiovascular disease and its risk factors[3]. In addition, some studies and meta-analyses also report the relationship between GGT and stroke[4]. However, most of the previous studies have some shortcomings, such as using GGT alone as a surrogate indicator of alcohol consumption, regardless of the impact of alcohol consumption on GGT, only analyzing a limited age group or gender, or can't show significant correlation because the sample size is small[5]. Therefore, at present, in real clinical practice, GGT has not been widely used to assess stroke risk. In this context, the independent relationship between GGT and stroke needs to be further clarified.

2. Methods

2.1 Study population

Baseline risk factor surveys were carried out in Southern China province, Guangdong in 2012 and 2017. In both years, the sample was randomly drawn from the participants aged 21 to 69 years and was stratified so that in each area at least 3000 subjects were chosen from each sex, according to the international WHO MONICA (MONItoring trends and determinants in CArdiovascular disease) project protocol.[6, 7] The survey samples included 19719 men and 12556 women. The participation rate was 78% among men and 86% among women. Of the participants, 679 were excluded from analysis because of a history of previous stroke. Another 16119 participants were excluded because of incomplete data on 1 or more risk factors. Thus, a total of 15457 people were included in the present analyses.

2.2 Data collection

The sex and age, measurements of height, weight, systolic blood pressure, fasting blood glucose, total cholesterol, hemoglobin, aspartate transaminase (AST), alanine transaminase (ALT), and GGT were routinely obtained for all participants at the time of their first general health examination. All blood tests were performed in the fasting state. Alcohol consumption, smoking status, physical activity, and medical histories of diabetes mellitus, stroke, or hypertension were reported through a standard questionnaire. Body mass index was calculated based on the height and weight. For alcohol consumption, participants reported both the frequency of drinking per week and amount of alcohol intake per sitting; we transformed the data to amount of alcohol intake per one week. The International Classification of Disease-Tenth revision (ICD-10) codes for each disease and the generic name codes for drugs recorded in NHIS-NSC were used to identify the aforementioned factors at the time of baseline examination.

2.3 Identification of stroke

Our primary outcome was time to adjudicated stroke. The following codes of the ICD-10 were used to identify stroke: ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. “Total stroke” was defined as a sum of ischemic stroke, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). Transient ischemic attack was excluded. Only patients who had been hospitalized with above mentioned codes were regarded as "incident stroke” in our study.

2.4 Statistical methods

We compared characteristics across quartiles of GGT using ANOVA tests for continuous variables and $\chi 2$ tests for categorical variables. Multivariate analyses were performed with the Cox proportional hazards model.[8, 9] The estimates of relative risks and their 95% confidence intervals were based on this model. We also estimate the smooth spline for the hazard ratio of stroke.[10]

3. Results

3.1 Study Participants

Among eligible participants during follow-up, the age, BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride and FPG of stroke patients were higher than those of the general population. Only high density lipoprotein, which is a good prognostic indicator was higher in the general population than in stroke patients (Table 1). Increasing serum GGT levels were associated with the increased risk of total stroke and ischemic stroke in both men and women. For GGT, the average of the general population was significantly lower than that of the stroke population, which prompts us to further explore GGT. ALT was the opposite of GGT, but not significant.

Table 1 Baseline characteristics and liver function indicators of study population

	Total study population	Ischemic stroke	Controls	P value
Number (n)	32275	400	31875	
Male (%)	19719(60.1%)	303(75.75%)	19416 (60.91%)	P<0.01
Age (years)	44.31±13.97	65.61±12.71	44.04±13.79	P<0.01
Marital status (%)	30104(93.27%)	399(99.75%)	29705(93.19%)	P<0.01
BMI (kg/m2)	25.11±3.54	26.30±3.31	25.09±3.54	P<0.01
SBP (mmHg)	119.17±16.16	129.63±14.91	119.04±16.13	P<0.01
DBP (mmHg)	75.17±10.35	78.12±9.46	75.13±10.35	P<0.01
LDL cholesterol (mmol/L)	2.95±0.75	3.05±0.82	2.95±0.76	P<0.05
HDL cholesterol (mmol/L)	1.36±0.32	1.32±0.29	1.36±0.32	P<0.05

Total cholesterol (mmol/L)	4.89±0.93	5.01±1.01	4.86±0.94	P<0.01
Triglycerides (mmol/L)	1.62±1.31	1.73±1.12	1.63±1.32	0.062
FPG (mmol/L)	5.49±1.15	6.30±1.86	5.48±1.14	P<0.01
Liver function indicators				
GGT (IU/L)	28.78±32.66	30.62±43.11	28.75±32.48	P<0.05
ALT (IU/L)	24.31±19.08	23.77±14.40	24.32±19.13	0.1318
AST (IU/L)	21.78±9.71	22.69±7.52	21.76±9.73	P<0.05

Notes: Values expressed are means (±SD) unless specified otherwise.Q1-Q4, ALT values were divided into 4 quartiles: < 17, 17-19, 20-23, ≥24 IU /L. The #sign represents a missing value for some people in the cohort study. The state of 3333 people is missing for the marital status; the state of 15497 people is missing for the case of diabetes.

