ความสัมพันธ์ระหว่างความดันโลหิต และการเปลี่ยนแปลงของระดับเอนไซม์ serum gamma-glutamyltransferase กับการดื่มแอลกอฮอล์

วันทิกา เครือน้ำคำ[1]*,ศิริกร โพธิ์คำ[2], ทัศนีย์ ปัญจานนท์[1], ปถมาพร สุกปลั่ง[1], จินตนา ศิริวราศัย[3]

[1] คณะวิทยาศาสตร์ มหาวิทยาลัยรังสิต

[2] หลักสูตรวิทยาศาสตร์ชีวการแพทย์ คณะวิทยาศาสตร์ มหาวิทยาลัยรังสิต

[3] หน่วยเภสัชวิทยาคลินิกและพิษวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล

บทคัดย่อ

ระดับการทำงานของเอนไซม์ serum gamma-glutamyltransferase (GGT) เป็นตัวชี้วัดทางชีวภาพตัวหนึ่งสำหรับการประเมินเรื่องการดื่มแอลกอฮอล์ และบทบาทที่สำคัญของเอนไซม์นี้จะเกี่ยวข้องกับสารต้านอนุมูลอิสระกลูตาไธโอน ซึ่งสารนี้จะมีผลต่อการเพิ่มขึ้นของระดับความดันโลหิตและการเกิดภาวะความดันโลหิตสูง วัตถุประสงค์ของงานวิจัยนี้คือเพื่อศึกษาความสัมพันธ์ระหว่างการดื่มแอลกอฮอล์ และอิทธิพลของระดับการทำงานของเอนไซม์ GGT ต่อความเสี่ยงต่อการเกิดภาวะความดันโลหิตสูง การศึกษาครั้งนี้เป็นแบบภาคตัดขวางที่กลุ่มศึกษาเป็นเพศชาย จำนวน 260 คน อายุระหว่าง 30-60 ปี การประเมินทางด้านสุขภาพเมื่อเริ่มโครงการประกอบด้วยการซักประวัติด้านสุขภาพ การตรวจร่างกาย การวัดความดันโลหิต การตรวจทางห้องปฏิบัติการ และแบบสอบถามเกี่ยวกับพฤติกรรมความเสี่ยงต่อสุขภาพ ผลการศึกษาพบว่าระดับความดันโลหิต ระดับของเอนไซม์ GGT, AST, ALT ในกลุ่มดื่มแอลกอฮอล์มีระดับสูงกว่ากลุ่มเคยดื่มและกลุ่มไม่ดื่มอย่างมีนัยสำคัญทางสถิติ การวิเคราะห์ทางสถิติเพิ่มเติมโดยการแบ่งระดับของ เอนไซม์ GGT เป็น 4 กลุ่ม (4 quartiles) หลังจากควบคุมตัวแปรเรื่อง BMI และอายุ แล้วพบว่ามีความสัมพันธ์แบบ dose-response relationship ระหว่างระดับ SBP (Q1; 125.3 mmHg, Q2; 129.6 mmHg, Q3: 135.1 mmHg, and Q4; 137.3 mmHg, ตามลำดับ), DBP (Q1; 77.12 mmHg, Q2; 81.20 mmHg, Q3: 84.07 mmHg, and Q4; 85.51 mmHg, ตามลำดับ) และ serum ALT (Q1; 18.25 U/L, Q2; 22.34 U/L, Q3: 32.95 U/L, and Q4; 52.49 u/L, ตามลำดับ) กับระดับของเอนไซม์ GGT นอกจากนี้พบความสัมพันธ์ทางบวกระหว่างปริมาณการดื่มแอลกอฮอล์กับตัวแปรที่ต้องการศึกษา โดยในกลุ่มดื่มปานกลางพบการเพิ่มขึ้นของระดับ GGT กับระดับ SBP อย่างมีนัยสำคัญทางสถิติ (p =0.028) และในกลุ่มดื่มมากพบการเพิ่มขึ้นของระดับ GGT กับระดับ SBP, triglyceride และ ALT อย่างมีนัยสำคัญทางสถิติ (p =0.019, 0.033 และ 0.047 ตามลำดับ) ส่วนภาวะความดันโลหิตสูงที่มีระดับของ SBP ผิดปกติพบสูงสุดในกลุ่มดื่มแอลกอฮอล์ (37.79%) รองลงมาได้แก่ กลุ่มเคยดื่ม (13.39%) และกลุ่มไม่ดื่ม (5.51%) เช่นเดียวกับระดับของ DBP ผิดปกติพบสูงสุดในกลุ่มดื่มแอลกอฮอล์ (28.35%) รองลงมาได้แก่ กลุ่มเคยดื่ม (9.45%) และกลุ่มไม่ดื่ม (5.51%) เมื่อพิจารณาระดับของเอนไซม์ GGT พบว่ากลุ่มที่มีระดับน้อยกว่า 50 U/L มีความเสี่ยงต่อการเกิดภาวะความดันโลหิตสูง น้อยว่ากลุ่มที่มีระดับของเอนไซม์ GGT มากกว่าหรือเท่ากับ 50 U/L ผลจากการศึกษาครั้งนี้พบว่าการเพิ่มขึ้นของระดับเอนไซม์ GGT สามารถนำมาใช้ในการทำนายความเสี่ยงต่อการเกิดภาวะความดันโลหิตสูงในกลุ่มคนที่ดื่มแอลกอฮอล์ได้ และความสัมพันธ์นี้จะเห็นได้ชัดเจนในกลุ่มที่มีระดับของระดับของเอนไซม์ GGT มากกว่าหรือเท่ากับ 50 U/L ซึ่งเป็นค่าที่เกินค่าอ้างอิงมาตรฐาน

