Clinical and Experimental Hypertension, 2013; 35(1): 16–19

ISSN 1064-1963 print/1525-6006 online
DOI: 10.3109/10641963.2012.685535

informa
healthcare

The Association of Oxidative Stress with Hypertensive Retinopathy

Mustafa Karaca,[1] Erkan Coban,[1] Rasih Felek,[2] Mustafa Unal[3]

[1]*Department of Internal Medicine, Akdeniz University Faculty of Medicine, Antalya, Turkey,* [2]*Medical Faculty Central Laboratory, Akdeniz University, Antalya, Turkey,* [3]*Department of Ophtalmology, Akdeniz University Faculty of Medicine, Antalya, Turkey*

Abstract

This study was designed to answer the following questions: (i) Do levels of serum gamma-glutamyl transferase (GGT), a marker of oxidative stress, change in hypertensive retinopathy (HR)? (ii) Is there any relation between degree of HR and GGT levels? This study included 80 hypertensive patients with HR. Group 1 comprised 40 patients with grade I HR, and group 2 comprised 40 patients with grade II HR. We selected 40 healthy subjects for the control group. Level of GGT in group 2 was significantly higher than in group 1 ($P = 0.005$) and control group ($P = 0.001$); it was also higher in group 1 than in control group ($P = 0.025$). Our study suggests that oxidative stress, mechanisms known to be involved in vascular lesions, may promote the development of HR.

Keywords: gamma-glutamyl transferase, oxidative stress, hypertension, hypertensive retinopathy

BACKGROUND

Gamma-glutamyl transferase (GGT) is a plasma membrane enzyme with a central role in glutathione homeostasis, which is important in maintaining adequate concentrations of intracellular glutathione to protect cells against oxidants. Elevated serum GGT activity is a sensitive marker of oxidative stress (1). Serum GGT is a clinical marker of several factors: hepatobiliary disease, alcohol consumption, body fat content, plasma lipid/lipoproteins and glucose levels, and medications (2,3). Serum GGT can also reflect other concomitant risk factors such as hypertension (4,5), diabetes mellitus (6,7), obesity (8), dislipidemia, and metabolic syndrome (9). In addition, some studies demonstrated that there is a relationship between diabetic retinopathy and GGT levels (10).

Hypertensive retinopathy (HR) is a condition characterized by a spectrum of retinal vascular signs in people with elevated blood pressure (BP) (11–13). The pathophysiological mechanism of HR is not fully established. Elevated BP alone does not fully account for the extent of retinopathy, other pathogenic mechanisms may be involved, such as increased oxidative stress. Therefore, this study was designed to answer the following questions: (i) Do GGT levels change in HR? (ii) Is there any relation between degree of HR and GGT levels?

MATERIALS AND METHODS

Patients

This study was performed at the outpatients' clinic of Department of Internal Medicine of Akdeniz University Hospital. Six hundred and fifty-four adult hypertensive patients were registered in the computer files of our departments. Eighty hypertensive patients without exclusion criteria were invited to participate in this study. None of the patients refused the study. The hypertensive patients were divided into two groups according to the Keith–Wagener classification (14). Group 1 comprised 40 hypertensive patients with grade I HR and group 2 comprised 40 hypertensive patients with grade II HR. Forty normotensive subjects, who were healthy participants and had undergone the checkup program, were used as the control group. The controls had similar body mass index (BMI), age, and sex distribution as the hypertensive group.

The exclusion criteria were as follows: stage 2 hypertension (according to the Eighth Report of the Joint National Committee) with BP > 160/100 mm Hg (15), grades 3 and 4 HR according to the Keith–Wagener Classification (as most of the patients had other complications that could interfere with the GGT results), diabetes mellitus, smoking, alcohol intake more than 30 g/day, hepatitis B or C infection or other known liver diseases, liver enzymes exceeding three times the upper reference range, use of hepatotoxic drugs,

Address correspondence to Erkan Coban, MD, Department of Internal Medicine, Akdeniz University Faculty of Medicine, 07070 Antalya, Turkey. E-mail: ecoban@akdeniz.edu.tr

Received 15 March 2012; accepted 6 April 2012.

dyslipidemia, obesity (BMI $\geq$ 30 kg/m^2), cardiac, renal, cerebral, and other systemic diseases, recent major surgery or illness.

