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ORIGINAL ARTICLE

Gamma-glutamyltransferase: an effect modifier in the association between age and hypertension in a 4-year follow-up study

D-H Lee[1], M-H Ha[2], K-Y Kim[1], D-G Jin[1] and DR Jacobs Jr[3,4]
[1]*Department of Preventive Medicine and Health Promotion Research Center, School of Medicine, Kyungpook University, Daegu, Korea;* [2]*Health Care Center, Pohang Steel Company, Pohang, Korea;* [3]*Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, MN, USA;* [4]*Institute for Nutrition Research, University of Oslo, Oslo, Norway*

We performed a prospective study to assess whether the relationship of age with hypertension was stronger in men with high normal serum gamma glutamyltransferase (GGT) than in those with lower GGT levels. The study population included 8170 healthy male workers in a steel manufacturing company who had undergone health examinations in both 1994 and 1998. The higher the baseline GGT level, the effect of age on the development of hypertension was stronger. The incidence of hypertension among those aged 25–34, 35–44 and 45–50 years was 0.9, 2.2, 3.8% in those with GGT $<$ 20 U/l; 1.0, 4.1, 12.5% in those with GGT between 20 and 39 U/l; and 1.9, 6.3, 17.2% in those with GGT $\geqslant$ 40 U/l, respectively. All relationships persisted after adjusting for baseline values of body mass index, alcohol intake, smoking, exercise, family history of hypertension, systolic and diastolic blood pressure, and changes of body mass index during 4 years (*P* for interaction = 0.03). Our data supported the hypothesis that the effect of age on the development of hypertension differed by baseline GGT level, although the underlying mechanism for this interaction is unclear.
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Introduction

In our previous longitudinal studies,[1,2] we reported a strong dose–response relationships between serum gamma glutamyltransferase (GGT) at baseline and development of type II diabetes. Although GGT has been widely used as a marker of alcohol consumption or liver disease,[3] neither alcohol nor hepatic dysfunction explained the observed relationships between GGT and diabetes. In addition, the typical relationships between age or obesity and type II diabetes were shown only among those with high normal GGT level at baseline.[1,2]

In the same cohorts,[2,4] GGT was a modest risk factor for hypertension. Furthermore, a strong interaction was found between GGT and alcohol consumption on the development of hypertension.[4] In this interaction, a positive association between alcohol consumption and hypertension was observed only in those with high normal GGT level. Among subjects with low GGT level, no matter how much alcohol the subjects drank, the risk of hypertension in drinkers was similar to that of nondrinkers.

Although serum and cellular GGT may not have the same biological meanings, it is interesting to note experimental studies in which GGT at a cellular level plays an important role in antioxidant systems through the maintenance of intracellular levels of glutathione.[5–7] Paradoxically, recent studies[8–11] have shown that GGT is itself able to play a pro-oxidant role, particularly in the presence of iron.

Emerging evidence suggests that hypertension and type II diabetes share pathophysiological mechanisms, especially oxidative stress.[12–15] So, by analogy with type II diabetes, the association between age and hypertension might also depend on GGT level. Therefore, we performed this prospective study with the hypothesis that the relationship between age and hypertension was modified by baseline GGT level.

Correspondence: Dr D-H Lee, Department of Preventive Medicine, School of Medicine, Kyungpook University 101 Dongin-dong, Jung-gu, Daegu 700422, Korea.
E-mail: lee_dh@knu.ac.kr
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Materials and methods

This study was based on the same cohort as our previous study of GGT and hypertension. [4] Study design, recruitment of participants, and methods have been described in detail elsewhere.[4] Briefly, our study population was 8170 male workers at one steel company in Korea, who were between 25 and 50 years without hypertension (systolic BP (SBP) $\geqslant$ 140 mmHg, diastolic BP (DBP) $\geqslant$ 90 mmHg, and/or taking antihypertensive medication) at baseline and examined in both 1994 and 1998 (follow-up rate: 73.7%). No specific informed consent for this study was obtained. Data are analysed pursuant to the Korean health regulation pertaining to factories, which states that the factory physician has an obligation to analyse health examination data to educate workers.