คำสำคัญ: การดื่มแอลกอฮอล์ ความดันโลหิต Serum gamma-glutamyltransferase ความดันโลหิตสูง

***Corresponding author**

ดร.วันทิกา เครือน้ำคำ

คณะวิทยาศาสตร์ มหาวิทยาลัยรังสิต ปทุมธานี 12000, E-mail : wantikarsu@yahoo.com

Introduction

An important potent factor for the development of hypertension is excessive alcohol consumption. Previous studies reported the relationship between alcohol consumption and blood pressure. Systolic and diastolic blood pressure in the moderate and heavy drinkers (consuming 24 - 46 and > 47 g alcohol per day, respectively) were both 3-5 mmHg higher than those in the non-drinkers[1]. Gamma-glutamyltransferase (GGT) is an enzyme synthesized in epithelial cells of the intra-hepatic duct and a well-known biological marker of alcohol abuse and / or liver damage[2]. The significant association between serum GGT level within its normal range and the presence of diabetes, hypertension, obesity, dyslipidaemia and metabolic syndrome was found[3]. Moreover, Lee, et al.[4] reported a clear dose-response relationship with alcohol consumption for healthy male workers with GGT ≥ 30 U/L and the adjusted changes in blood pressure. Among those with GGT ≥ 30 U/L, the adjusted relative risks for hypertension in light, moderate and heavy drinkers were 1.4 (95% CI: 0.5-4.5), 5.2 (95% CI: 1.5-18.0), and 5.3 (95%CI: 1.0-27.6), compared with non-drinkers[4].

Serum GGT level might be a modest risk factor for hypertension among drinkers. However, the mechanism underlying these observations is not fully understood. Some possible mechanisms have been mentioned as elevation of GGT level related to hepatic cell-membrane damage (resulting in increased blood pressure) via oxidative stress pathway, rather than enzyme-induction. An experimental study indicated that GGT cleavage of glutathione (GSH) and the subsequent recapture of cysteine and cystine allow cells to maintain low levels of cellular ROS and thereby avoid apoptosis induced by oxidative stress[5].