Dyslipidemia was defined in the presence of at least one of the following conditions: raised plasma triglycerides (>200 mg/dL), total cholesterol (>200 mg/dL), low-density lipoprotein (LDL)-cholesterol (>130 mg/dL), and decreased high-density lipoprotein (HDL)-cholesterol (<40 mg/dL for men and <50 mg/dL for women) (16).

Eligible subjects underwent a comprehensive assessment including documentation of medical history, physical examination, and measurement of laboratory variables. Body weight and height were measured with the subjects in light clothes and without shoes. Body mass index was calculated as the weight (kg)/height squared (m^2). The resting electrocardiograms of all the subjects were normal. All patients gave their informed consent to participate in the study.

Measurement of BP

Arterial BP was measured by a mercury sphygmomanometer after the patient had been in a sitting position for 5 minutes. For each subject, we recorded the average of three readings obtained within 5 minutes. Hypertension was defined as SBP (systolic BP) $\geq$ 140 mm Hg or DBP (diastolic BP) $\geq$ 90 mm Hg, as recommended in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (15).

Fundoscopic Examination

For the HR evaluation, direct and indirect ophthalmoscopy was performed in all subjects after dilatation of the pupils. A single-blinded observer performed the fundoscopic examinations. The grade of HR was determined according to the Keith–Wagener classification (14).

Biochemical Measurements

Blood samples were collected from antecubital vein without the use of a tourniquet, between 08.30 and 09.00 hours, after an overnight fast to avoid the differences of diurnal variation. Enzymatic colorimetric assay method (Roche Diagnostics GmbH, Mannheim, Germany) was used to measure triglyceride, cholesterol, and high-density lipoprotein-cholesterol levels. Low-density lipoprotein-cholesterol level was calculated according to the Friedewald formula (17). Fasting glucose level was measured using the enzymatic colorimetric assay method (GLU, Roche Diagnostics GmbH). Serum GGT is measured colorimetrically using nitroanilide method on a Cobas instrument (Roche Diagnostics GmbH).

Statistical Analysis

Statistical analysis was done using SPSS statistical software (SPSS for Windows 16.0, Chicago, IL, USA). For $a = 0.05$ (between each group) and a power of 80%, a sample size per group >31 subjects was needed to detect an actual difference. The normality of the distribution was checked by stem and leaf plots. Gamma-glutamyl transferase values across groups were compared with one-way analysis of variance (ANOVA) followed by the post hoc Bonferroni test. In addition, Pearson's correlation was used to evaluate the association between GGT and degree of HR. Summary data for GGT and other continuous variables are expressed as mean $\pm$ SD. Statistical significance was defined as $P < .05$.

RESULTS

The main characteristics, BPs, and laboratory results of study populations are reported in Table 1. Age, gender distribution, and BMI did not differ among the groups. Similarly, metabolic parameters were not different among the study groups as a result of the selection process.

The level of GGT in group 2 was significantly higher than in group 1 (30.57 $\pm$ 6.01 U/L vs. 26.57 $\pm$ 6.25 U/L, $P = .004$) and normotensive control group (30.57 $\pm$ 6.01 U/L vs. 23.27 $\pm$ 3.94 U/L, $P = .001$); it was also higher in group 1 than in normotensive control group (26.57 $\pm$ 6.25 U/L vs. 23.27 $\pm$ 3.94 U/L, $P = .025$). In addition, GGT showed positive correlation with degree of HR in hypertensive group ($r = 0.309$, $P = .004$).

DISCUSSION

Recent epidemiologic and clinical studies have reported a strong association between GGT, a commonly used biochemical liver test, and hypertension. This association has been shown to be independent of alcohol consumption and to be present among both drinkers and nondrinkers (18,19). Our findings are consistent with previous work. On the contrary, this is the first study, to the best of our knowledge, specifically, to evaluate GGT levels in hypertensive patients with HR. Our study demonstrates that hypertensive patients with retinopathy have increased GGT activity, a marker of oxidative stress. In addition, GGT levels showed positive correlations with a degree of HR in hypertensive group.

Recent studies suggest that excessive production of reactive oxygen species, outstripping endogenous antioxidant defense mechanisms, may be involved in the pathogenesis and complications of hypertension (20–22). Giner et al. (23) reported that oxidative stress is a determinant of microalbuminuria independent BP levels in hypertensive patients. Minuz et al. (24) demonstrated increased oxidative stress and persistent platelet activation in essential hypertension with advanced vascular lesions. Purushothaman et al. (25) reported that oxidative stress promotes left ventricular hypertrophy.