3.2 Gamma-glutamyl transferase and Risk of stroke

The risk ratios (logarithmic transformation of GGT) in Q2/Q3/Q4 were 2.85, 3.98, 4.12 compared with Q1 (Table 2). These results are significant, but the relationship between serum GGT and stroke remained statistically significant also after adjustment for smoking, serum cholesterol, BMI, and systolic blood pressure. After age and gender adjustment, HR is still about 1.5 times higher than Q1, suggesting that high levels of GGT are highly correlated with stroke, which greatly increases the risk of stroke.

Table 2 Cox proportional hazard model analysis for association of GGT levels with the incidence of ischemic stroke

	Person-year	No. of participants	No. of incident stroke	Model 1(adjusted nothing)					Mode 2(adjusted gender/age)				
				HR	95% CI		P value	P trend	HR	95% CI		P value	P trend
					Lower	Upper				Lower	Upper		
ALT quartiles								0.00					0.00
Q1	8562	3200	7	1.00	1.00	1.00			1.00	1.00	1.00		
Q2	11919	4267	28	2.85	1.24	6.53	0.01		1.59	1.04	1.36	0.02	
Q3	12091	4133	40	3.98	1.78	8.88	0.00		1.42	1.25	2.54	0.01	
Q4	12067	3877	42	4.12	1.85	9.19	0.00		1.52	1.37	4.49	0.01	

Notes: Model1 was adjusted nothing. Model2 was adjusted age and sex.

Based on the integrity of the data we collected, more covariates can be adjusted to get more accurate results. After adjustment by adding bmi, total cholesterol, glu, cigarette, alcohol, the HR values of GGT and stroke in Q3/Q4 stratification decreased, but they were still 1.3 and 1.43 times higher than those in Q1. And the p value is less than 0.05, and the confidence interval is above 1.

Table 3 Cox proportional hazard model analysis for association of GGT levels with the incidence of ischemic stroke(adjusted plus bmi, total cholesterol, glu, cigarette, alcohol)

	Person-year	No. of participants	No. of incident stroke	Model 3(adjusted more covariates)				
				HR	95% CI		P value	P trend
					Lower	Upper		
ALT quartiles								0.00
Q1	8562	3200	7	1.00	1.00	1.00		
Q2	11919	4267	28	1.57	1.24	6.53	0.03	
Q3	12091	4133	40	1.30	1.28	8.88	0.02	
Q4	12067	3877	42	1.43	1.35	9.19	0.02	

Notes: Model 3 was further adjusted for bmi, total cholesterol, glu, cigarette, alcohol.