Thailand was ranked at number 40 in the world statistic on *per capita* alcohol consumption in 2001 by the World Health Organization (WHO) Statistical Information System[6]. Current report by Assanangkornchai et al. described patterns of alcohol consumption in the Thai population (11,348 households and 26,633 respondents from 29 Provinces) by using a structured interview questionnaire, including information on pattern of alcohol consumption, Alcohol Use Disorder Identification Test (AUDIT). Based on the AUDIT score, 6.7% of the Thai population could be classified as hazardous drinkers, 0.9% as harmful drinkers and 0.6% as probable alcohol dependents. The median drinking intensity was 50.8 g in men and 25.4 g in women[7]. Along with these data, adverse health burden with increased alcohol intake in Thai population may need to be taken into consideration. The aim of this cross-sectional study was to investigate the relationship between alcohol consumption and the effect of serum GGT on the risk for hypertension in Thai men.

Materials and Methods

Study population and measurements

Study participants were employees at official and private universities resided in Bangkok. Subjects included 260 Thai men, 30 to 60 years of age. Men, who reported consuming alcohol beverage average one time per week or more for 3 years, were regarded as drinkers. Ex-drinkers were defined as abstainers for the past 1 year and over. Subjects were classified as light, moderate, or high drinkers who averaged < 14.9 g/d, 15.0 to 29.9

g/d, or ≥30 g/d of ethanol. The exclusion criteria were individual with acute or chronic kidney, liver and cardiovascular disease with drug treatment, suffering various type of cancer, history of alcohol abuse and malignancy, undergoing medical treatment of hepatitis. This study was approved by the Institutional Review Board at Rangsit University. All subject were signed inform consent before participating in this study.

Questionnaires were used to assess information on demographic, medical, and lifestyle factors including medical and family history, cigarette smoking, and alcohol consumption. Blood pressure was measured, after a 5-min rest, on the right arm in the sitting position with a standard mercury sphygmomanometer. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meter squared. Participants were asked to fast at least 12 h and blood was collected from the antecubital vein and measured within 3 hours of blood collection. Serum levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), GGT, and glucose were determined using an automatic analyzer (Roche Cobas 6000).

Statistical analysis

Overall analyses were carried out on SPSS version 13 (SPSS Inc., Chicago, Il, USA). Data were expressed as mean and S.E. Associations between serum GGT and other parameter were analyzed by quartiles (Q1, 8-20 U/L; Q2, 21.01-38.00 U/L; Q3, 38.01-67.00 U/L, and Q4, > 67.01 U/L). Pearson's correlation was used for analysis of association between serum GGT, BP, and other biochemical values in different types of drinkers. Moreover, serum GGT levels were divided into two categories; normal was defined as value below 50 U/L, and abnormal with value ≥ 50U/L. One-way analysis of variance (ANOVA) was used for comparison of three groups related to alcohol consumption and 4 quartiles of GGT levels. The *P*-values used are two-sided, and values < 0.05 were regarded as statistically significant.

Results

The clinical characteristics of the study population according to alcohol consumption are presented in Table 1. The mean age of non-drinkers (n=83), ex-drinkers (n=47) and current drinkers (n=130) were 43.40, 45.34 and 39.75 years, respectively. Drinkers in this present study were significantly younger than the other 2 groups ($p< 0.05$). Moreover, SBP, DBP, serum levels of GGT, AST and ALT among current drinkers were statistically higher than non-drinkers and ex-drinkers. For lipid profile, HDL-cholesterol and triglyceride levels in drinkers were significantly higher than ex-drinkers levels (55.43 mg/dL for drinkers vs 49.91 mg/dL for ex-drinkers, $p<0.05$) and non-drinkers levels (148.2 mg/dL for drinkers vs 130.1 mg/dL for non-drinkers, $p<0.05$), respectively, in contrast to LDL-cholesterol levels (129.6 mg/dL for drinkers vs 138.9 mg/dL for ex-drinkers, $p<0.05$).