Table 1. The main characteristics and laboratory results of the study groups

Parameters	Group1	Group 2	Control group
n (men/women)	40 (21/19)	40 (20/20)	40 (20/20)
Age (y)	53 ± 2	52 ± 9	53 ± 1
BMI (kg/m^2)	25.7 ± 3.1	25.3 ± 3.2	25.4 ± 3.0
SBP (mm Hg)	150 ± 4.6**	149 ± 4.8**	127 ± 4.9
DBP (mm Hg)	98 ± 5.7**	98 ± 5.6**	81 ± 4.7
Fasting glucose (mg/dL)	87.4 ± 9.7	87.9 ± 9.8	87.5 ± 9.6
Creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2
Alanine aminotransferase (U/L)	25.7 ± 3.5	26.6 ± 3.6	25.9 ± 3.5
Total cholesterol (mg/dL)	170.0 ± 22.5	169.4 ± 22.8	169.8 ± 22.9
LDL-cholesterol (mg/dL)	84.3 ± 11.1	83.9 ± 12.2	84.0 ± 12.3
HDL-cholesterol (mg/dL)	50.2 ± 5.2	50.8 ± 5,0	50.4 ± 5.1
Triglyceride (mg/dL)	127.9 ± 15.8	128.0 ± 16.2	127.7 ± 16.7
White blood cell ($\times 10^9$/L)	5.8 ± 1.5	5.9 ± 1.6	5.9 ± 1.4
GGT (U/L)	26.57 ± 6.25*	30.57 ± 6.01***†	23.27 ± 3.94

Abbreviations: BMI – body mass index; DBP – diastolic blood pressure; GGT – gamma-glutamyl transferase; HDL – high-density lipoprotein; LDL – low-density lipoprotein.
*$P < .05$, group 1 versus control group; **$P < .001$, groups 1 and 2 versus control group; ***$P < .001$, group 2 versus control group; †$P < .005$ group 1 versus group 2.

Hypertensive retinopathy is an important complication and a major site of target organ damage from hypertension. It is known that the autoregulation of the retinal circulation fails as BP increases beyond a critical limit. However, elevated BP alone does not fully account for the extent of HR (26–28). There are cases in which retinopathy was resolved despite the persistence of high BP (29). Although the BP levels in group 1 and group 2 were similar, levels of GGT were higher in group 2 than in group 1 in our study. Thus, the presence of high GGT levels in HR and the correlation of the amount of GGT with the severity of HR imply that oxidative stress may be involved in the mechanism of HR. Moreover, recently we found that there is a relationship between levels of ferritin, a marker of oxidative stress, and HR in essential hypertension (30).

This study has some limitations. Firstly, we accept that our study is a case–control design; it is not easy to predict exactly whether the high GGT levels precede retinopathy or vice versa. Future cohort studies will be helpful in providing an answer. Secondly, the study was conducted while the patients were taking antihypertensive treatment. However, distribution of drug use was similar in both hypertensive groups. Thirdly, grade 1–2 HR is not specific to hypertension.

CONCLUSION

Our study suggests that there is a relationship between HR and GGT levels in essential hypertension. Oxidative stress, mechanisms known to be involved in vascular lesions, may promote the development of HR. Also upcoming studies will point out whether or not GGT is a predictor of hypertensive vascular outcomes.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