SBP and DBP were recorded oscillometrically with an automatic device (TM-2650A; A&D Company, Japan) in the sitting position after the subjects rested on a chair for 5 min or longer. For employees with SBP $\geqslant$ 160 mmHg or $\geqslant$ 95 mmHg, BP were measured again with an ordinary sphygmomanometer by an experienced nurse after another 5 min of rest. Serum GGT concentrations were measured at 37°C with an automatic analyzer (normal range 0–50 U/L, Hitachi 7170, Japan).

In this study, 169 men met the definition of hypertension was SBP $\geqslant$ 160 mmHg or DBP $\geqslant$ 95 mmHg or under antihypertensive medication. First, we examined the relationship between age (25–29, 30–34, 35–39, 40–44, 45–50 years) and SBP or DBP changes within three GGT categories at baseline GGT (0–19, 20–39, $\geqslant$ 40 U/l) by an analysis of covariance. Next, the relationship between age and incidence of hypertension was examined within the each category of GGT. We performed logistic regression analyses including interaction terms for GGT (0–19, 20–39, $\geqslant$ 40 U/l) and age (25–34, 35–44, 45–50 years). Covariates were the baseline values of body mass index (BMI) (kg/m^2), cigarette smoking (pack years), alcohol consumption (g/week), exercise (frequency/week), family history of hypertension, either SBP (mmHg) or DBP (mmHg), and the changes in BMI during 4 years. The SAS statistical program, version 8.02, was used in all analyses, the *P*-values quoted are two-sided, and those values <0.05 are regarded as statistically significant.

Results

Relationships between age and changes in SBP or DBP varied by baseline GGT level. There were stronger dose–response relationships between age and changes in both SBP and DBP for baseline GGT level $\geqslant$ 40 U/l than for lower GGT levels (Figures 1 and 2) (*P* for multiplicative interaction, <0.01 for SBP; 0.04 for DBP). In addition, the associations of GGT with both SBP and DBP varied by age. There were positive associations between GGT and changes in SBP or DBP among those with age $\geqslant$ 35, whereas there was no association among those with age <35.

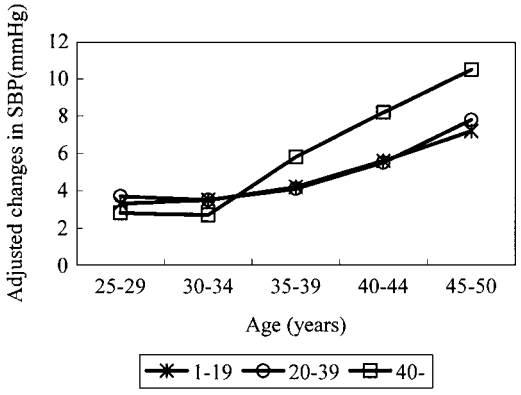

Figure 1 Changes in SBP by age and baseline GGT levels, adjusted for the baseline values of BMI, smoking, alcohol consumption, exercise, family history of hypertension, SBP, and the changes of BMI during 4 years.

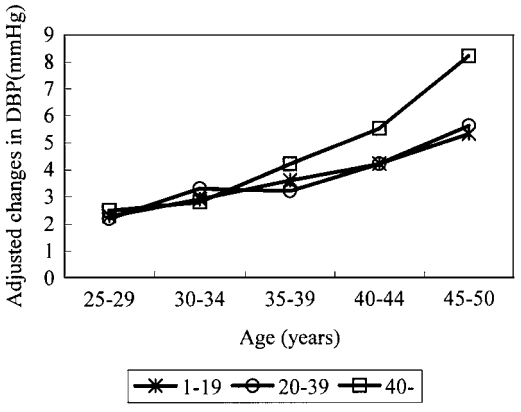

Figure 2 Changes in DBP by age and baseline GGT levels, adjusted for the baseline values of BMI, smoking, alcohol consumption, exercise, family history of hypertension, DBP, and the changes of BMI during 4 years.