3.3 Correlation Between GGT and Stroke

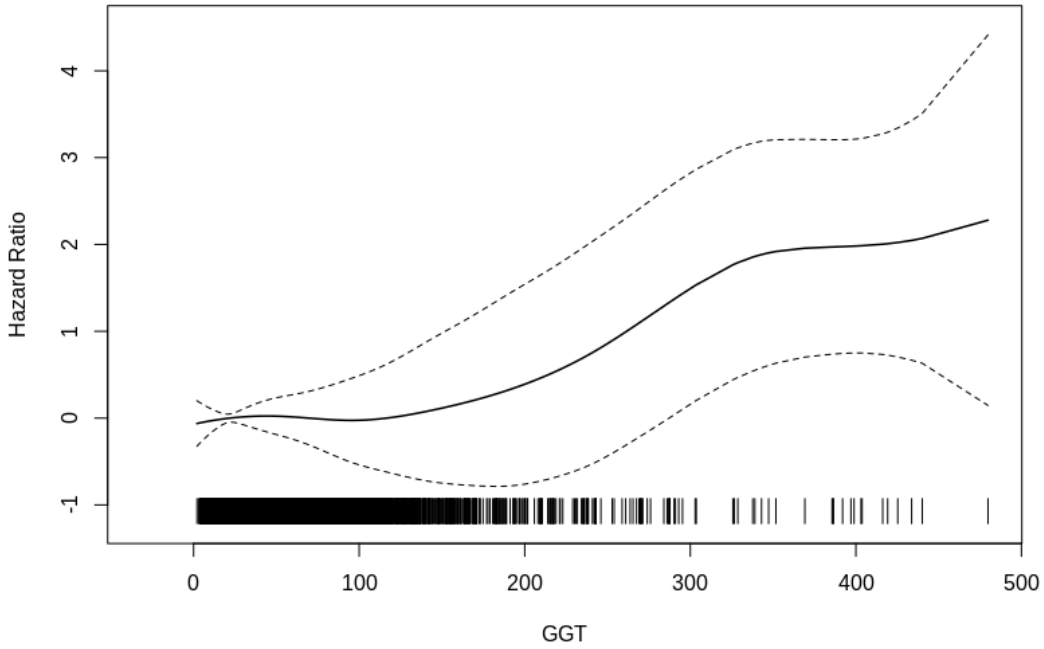

Fig. 1 Multivariable association of GGT with storke. The smooth spline estimates the hazard ratio of stroke, according to GGT (IU/L) measured among the study participants. All analyses are adjusted for age, sex, body mass index, diabetes mellitus, cigarette. Dotted lines represent 95% confidenceintervals. Below each spline is the density of the distribution of GGT to indicate the range of the majority of the data.

The relationship between GGT level and stroke risk can be seen more intuitively by The smooth splines(Fig. 1). As can be seen from the figure, when the GGT level is low (less than 100), the risk ratio is almost zero. But when it is greater than 100, the risk ratio begins to rise, and when it is greater than 200, it rises sharply. the GGT levels about 400 and it's starting to flatten out. It is very important to guide the actual clinical prediction.

4. Discussion

In the present study the increase in serum GGT concentration, which was regarded as a biological marker of excessive alcohol drinking, was associated with the increased risk of ischemic stroke as well as of total strokes in both genders. A significant relationship was also found between serum GGT and strokes, even though the results were inconsistent in men and women. Besides stroke, GGT also has a close relationship with the occurrence of atrial fibrillation[11, 12], which is one of the major risk factors for ischemic stroke (especially cardioembolic subtype of it). GGT has also been continuously reported to be independently associated with AF[13-15]. Higher GGT levels may reflect an increase in systemic oxidative stress or inflammatory processes that are prone to cardiac metabolic risk factors and atrial fibrillation. Considering the severe burden of atrial fibrillation on ischemic stroke, elevated GGT and stroke may be mediated through atrial fibrillation[16-19].

The role of GGT and the function of extracellular GGT is not fully understood. GGT is usually localized to the extracellular domain of the cell membrane, including liver, kidney, blood vessels, brain and heart. Extracellular GGT transports amino acids into cells and is involved in the metabolism of glutathione[19, 20], which is the most important antioxidant in the cell. There are two hypotheses about the meaning of elevated serum GGT levels. One is that it is a marker of a highly active

antioxidant system that causes extracellular GGT to be released into the bloodstream[21-23], and another possibility is that GGT acts directly on the paradoxical production of oxidative substances based on experimental evidence[24, 25]. Even though it has not yet reached which one is the dominant mechanism, some observation reports have reported serum. GGT is closely associated with increased systemic oxidative stress loading. For example, GGT is a positive correlation between serum antioxidant vitamins and serum GGT levels. Prediction of coronary artery risk development in young people 15 years after F5 isoprostol (a more expensive and specific systemic lipid oxidation marker than GGT). As mentioned earlier, the cause of stroke is atherosclerosis and cardiac embolism, both of which may be associated with an increased systemic burden of oxidative stress. Although caution should be interpreted, elevated serum GGT may reflect elevated levels of oxidative stress in patients susceptible to stroke.

Some limitations in the current study must be noted. First, although the population we used was well standardized, only Southern China people were included in this study. Thus, these findings remain to be validated in other ethnic groups. Second, those who did not report a stroke to the hospital were not included in the analysis, and there were too many people missing the survey. The understanding of the GGT level remains to be further studied.

5. Conclusion

Although people underestimate the GGT, because it is only a substitute for alcohol consumption. In fact, it alone can predict the occurrence of a stroke. Given the current study cohort, this study validated the association between GGT and stroke in the southern Chinese population but did not cover it across the country. GGT can be used as a cheap, convenient and effective biomarker to predict the occurrence of stroke.

Acknowledgements

I would like to thank the tutors and doctors of Guangzhou Overseas Chinese Hospital for their financial support and generous help.

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