[1] Whitfield JB. Gamma glutamyl transferase. Crit Rev Clin Lab Sci 2001; 38:263–355.
[2] Kawamoto R, Kohara K, Tabara Y, Miki T, Otsuka N. Serum gamma-glutamyl transferase levels are associated with metabolic syndrome in community-dwelling individuals. J Atheroscler Thromb 2009; 16:355–362.
[3] Emdin M, Pompella A, Paolicchi A. Gamma-glutamyltransferase, atherosclerosis, and cardiovascular disease: triggering oxidative stress within the plaque. Circulation 2005; 112:2078–2080.
[4] Lee DH, Jacobs DR Jr, Gross M, et al. Gamma-glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Clin Chem 2003; 49:1358–1366.
[5] Shankar A, Li J. Association between serum gamma-glutamyl transferase level and prehypertension among US adults. Circ J 2007; 71:1567–1572.
[6] André P, Balkau B, Born C, Charles MA, Eschwège E; D.E.S.I.R Study Group. Three-year increase of gamma-glutamyltransferase level and development of type 2 diabetes in middle-aged men and women: the D.E.S.I.R cohort. Diabetologia 2006; 49:2599–2603.
[7] Nakanishi N, Suzuki K, Tatara K. Serum gamma-glutamyltransferase and risk of metabolic syndrome and type 2 diabetes in middle-aged Japanese men. Diabetes Care 2004; 27:1427–1432.
[8] Poikolainen K, Vartiainen E. Determinants of gamma-glutamyltransferase: positive interaction with alcohol and body mass index, negative association with coffee. Am J Epidemiol 1997; 146:1019–1024.
[9] 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; 27:127–133.
[10] Arkkila PE, Koskinen PJ, Kantola IM, Rönnemaa T, Seppänen E, Viikari JS. Diabetic complications are associated with liver enzyme

activities in people with type 1 diabetes. Diabetes Res Clin Pract 2001; 52:113–118.
[11] Wong TY, Mitchell P. The eye in hypertension. N Engl J Med 2007; 369:425–435.
[12] Porta M, Grosso A, Veglio F. Hypertensive retinopathy: there's more than meets the eye. J Hypertens 2005; 23:683–696.
[13] Wong TY, McIntosh R. Hypertensive retinopathy signs as risk indicators of cardiovascular morbidity and mortality. Br Med Bull 2005; 73–74:57–70.
[14] Keith NM, Wagener HP, Barker NW. Some different types of essential hypertension: their course and prognosis. Am J Med Sci 1974; 268:336–345.
[15] Chobanian AV, Bakris GL, Black HR, et al.; National Heart Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report. JAMA 2003; 289: 2560–2571.
[16] 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; 285:2486–2497.
[17] Friedewald WT, Levi RI, Fredricksen DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18:499–502.
[18] Lee DH, Ha MH, Kim KY, Jin DG, Jacobs DR. Gamma-glutamyltransferase: an effect modifier in the association between age and hypertension in a 4-year follow-up study. J Hum Hypertens 2004; 18:803–807.
[19] Yamada Y, Ikai E, Tsuritani I, Ishizaki M, Honda R, Ishida M. The relationship between serum gamma-glutamyl transpeptidase levels and hypertension: common in drinkers and nondrinkers. Hypertens Res 1995; 18:295–301.
[20] Manning RD Jr, Tian N, Meng S. Oxidative stress and antioxidant treatment in hypertension and the associated renal damage. Am J Nephrol 2005; 25:311–317.
[21] Zeng C, Villar VA, Yu P, Zhou L, Jose PA. Reactive oxygen species and dopamine receptor function in essential hypertension. Clin Exp Hypertens 2009; 2:156–178.
[22] Portaluppi F, Boari B, Manfredini R. Oxidative stress in essential hypertension. Curr Pharm Des 2004; 10:1695–1698.
[23] Giner V, Tormos C, Chavas FJ, Saez G, Redon J. Microalbuminuria and oxidative stress in essential hypertension. J Intern Med 2004; 255:588–594.
[24] Minuz P, Patrignani P, Gaino S, et al. Determinants of platelet activation in human essential hypertension. Hypertension 2004; 43:64–70.
[25] Purushothaman S, Nair RR, Harikrishnan VS, Fernandez AC. Temporal relation of cardiac hypertrophy, oxidative stress, and fatty acid metabolism in spontaneously hypertensive rat. Mol Cell Biochem 2011; 351:59–64.
[26] Yilmaz MI, Sonmez A, Kilic S, et al. The association of plasma adiponectin levels with hypertensive retinopathy. Eur J Endocrinol 2005; 152:233–240.
[27] DellaCroce JT, Vitale AT. Hypertension and the eye. Curr Opin Ophthalmol 2008; 19:493–498.
[28] Wong TY, Mitchell P. The eye in hypertension. Lancet 2007; 369:425–435.
[29] Lowenthal MN, Zimlichman R. Resolution of hypertensive retinopathy despite persistent high diastolic pressure. South Med J 1993; 86:190–193.
[30] Coban E, Alkan E, Altuntas S, Akar Y. Serum ferritin levels correlate with hypertensive retinopathy. Med Sci Monit 2010; 16:CR92–CR95.