The association of age with incidence of hypertension also varied by baseline GGT level. As baseline GGT level increased, the association between age and incidence of hypertension strengthened ($P = 0.03$ for multiplicative interaction) (Figure 3). Using those aged <35 years and GGT <20 as a reference group, adjusted relative risks for those age <35, 35–44, and $\geqslant$45 years were 1.0, 2.7, 4.5 in those with GGT <20 U/l, 0.6, 3.0, 10.9 in those with GGT between 20 and 39 U/l, and 0.9, 3.9, 19.7 in those with GGT $\geqslant$ 40 U/l (Table 1). The interaction was similarly observed among nondrinkers, drinkers, and subjects with normal GGT (data not shown). On the other hand, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) did not show any relationship with age in the development of hypertension. For example, adjusted relative risks for those aged $\geqslant$45 years compared to those aged <35 years was 8.8 (unadjusted inci-

Table 1 Adjusted[a] relative risks (aRR) (95% confidence interval (CI)) for incidence of hypertension during the follow-up period by age and gamma-glutamly transferase (GGT) in 1994 among 8170 male workers

	Age (years)					
	25–34		*35–44*		*45–50*	
GGT	*Cases/pop (%)*	*aRR (95% CI)*	*Cases/pop (%)*	*aRR (95% CI)*	*Cases/pop (%)*	*aRR (95% CI)*
⩽19	30/3433 (0.9%)	1.0[b]	54/2506 (2.2%)	2.7 (1.7–4.5)	10/264 (3.8%)	4.5 (2.1–9.7)
20–39	6/629 (1.0%)	0.6 (0.3–1.5)	30/732 (4.1%)	3.0 (1.7–5.2)	10/80 (12.5%)	10.9 (4.7–25.1)
⩾40	3/161 (1.9%)	0.9 (0.3–3.1)	21/336 (6.3%)	3.9 (2.1–7.3)	5/29 (17.2%)	19.7 (6.3–61.3)

[a]Adjusted for the baseline values of BMI, smoking, alcohol consumption, exercise, family history of hypertension, SBP and the changes of BMI during 4 years; [b]Reference group.

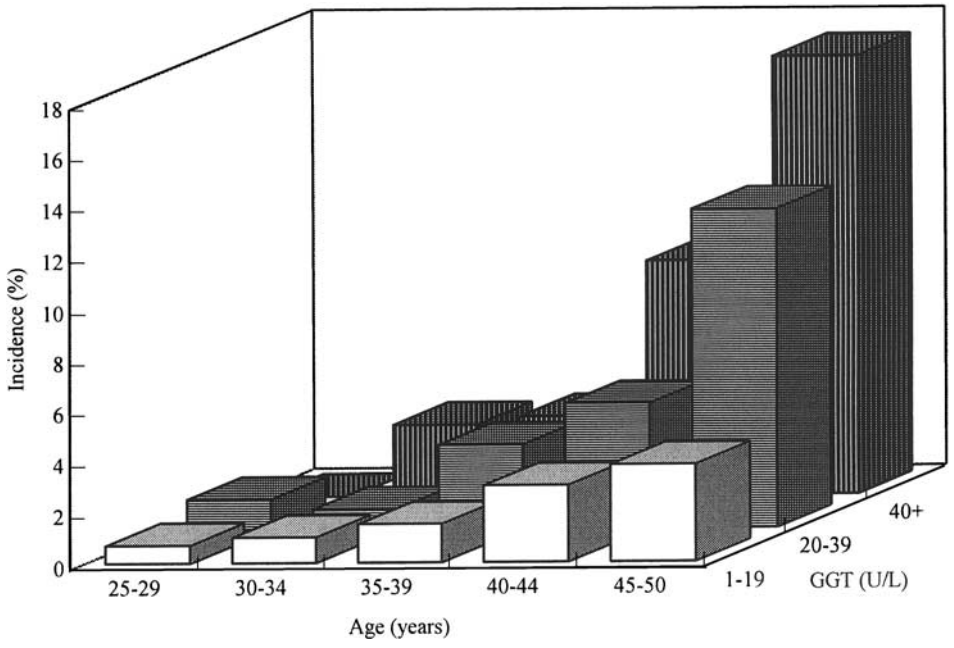

Figure 3 Crude incidence of hypertension by age and baseline GGT level.