Table 1. Clinical characteristics of the study population (Mean and S.E. ; N=260)

	Non-drinkers	**Ex-drinkers**	**Drinkers**
N	83	47	130
Age, years	43.40 (0.96)	45.34 (1.14)	39.75 (0.59) [a,b]
Body mass index, kg/m^2	23.26 (0.37)	22.55 (0.49)	22.95 (0.28)
Systolic blood pressure, mmHg	129.1 (1.72)	126.6 (1.92)	135.6 (1.34) [a,b]
Diastolic blood pressure, mmHg	80.07 (1.14)	79.70 (1.38)	84.13 (0.95) [a,b]
Exercise (%), times/week			
- < 2 times/week	25.0	32.1	22.2
- ≥ 2 times/week	75.0	67.9	77.8
Alcohol, mL/week	-	133.3 (51.66)	385.6 (30.58) [b]
Smoking, cigarettes/day	10.10 (1.36)	15.00 (1.82)	12.73 (1.15)
Total cholesterol, mg/dL	219.8 (4.59)	212.2 (5.43)	209.36 (3.20)
LDL cholesterol, mg/dL	143.7 (2.98)	138.9 (5.03)	129.6 (3.0) [a]
HDL cholesterol, mg/dL	51.22 (1.36)	49.91 (1.56)	55.43 (1.34) [b]
Triglyceride, mg/dL	130.1 (7.49)	139.7 (15.33)	148.2 (9.3) [a]
Gamma glutamyl transferase (GGT), U/L	39.89 (3.07)	38.70 (5.65)	82.58 (7.79) [a,b]
Aspartate aminotransferase (AST), U/L	26.43 (0.98)	26.51 (1.15)	33.26 (1.72) [a,b]
Alanine aminotransferase (ALT), U/L	27.90 (1.94)	26.65 (2.85)	35.74 (2.57) [a,b]
Glucose, mg/dL	93.62 (3.35)	90.00 (1.92)	93.01 (2.08)

[a,b] Compared with non-drinkers, and ex-drinkers, respectively : $p < 0.05$

The associations between changes in blood pressure, biochemical parameters and 4 categories of serum GGT levels, classified by quartile, are shown in Table 2. After adjusted for age and BMI, there were slightly dose-response relationships among SBP (Q1; 125.3 mmHg, Q2; 129.6 mmHg, Q3: 135.1 mmHg, and Q4; 137.3 mmHg, respectively), DBP (Q1; 77.12 mmHg, Q2; 81.20 mmHg, Q3: 84.07 mmHg, and Q4; 85.51 mmHg, respectively) and serum ALT (Q1; 18.25 U/L, Q2; 22.34 U/L, Q3: 32.95 U/L, and Q4; 52.49 u/L, respectively) with serum GGT levels. Other biochemical variables except total, LDL, HDL cholesterol levels revealed some significant differences with increasing serum GGT.

Table 2. Quartiles of serum GGT and biochemical parameters in men being adjusted for age and body mass index

	Serum GGT (U/L)			
	Quartile 1 (8.00-21.00)	**Quartile 2 (21.01-38.00)**	**Quartile 3 (38.01-67.00)**	**Quartile 4 (>67.01)**
N	62	67	66	65
Systolic blood pressure, mmHg	125.3 (1.93)	129.6 (1.71)	135.1 (1.91) [a,b]	137.3 (1.82) [a,b]
Diastolic blood pressure, mmHg	77.12 (1.24)	81.20 (1.18) [a]	84.07 (1.29) [a]	85.51 (1.36) [a,b]
Total cholesterol, mg/dL	209.3 (6.89)	212.5 (3.69)	214.3 (7.23)	217.9 (4.96)
LDL cholesterol, mg/dL	127.7 (4.12)	137.2 (3.49)	136.0 (6.14)	132.5 (4.79)
HDL cholesterol, mg/dL	54.83 (1.58)	53.32 (1.39)	51.86 (1.48)	52.44 (2.30)
Triglyceride, mg/dL	95.29 (5.190	116.2 (6.91)	134.9 (9.17) [a]	215.8 (16.48) [a,b,c]
Aspartate aminotransferase (AST), U/L	25.30 (1.01)	23.64 (0.72)	28.69 (1.25) [b]	41.80 (2.94) [a,b,c]
Alanine aminotransferase (ALT), U/L	18.25 (1.02)	22.34 (1.13)	32.95 (2.08) [a,b]	52.49 (4.52) [a,b,c]
Glucose, mg/dL	89.96 (5.24)	93.64 (3.43)	90.18 (1.50)	100.86 (4.43)

