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Letter to the Editor

Changes in serum gamma-glutamyl transferase and blood pressure levels in subjects with normal blood pressure and prehypertension

Dear editor:

Recently, serum gamma-glutamyltransferase (GGT), a marker of oxidative stress, has been considered to be linked with the development of cardiovascular disorders [1]. In light of the overall positive associations between serum GGT and hypertension (HT) in previous reports [2–7], similarly, a significant and positive association between GGT and prehypertension (PreHT) has more recently reported in the general population [8]. PreHT, defined as systolic blood pressure (SBP) ranging from 120–139 mmHg or diastolic blood pressure (DBP) ranging from 80–89 mmHg (by the Seventh Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure), is identified as a predictor for the occurrence of HT and a stage when primary prevention of HT is still possible [9–12]. The result of the association of GGT with PreHT may contribute to preventive cardiology because the clinical usage of GGT is easy as a biochemical marker; however, a study examining the association of GGT with PreHT was cross-sectional [8], so it is important to confirm the association of GGT changes with SBP/DBP changes in PreHT levels in a longitudinal (over a period of at least 1 y) study.

Moreover, the Seventh Joint National Committee defines <120/80 mmHg of SBP/DBP as normal blood pressure (NBP) [9]. Individuals with NBP are also thought to be in a more possible stage of primary prevention of HT than PreHT; however, no study has examined the association of GGT with NBP.

This background encouraged us to examine whether SBP/DBP changes could be accompanied by GGT changes in subjects with PreHT and NBP. Thus, we conducted a one-year observational study to investigate this association and to observe whether there were any differences between PreHT and NBP subjects.

Overall, 364 asymptomatic Japanese subjects were studied during a 1-y study period: 259 PreHT subjects (79 men and 180 women; mean age: 49.8±6.9 [range: 35–64] y) and 105 NBP subjects (50 men and 55 women; mean: 47.9±6.0 [37–61] y) were included. This study was approved by the Tottori University Ethics Committee and each subject gave informed consent. All subjects were negative for both hepatitis B surface antigen and hepatitis C virus antibody, did not take any continuous medication (untreated during the study period), had no alcohol consumption or smoking habit, and no medical history of cardiovascular, renal, thyroid, malignant or collagen disorders. After a 12-h fast, seated SBP/DBP, body mass index (BMI), serum lipids (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], triglyceride [TG]), plasma glucose (PG) and GGT were respectively measured. SBP/DBP was measured 3 times with an automatic electronic sphygmomanometer (BP-103i II; Nippon Colin, Japan) and the 3 measurements were averaged. PG was measured with an automatic analyzer (BM2250, JEOL Co. Ltd., Japan). TC, TG, HDL-C and GGT were assayed with an automatic analyzer (TBA-200FR, Toshiba, Japan). In the pre-study data, subjects >100 U/l in serum GGT levels were not included (basically, there is no clear gender difference in the association between GGT and BP [8]). All subjects were of relatively ordinary health, and those with the following pre-study data (mild dyslipidemia and impaired fasting glucose tolerance) were included:<6.2 mmol/l in TC; 0.8–2.6 mmol/l in HDL-C;<2.8 mmol/l in TG; <7.0 mmol/l in PG. In the post-study period, the same variables such as SBP/DBP, BMI and GGT were reexamined.

All values were expressed as the means±SD (geometric means in GGT only). Multiple regression analysis of SBP/DBP changes was used to analyze the correlation with GGT changes after adjusting for measured confounders (age, gender and BMI changes). Because of the skewed distribution, GGT was log-transformed for this analysis. A $P<0.05$ was considered significant.

In PreHT, the pre-study mean levels and post-study mean levels (followed by mean change levels [range]) in each variable were as follows: 126.7±8.0 and 125.3±12.0 (−1.4±11.2 [−30–30]) mmHg in SBP; 82.1±6.0 and 81.7±8.3 (−0.4±8.9 [−28–27]) mmHg in DBP; 23.4±2.8 and 23.4±2.9 (0.0±0.7 [−3.1–1.7]) kg/m^2 in BMI; 40.2±1.7 and 38.8±1.8 (1.0±1.5 [−68–80]) U/l in GGT. Similarly, in NBP, the pre-study mean levels and post-study mean levels (mean change levels [range]) in each variable were as follows: 104.6±7.3 and 110.2±10.8 (5.7±9.5 [−19–26]) mmHg in SBP; 67.2±6.5 and 70.6±8.4 (3.4±8.1 [−17–26]) mmHg in DBP; 21.5±2.3 and 21.6±2.5 (0.1±0.8 [−3.3–2.1]) kg/m^2 in BMI; 28.1±1.6 and 28.6±1.7 (1.0±1.0 [−68–80]) U/l in GGT.

