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Serum Gamma-Glutamyl Transferase (GGT) Levels and Inflammatory Activity in Patients With Non-dipper Hypertension

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Abstract

Non-dipper hypertension is associated with increased cardiovascular morbidity and mortality. We aimed to evaluate serum gamma-glutamyl transferase (GGT) level, which is accepted as a marker for oxidative stress and its relationship with inflammatory activity in patients with non-dipper hypertension. Age and sex matched 43 dipper hypertensive patients, 40 non-dipper patients, and 46 healthy subjects were included into the study. Serum GGT and C-reactive protein (CRP) levels were measured and compared between each of the groups. Serum GGT activity was higher in the non-dipper and the dipper hypertensive groups than in the control group (33.5 $\pm$ 11.8 and 28.1 $\pm$ 10.1 U/l, respectively, vs. 21.2 $\pm$ 6.5U/l; $p < 0.001$). There was a statistically significant difference in serum GGT activity between the non-dippers and the dippers ($p = 0.021$). When compared with the control group, serum CRP levels were significantly increased in both the non-dipper and the dipper hypertensive groups (6.1 $\pm$ 2.6 and 5.4 $\pm$ 2.1 mg/l, respectively, vs. 2.8 $\pm$ 1.7mg/L; $p < 0.001$). Increased CRP levels were higher in non-dippers than dippers ($p = 0.046$). A significant correlation was found between GGT and CRP measurements ($r = 0.37$, $p = 0.002$). Serum GGT levels, which are markers of the oxidative stress and CRP levels, are both increased in non-dipper hypertension. Increased GGT activity, found to be correlated with CRP levels, may be one of the reasons behind the non-dipper hypertension related cardiovascular complications.

Keywords: non-dipper hypertension, Gamma-glutamyl transferase and CRP

INTRODUCTION

Hypertension is a common chronic condition affecting up to 35% of the adults (1). Most of the hypertensive patients exhibit a blood pressure (BP) fall between 10% and 20% during nighttime hours, who are called dippers. Recent studies implicated that the lack of nocturnal BP fall of less than 10% of the daytime (non-dippers) is associated with increased cardiovascular mortality, silent cerebrovascular disease, and progressive nephropathy, compared to the patients with dipper BP (2–4).

Serum gamma-glutamyl transferase (GGT) activity has been used as a marker for alcohol consumption or hepatobiliary disease (5). Gamma-glutamyl transferase is a plasma membrane enzyme that provides antioxidant glutathione resynthesis (6). Recent reports also indicate a direct role for GGT in the generation of reactive oxygen species (7–9). In this context, evidence from epidemiological studies point out that GGT may have a role in the pathogenesis of cardiovascular disease, diabetes mellitus, and metabolic syndrome (10–12). Similarly, recent cross-sectional and longitudinal studies have also noted a relatively independent association between elevated serum GGT levels and hypertension (12–14).

Studies evaluating the relationship between inflammatory markers and circadian BP variations showed that non-dipper hypertension is characterized by increased inflammatory activity when compared to the dippers and normotensives (15, 16). However, there is no data indicating the relation between the diurnal BP pattern and serum GGT levels in hypertensive patients. In this study, we aimed to evaluate serum GGT levels together with the inflammatory activity in patients with hypertension in terms of circadian BP patterns.

METHODS

Patients

A total of 83 patients with hypertension and 46 healthy control subjects (22 male, 24 female, mean age: 52.8 $\pm$ 9.6 years) were included in the study. Hypertensive

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patients were divided into two subgroups: 43 dipper (19 male, 24 female, mean age: 53.9 ± 10.5 years) and 40 non-dippers (18 male, 22 female, mean age 54.3 ± 9.6 years).

Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg or presence of the history of taking antihypertensive medication. Non-dipper hypertension was defined as less than 10% decrease in either SBP or DBP during nighttime record over 24-h ambulatory BP monitoring (ABPM). Exclusion criteria were the evidence of coronary artery disease, renal or hepatic dysfunction, active hepatobiliary disease, and alcohol consumption, hematologic disease, cancer, systemic inflammatory conditions, autoimmune disease, anemia, hyperthyroidism, and obstructive sleep apnea. Written informed consent was obtained from each subject and institutional review board approved the study protocol.