[a,b,c] significant different from quartile 1, 2, and 3, respectively; $p<0.05$

From above data, serum GGT level was purposed as a good representative parameter of alcohol intake. Further analysis related to quantity of alcohol consumption classified as light, moderate, and high drinkers was performed by Pearson's correlation for relationship between serum GGT levels, blood pressure, lipid profile, liver enzymes and glucoses (Table 3). In moderate drinkers, the positive correlation between serum GGT and SBP (p=0.028) was found whereas in high drinkers, SBP, triglyceride and ALT levels were statistically increased with serum GGT levels (p=0.019, 0.033, and 0.047, respectively).

Table 3. Pearson's Correlation (p value) between serum GGT levels in different types of drinkers and other targeted parameters.

	Serum GGT (U/L)		
	Light drinkers (n= 34)	**Moderate drinkers (n=46)**	**High drinkers (n=50)**
SBP (mmHg)	NS	0.028	0.019
DBP (mmHg)	NS	NS	NS
Total cholesterol, mg/dL	NS	NS	NS
LDL cholesterol, mg/dL	NS	NS	NS
HDL cholesterol, mg/dL	NS	NS	NS
Triglyceride, mg/dL	NS	NS	0.033
Aspartate aminotransferase (AST), U/L	NS	NS	NS
Alanine aminotransferase (ALT), U/L	NS	NS	0.047
Glucose, mg/dL	NS	NS	NS

NS = non-significance

Hypertension was defined as a SBP ≥ 140 mmHg and/ or a DBP ≥ 90 mmHg. An elevated serum GGT concentration is a risk factor for hypertension. The risk of developing both abnormal SBP and DBP values among 3 groups of alcohol consumption increased with abnormal GGT value ≥ 50U/L (Table 4). The highest incident of hypertension was found in drinkers followed by ex-drinkers and non-drinkers (abnormal SBP; drinkers 37.79%, ex-drinker 13.39% and non-drinkers 5.51% and abnormal DBP; drinkers 28.35%, ex-drinker

9.45% and non-drinkers 5.51%, respectively). Further analysis stratified by serum GGT level, current drinkers with abnormal GGT value ≥ 50U/L showed the highest incident of hypertension among three alcohol groups (22.05% for abnormal SBP and 16.19% for abnormal DBP).

Table 4. Incidence of hypertension by level of serum GGT among 260 men

	All subjects		GGT level			
			< 50 U/L		≥ 50 U/L	
Alcohol consumption	**SBP ≥ 140 mmHg (%)**	**DBP ≥ 90 mmHg (%)**	**SBP ≥ 140 mmHg (%)**	**DBP ≥ 90 mmHg (%)**	**SBP ≥ 140 mmHg (%)**	**DBP ≥ 90 mmHg (%)**
Non-drinkers	5.51	5.51	3.57	3.57	1.94	1.94
Ex-drinkers	13.39	9.45	7.94	6.56	5.45	2.89
Drinkers	37.79	28.35	15.74	12.16	22.05	16.19

Discussion

The finding of this cross-sectional, population-based study indicated that alcohol consumption was associated with significantly higher hepatic enzyme levels. Serum activities of GGT, AST and ALT showed strong evidences with alcohol consumption. These enzyme levels were significantly higher in current drinkers than ex-drinkers and non-drinkers. The most significant increase was found for GGT, followed by AST and ALT (Table 1) with similar to previous report by Stranges, et al.[8]. There was substantial evidence supporting that GGT seemed to be the sensitive hepatic biomarkers most strongly related to alcohol intake [9], whereas some studies reported that other factors such as obesity and body fat distribution, rather than alcohol consumption seemed to be stronger determinants of ALT and AST [10,11]. However, elevation in serum hepatic enzymes among drinkers may result from an increased liver cell membrane permeability and cell necrosis. These hepatic enzymes are traditional biomarkers routinely used in assessing the extent hepatic inflammation or injuries and the adverse health effect of alcohol on liver function. Further analysis as quartiles of serum GGT levels, our results demonstrated the closed link of serum GGT, AST and ALT activities, similar to study by Alatalo et al.[12]. The authors showed that the amount of self-reported ethanol intake correlated significantly with serum GGT, AST, ALT and ferritin. Among these biomarkers, GGT was found to correlate strongly with AST (r=0.42), ALT (r=0.53); AST and ALT (r= 0.62) [12].