dence: 6.0% (10/168) *vs* 0.8% (18/2240)) in those with ALT <20 U/l and 8.7 (unadjusted incidence: 8.7% (4/46) *vs* 1.5% (7/479)) in those with ALT-⩾40 U/l, very similar between low-normal ALT group and high-normal ALT group. Neither exclusion of participants who had abnormal ALT or AST nor additional adjustment for ALT or AST attenuated the associations among incident hypertension, GGT, and age shown in Table 1 and Figure 3.

Discussion

In agreement with our hypothesis, this study found that the association of age with the risk of hypertension varied by baseline GGT level. Among those with high normal GGT, the effect of age on the development of hypertension was much greater than among those with low GGT. Another way to view the findings of this study is that the effect of GGT on the development of hypertension differed by age. Among young subjects, there was no effect of GGT for the risk of hypertension, whereas among old subjects, GGT showed a strong association. However, other liver enzymes such as ALT or AST did not show a relationship with incident hypertension, suggesting that the association between GGT, age and hypertension is not mediated by liver damage. This finding is consistent with the findings shown in the relationship between age and type II diabetes,[1] supporting the concept that underlying mechanisms of hypertension and type II diabetes

are closely related, which was suggested by other studies.[12–15]

Although GGT has been used clinically as a marker of alcohol consumption or liver disease, GGT plays an important role in antioxidant systems at a cellular level.[5–7] The maintenance of intracellular levels of glutathione is critical for antioxidant defence mechanisms of the cell, but intact extracellular glutathione is poorly transported across cell membranes. GGT is a key enzyme for transport of glutathione into cells. Furthermore, recent experimental studies[8–11] indicated that under physiological conditions, especially in the presence of iron, GGT is involved directly in reactive oxygen species generation as a pro-oxidant. Thus, it may be that GGT plays an antioxidant or pro-oxidant role, depending on the presence of iron or similar oxidative stress.

On the other hand, aging itself is also related to oxidative stress.[16,17] For example, aging has been proposed to be related to accumulation of mutations in DNA, damage to mitochondrial DNA, or advanced glycation end products, all of which could result from overproduction of reactive oxygen species. Hypertension and diabetes are major risk factors for cardiovascular disease, and the mechanisms underlying these disorders are not completely clear.[12] Recent studies suggest that excessive production of reactive oxygen species, outstripping endogenous antioxidant defence mechanisms, may be involved in the pathogenesis and complications of both conditions.[13–15] Therefore, the interaction between age and serum GGT level might be interpreted as a synergic action of two markers of oxidative stress. Alternatively, we are interested in the possibility that body iron storage plays a role in this interaction between GGT and age, because the cellular role of GGT differs depending on iron storage.[8–11] In this study, among young subjects who probably had low body iron storage,[18] GGT showed no relationship with hypertension, whereas among old age subjects who probably had high body iron storage,[18] GGT was a strong risk factor for hypertension.

The use of a single reading of BP in our study may have served as a drawback. A single reading is generally considered inadequate for determining the individual's usual BP level because of large random fluctuations in casual readings. However, although random errors due to single determinations weaken the association, they should not cause a spurious association. Moreover, our diagnosis of hypertension was based on two measurements of BP. In addition, because 42.6% of all hypertension cases ($n = 77$) were taking antihypertensive medication at follow-up, use of such medication could lead to misclassification of changes in BP. To assess this possibility, the changes in BP analyses were repeated with the 77 treated hypertensives excluded or including medication as a possible confounder. The results were unchanged. It should be also stressed that the present study was conducted among healthy male workers only, and should be replicated among female before any generalizations can be made.

In conclusion, our data supported our hypothesis that the effect of age on the development of hypertension differed markedly by baseline GGT level, similarly to our findings with incidence of type II diabetes. However, at this point, the underlying mechanism is unclear. Further study on the role of GGT in the development of hypertension and type II diabetes is needed.

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