ABPM Recordings

Blood pressure was measured using a mercury sphygmomanometer in an office setting. Following a 5-min resting period, SBP and DBP was recorded at Korotkoff phases I and V, respectively. The 24-h ABPM was performed using a portable compact digital recorder (Delmar Reynolds, Tracker NIBP2, Hertford, UK) and analyzer using costumed analytic software. The device was set to obtain BP readings at 15-min intervals during the day (07.00–23.00 h) and at 30-min intervals during the night (23.00–07.00 h). The patients were instructed to attend their usual daily activities but to stay inactive during measurements. Recordings were accepted only if more than 85% of the raw data were valid. The absolute and percentages of the decrease of nighttime SBP vs. daytime SBP were calculated in all subjects.

Biochemical Measurements

Blood samples were drawn following a fasting period of 12 h. Glucose, creatinine, and lipid profiles were determined by standard methods. The activity of GGT was measured by using an Abbott-Architect auto analyzer (Abbott, Chicago, IL, USA) with original kits. C-reactive protein was calculated by the nephelometric method (Behring Nephelometer Analyzer, Marbug, Germany) and expressed as mg/l.

Statistical Analysis

Statistical analysis was performed using the SPSS for Windows (version 11.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics of patients, including frequencies and percentages, were computed. Continuous variables are expressed as mean ± standard deviation. Nominal parameters were expressed as percents. Significance of differences between the three groups was assessed by using one-way ANOVA, followed by the Sheffe post-hoc test for ordinal parameters displaying normal distribution and the Kruskal-Wallis test followed by the Bonferroni corrected Mann-Whitney U post-hoc test for ordinal parameters not displaying normal distribution. Significance of differences between groups for nominal parameters was assessed by using chi-square test. Correlation between GGT activity and CRP levels were evaluated by the Pearson and Spearman rank correlation test. Statistical significance was accepted as p value less than 0.05.

RESULTS

Comparison of baseline characteristics of the non-dippers, dippers, and controls were shown in Table 1. There was no significant difference among the groups with respect to age, gender, resting heart rate, diabetes mellitus, serum creatinine levels, and body mass index (BMI). Triglyceride, total cholesterol, and low-density lipoprotein (LDL) cholesterol levels were higher in the dippers and non-dippers when compared to the controls ($p < 0.05$). Clinical SBPs and DBPs in office settings were similar in both hypertensive groups but were higher than normotensives, as expected ($p < 0.001$). Distribution of the antihypertensive drugs was also illustrated in Table 1. There was no difference between the dippers and non-dippers with respect to the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and diuretics. The average daytime SBPs, DBPs, and mean BP levels were shown in Table 2.

Serum GGT activity was higher in dipper and non-dipper hypertensive groups than normotensives (28.1 ± 10.1 and 33.5 ± 11.8 U/l, respectively, vs. 21.2 ± 6.5 U/l; $p < 0.001$) and increased GGT activity was more pronounced in the non-dipper group ($p = 0.021$) (Table 1 and Figure 1). When compared to the control group, serum CRP levels were significantly increased in both dipper and non-dippers (5.4 ± 2.1 and 6.1 ± 2.6 mg/dl, respectively, vs. 2.8 ± 1.7 mg /dl; $p < 0.001$). Increased CRP levels were higher in non-dippers than in dippers ($p = 0.046$) (Table 1). A significant correlation was found between GGT activity and CRP measurements ($r = 0.37$, $p = 0.002$), (Figure 2).

DISCUSSION

In this study, we found that serum GGT activity and CRP levels were significantly increased in patients with non-dipper hypertension, when compared to the dippers and normotensives. We also found a significant correlation between serum GGT levels and inflammatory activity. To our knowledge, this is the first study comparing GGT and CRP levels together in patients with different circadian BP patterns.

During the last two decades, most of the studies have demonstrated a significant correlation between