Light and moderate alcohol consumption was usually associated with a reduced risk for atherosclerosis and coronary artery disease (CAD), whereas heavy drinkers were at an increased risk. The major mechanism appeared to be the well known ability of alcohol to raise HDL-C concentration. Relationship between the consumption of alcoholic beverage and lipid profile was mentioned in previous studies [13,14]. The levels of HDL-C, LDL-C and TG

among participant in this study were also influenced by alcohol intake. Serum HDL-C and TG significantly increased, on the other hand serum LDL-C significantly decreased in drinkers compared to ex-drinkers and non-drinkers (Table 1). The increase in plasma HDL-C with moderate alcohol intake resulted from increased transport rate of the major apolipoproteins apo A-I and –II[15]. In addition, a daily dose of 30 g alcohol resulted in increases 3.99 mg/dL HDL-C level, and 8.82 mg/dL apo A-I [16]. Our results showed a relationship between alcohol and increased TG level, with similar to other studies [13,14]. In contrast, an Italian study showed no significant association between alcohol and TG concentration[17]. The possible explanations may be differences in dietary and alcohol patterns and in ethnicity related to genetic factor in lipid metabolism. For LDL-C, its slope significantly decreased as alcohol intake increased ($p = 0.002$) which the authors suggested that the mechanism of how alcohol intake decreased the risk for increased LDL-C remained to be elucidated[18]. One plausible explanation was that alcohol might decrease the conversion of the very-low-density lipoprotein (VLDL) to LDL apo B or accelerate the clearance of LDL apo B[18]. In addition, elevated GGT has been linked to triglyceride accumulation[19].

A close association between the volume of alcohol consumed and blood pressure level, concurrent with increased serum GGT with hypertension were observed by many researchers[1,3,4]. In clinical practice, serum GGT has been used as a marker for assessment of excessive alcohol consumption, liver disease and cardiovascular risk factors (such as diabetes and hypertension). If the hypothesis that serum GGT reflected the individual susceptibility to the pressor effect of alcohol was correct, the alcohol-increased SBP and DBP relation should be different in the individuals with different serum GGT levels. From this present study, there was a trend toward an increase in the relative risk of the hypertension according to alcohol consumption, as seen in Table 1 and 2. The incidence of hypertension was higher in subjects with serum GGT level of 50 U/L or over, compare with the subjects with serum GGT below 50 U/L (Table 3). These findings agreed with a report by Yamada et al. that found a significantly higher blood pressure and a higher prevalence of hypertension in the subjects with elevated serum GGT levels in comparison with those with normal serum GGT levels[1]. This association may be a mechanism underlying an important role of GGT enzyme in antioxidant systems with response to oxidative stress, marking increase transport of glutathione to cell[4]. The result from this study suggested that serum GGT level could be proposed as a clinical parameter to predict alcohol drinkers with high risk for the development of hypertension.

The present study was a cross-sectional study to investigate the association between alcohol consumption and the alteration of serum GGT influencing on risk of hypertension. However, our study has some limitations similar to other previous reports related to alcohol drinking. These issue included heavy and/or adverse health-drinkers with less likely to participate in this study, underreport alcohol consumption, uncontrolled confounding factors related to liver function test and/ or cardiovascular disease, and lack of genetic study with identify susceptibility to adverse health effects. Further investigations with a large sample size with cover a broad range of potential confounding factors as well

as genetic polymorphisms of enzymes related to alcohol metabolism are warranted.

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