In PreHT, SBP as well as DBP changes significantly, independently and positively correlated with GGT changes (Table 1). SBP changes also significantly correlated with BMI changes. Age correlated with SBP changes, but did not reach statistical significance. In NBP, only one significant correlation was seen: SBP changes positively correlated with BMI changes.

We found a significant, independent and positive association between GGT and SBP/DBP changes in a population with PreHT, whereas a weak association in NBP. This suggests that GGT may be a predictive biochemical marker for SBP/DBP changes in PreHT, extending the recent cross-sectional data on

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Table 1
Multiple regression analysis of variables correlated to blood pressure changes

Variable	Prehypertension	Normal blood pressure
	β-coefficient (*P* value)	β-coefficient (*P* value)
For Δ systolic blood pressure		
Age	0.118 (0.053)	0.107 (NS)
Gender, male	0.082 (NS)	0.072 (NS)
Δ body mass index	0.128 (0.048 *)	0.232 (0.017 *)
Δ GGT[a]	0.162 (0.012 *)	0.120 (NS)
For Δ diastolic blood pressure		
Age	0.030 (NS)	0.159 (NS)
Gender, male	0.059 (NS)	0.080 (0.420)
Δ body mass index	0.087 (NS)	−0.021 (NS)
Δ GGT[a]	0.150 (0.023 *)	0.132 (NS)

GGT: gamma-glutamyl transferase. Δ(change levels) means the values by subtracting pre-study values from post-study values.
[a] GGT was analyzed after log-transformation because of the skewed distribution.
* Significance: $P<0.05$.

the association between GGT and PreHT [8]. The association between BMI and SBP changes, observed in PreHT and NBP, is consistent with previous reports [13,14]. Additionally, it is interesting that the effects of GGT on SBP/DBP may be somewhat different between PreHT and NBP. Although the mechanism of the association between GGT and blood pressure remains largely unknown, some plausible explanations exist; e.g., its direct involvement in the generation of reactive oxygen species; on the other hand, its indirect role in maintaining intracellular antioxidant glutathione (in response to oxidative stress, increased transport of glutathione into cells by increased GGT activity); its relation to chronic inflammation and insulin resistance affecting the cardiovascular system [1,2,8]. A significant association of GGT with PreHT, rather than NBP, may be explained in considering the above speculation. Namely, PreHT may be a status with oxidative stress, inflammation or insulin resistance, linked to increased GGT activity, more than NBP. If so, GGT is related to clinically relevant BP stages, at least from the PreHT stage; therefore, GGT could be useful to monitor the disease continuum of HT. In addition, exploring the biological roles of GGT might partly clarify the mechanism of HT development.

Our study had study several limitations. BP measured in a single day could be a relatively weak point, although many epidemiological studies have adopted this methodology. Concerning the short-term period and population number, more studies with a longer follow-up period and a larger sample (particularly in NBP subjects) will be needed as a future challenge.

In conclusion, during 1 y, serum GGT level changes were found to be significantly and positively correlated with SBP/DBP level changes, particularly in PreHT. The impact of GGT on SBP/DBP in PreHT was suggested to be greater relative to NBP, maybe reflecting the difference in both pathophysiologic conditions.

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Kazuhiko Kotani
Division of Health Administration and Promotion, Faculty of Medicine, Tottori University, Yonago, Japan
E-mail address: kakotani@grape.med.tottori-u.ac.jp.
Corresponding author. Division of Health Administration and Promotion, Faculty of Medicine, Tottori University, 86 Nishi-cho, Yonago 683-8503, Japan. Tel.: +81 859 38 6113; fax: +81 859 38 6110.

Hisashi Shimohiro
Division of Clinical Laboratory, Tottori University Hospital, Yonago, Japan

Seiji Adachi
Division of General Medicine and Community Medicine, Fujii Masao Memorial Hospital, Kurayoshi, Japan

Naoki Sakane
Department of Preventive Medicine and Diabetes Education, Clinical Research Center for Endocrine and Metabolic Disease, National Hospital Organization Kyoto Medical Center, Kyoto, Japan

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