Table 1. Laboratory parameters and clinical characteristics of study groups

	Non-dippers (n = 40)	Dippers (n = 43)	Normotensives (n = 46)
Age	54.3 ± 9.6	53.9 ± 10.5	52.8 ± 9.6
Men n/%	18 (45)	19 (44.1)	22 (47.8 %)
BMI(kg/m^2)	26.8 ± 4.4	27.3 ± 3.6	26.1 ± 3.9
Clinic SBP (mmHg)	149.8 ± 13.4*	148.3 ± 15.2*	110.8 ± 13.1
Clinic DBP (mmHg)	94.2 ± 9.2*	93.6 ± 11.4*	71.7 ± 8.6
Resting heart rate (bpm)	73.5 ± 8.3	72.6 ± 9.2	71.1 ± 6.4
Diabetes, n/%	5 (12.5)	6 (14)	7 (15.2)
Total cholesterol (mg/dl)	198.4 ± 32.7*	202.6 ± 41.2*	186.9 ± 26.9
LDL cholesterol (mg/dl)	130.2 ± 41.5*	132.1 ± 45.5*	119.2 ± 24.5
HDL cholesterol	38.5 ± 11,3	42.4 ± 10.2	41.6 ± 12.5
Triglyceride (mg/dl)	144.6 ± 52.6*	149.6 ± 58.2*	139.6 ± 39.8
Gamma-glutamyl transferase (U/L)	33.5 ± 11.8$^{\star\#}$	28.1 ± 10.1*	21.2 ± 6.5
Aspartate aminotransferase (U/L)	24.3 ± 10.1	24.6 ± 8.7	23.4 ± 7.1
Alanine aminotransferase (U/L)	23.9 ± 8.1	23.6 ± 8.5	21.1 ± 7.4
CRP	6.1 ± 2.6$^{\star\#}$	5.4 ± 2.1*	2.8 ± 1.7
Creatinine (mg/dl)	0.9 ± 0.13	0.88 ± 0.16	0.86 ± 0.21
ACE inh. n/%	14 (35)	16 (35.6)	–
ARB, n/%	24 (60)	25 (58.1)	–
Ca channel blockers, n/%	9 (22.6)	10 (23.2)	–
Diuretics, n/%	24 (60.0)	26 (60.1)	–

Abbreviations: SBP - systolic blood pressure; DBP - diastolic blood pressure; bpm - beats per minute; BMI - body mass index; ACE inh - angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker.
*:$p < 0.05$ non-dippers and dippers vs. normotensives.
$^\#$:$p < 0.05$ non-dippers vs. Dippers.

Table 2. Comparison of ambulatory BP monitoring results of dippers and non-dippers

	Non-Dippers	Dippers	p Value
24-h systolic BP	141.5 ± 9.3	134.5 ± 7.3	<0.001
24-h diastolic BP	90.0 ± 6.8	83.2 ± 5.9	<0.001
24-h mean BP	107.2 ± 7.3	100.2 ± 6.1	<0.001
Daytime systolic BP	145.2 ± 5.8	143.7 ± 6.4	NS
Daytime diastolic BP	90.3 ± 7.1	89.3 ± 7.7	NS
Daytime mean BP	108.5 ± 5.1	107.4 ± 5.7	NS
Nighttime systolic BP	137.8 ± 7.9	126.2 ± 6.3	<0.001
Nighttime diastolic BP	88.5 ± 6.2	78.1 ± 5.0	<0.001
Nighttime mean BP	104.9 ± 5.4	94.1 ± 4.1	<0.001

Abbreviations: BP - blood pressure; NS - nonsignificant.

ABPM recordings and the prevalence and extent of cardiovascular events. The first study showing the relationship between reduced nocturnal BP fall in hypertensive subjects and cardiovascular events was reported by Verdechia et al. (17). In their study, non-dipper hypertensives were reported to have three-fold increased risk for cardiovascular complications compared to the dippers (15).

Previous studies have reported an association between BP and CRP level, which is used as the standard assay to identify and monitor the inflammatory activity (18, 19). In the Women's Health Study cohort, Blake et al. reported an independent association between CRP and high BP (18). Increasing categories of BP levels were found to be significant predictors of increased CRP levels, after being adjusted for potential confounders. In literature, there are some studies evaluating the relationship between inflammatory activity and circadian BP variations (15, 16). A most recent study comparing CRP levels between the dippers and non- dippers was carried out by Kaya et al. (16) and CRP levels were reported to be increased in patients showing a non-dipper BP profile. In agreement with this study, we also found increased CRP levels in the non-dippers.

In clinical practice, GGT, which is the enzyme responsible for the extracellular catabolism of glutathione (20), is a commonly used diagnostic test. Gamma-glutamyl transferase has an important role in antioxidant defense systems and as a biomarker would fall under a new classification of ''oxidative stress'' in view of its role in the degradation of the antioxidant glutathione (8, 9, 21). Oxidative stress is involved in the pathophysiology of some diseases including cardiovascular disease and/or metabolic regulation. Several evidences suggest a plausible relationship between serum GGT level and hypertension, including the following: 1. GGT has a direct role in the generation of

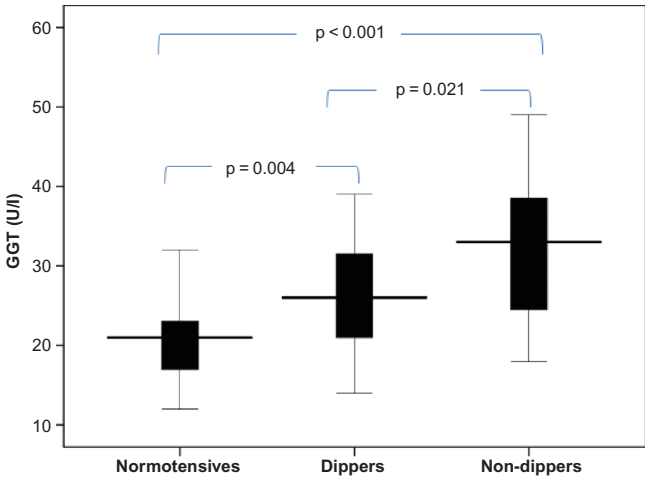

Figure 1. Comparison of serum GGT levels among the three study groups.

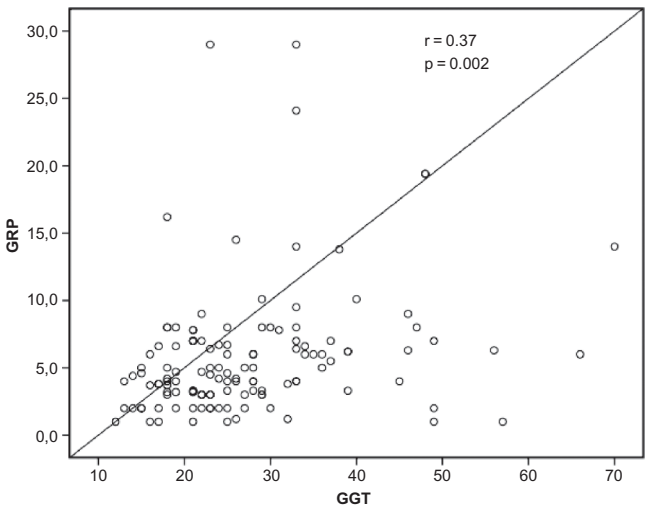

Figure 2. Positive correlation between serum GGT levels and inflammatory activity is shown.

reactive oxygen species; 2. GGT has indirect role as a marker for increased extracellular catabolism of antioxidant glutathione in response to oxidative stress; 3. it has a relationship with inflammatory markers; 4. GGT has also a relationship with insulin-resistance and the other components of the metabolic syndrome (7–9, 21–24).

It is known that oxidative stress is a key component of many reactions associated with chronic inflammation (23, 25). Multiple oxidative processes play a critical role in inflammation and act on various intra- and extracellular pathways through specific mediators in conjunction with free radicals that amplify inflammatory reactions at specific sites (22). In this context, in the Coronary Artery Risk Development in Young Adults (CARDIA) study (12), serum GGT concentrations predicted future serum CRP levels, which was measured 15 years after the earlier GGT measurement and 5 years after the later in dose-response manners. In another study confirming our results, Lee and Jacobs showed a strong association between serum gamma-glutamyltransferase and C-reactive protein in 12,110 adult participants in the third U.S. National Health and Nutrition Examination Survey (22).

Oxidative stress has been implicated in initiating inflammatory response through chromatin modeling (histone acetylation/deacetylation), the activation of transcription factors such as nuclear factor-kappa B and activator protein-1 leading to gene expression of proinflammatory mediators (22). Previous studies and our findings suggest that the elevation of serum GGT is involved in the inflammatory response (12, 22, 23). Due to an interrelation between oxidative stress and inflammatory reactivity, it is reasonable to say that one of the triggering pathologies is increased oxidative stress for future cardiovascular events in non-dipper hypertension.

The most important limitations of our study are the small sample size and cross-sectional design of the study which limit our results to generalize. The study was conducted while the patients were taking antihypertensive treatment. However, distribution of drug use was similar in both hypertensive groups. Another limitation is the lack of other markers for defining oxidative stress (i.e., malondialdehyde, superoxide dismutase, and glutathione) and inflammatory markers (i.e., interleukin-6, tumor necrosis factor-α). Finally, the fact that the diagnosis of dipper vs. non-dippers was based on single BP measurements could be one additional limitation of the study.

From a clinical standpoint, our results showed that both serums GGT levels, which is a marker of the oxidative stress, and CRP levels are correlated with each other and both are increased in non-dippers. Thus, increased oxidative stress may be one of the reasons behind the non-dipper hypertension-related cardiovascular complications.

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

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