The Relationship between Serum Gamma-Glutamyl Transpeptidase Levels and Hypertension: Common in Drinkers and Nondrinkers

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A significant association between elevations of serum gamma-glutamyl transpeptidase (γ-GTP) levels and those of blood pressure and hypertension has been reported separately in drinkers and nondrinkers. The aim of the present study is to evaluate whether the relationship between serum γ-GTP and the prevalence of hypertension is the same or similar in both drinkers and nondrinkers. The study subjects comprised 4,920 male nondrinkers, 9,390 male daily drinkers, 8,081 female nondrinkers, and 278 female daily drinkers, who were aged 40 to 59 years. The prevalence of hypertension in the male and female daily drinkers was 1.5 and 1.3 times, respectively, higher than in the nondrinkers. Mean systolic blood pressure in the male and female drinkers was 4.4 and 3.1 mmHg, respectively, higher than in the nondrinkers. After adjusting for age, body mass index, and serum γ-GTP levels, the differences in the prevalence of hypertension and the mean systolic blood pressure level between the drinkers and nondrinkers decreased to 1.2 times and 2.7 mmHg, respectively. Although these small differences remained statistically significant, the association between serum γ-GTP and hypertension appears to be quite similar in both drinkers and nondrinkers, suggesting that hepatic steatosis may play a common, pathogenetic role in the development of hypertension. (*Hypertens Res* 1995; 18: 295-301)

Key words: serum γ-glutamyl transpeptidase, hypertension, alcohol, obesity, hepatic steatosis

A large number of epidemiological studies have confirmed an association between the volume of alcohol consumed and blood pressure levels (*1, 2*). The reliability of the reported alcohol consumption data in epidemiological studies has been questioned, but a close association between the level of serum gamma-glutamyl transpeptidase (γ-GTP), which is a well-known biological indicator of alcohol consumption, and blood pressure has also been observed by many researchers (*3-7*).

The mechanism underlying the elevation of γ-GTP in the sera of alcohol consumers has been debated, but hepatic cell-membrane damage (*8-10*), rather than enzyme-induction (*10, 11*), has been suggested to be the major mechanism. The association of serum γ-GTP with blood pressure elevations in alcohol consumers was also suggested to be a reflection of hepatic cell damage rather than enzyme induction, since serum angiotensin-converting enzyme (ACE), which is elevated in alcoholic liver disease but not induced in the liver cells (*12, 13*), also showed an association with blood pressure in alcohol consumers (*14*). The hepatic cell damage must be related to hepatic steatosis since it is the earliest liver manifestation in alcohol consumers (*15, 16*).

On the other hand, a significant association of serum γ-GTP with blood pressure and hypertension has been found even in nondrinkers (*17-19*). In people without a drinking habit, elevations of serum γ-GTP, as well as those of other serum hepatic enzymes such as asparate aminotransferase (AST) and alanine aminotransferase (ALT), are thought to reflect the progression of hepatic steatosis with increasing body weight (*20, 21*). Hepatic steatosis may play an important role in the development of insulin resistance and hyperinsulinemia, resulting in hypertension (*22, 23*).

These previous findings suggest that elevations of serum γ-GTP levels, which could be a reflection of hepatic steatosis, may relate to blood pressure elevations and hypertension in both alcohol drinkers and nondrinkers. However, drinkers and nondrinkers have been evaluated for the relationship separately, and the similarity of the relationship has not been fully evaluated. In the present study, we compared the relationship between serum γ-GTP levels and blood pressure and hypertension in middle-aged men and women who consumed alcohol or did not to determine if that relationship is similar in alcohol drinkers and nondrinkers.

Table 1. Means and Standard Deviations of Age, Body Mass Index, Serum γ-GTP Level and Blood Pressure in Middle-Aged Men and Women with or without Alcohol Consumption

Variables	Men		Women	
	ND* ($n=4920$) Mean (SD)	DD ($n=9390$) Mean (SD)	ND ($n=8081$) Mean (SD)	DD ($n=278$) Mean (SD)
Age (y. o)	49.7 (6.6)	49.6 (6.4)	48.3 (6.0)	48.4 (6.1)
BMI (kg/m²)	23.1 (2.9)	23.0 (2.7)	22.7 (2.9)	22.3 (2.9)
γ-GTP (U/l)†	19.5 (2.0)	33.0 (2.2)	10.4 (1.6)	15.2 (1.9)
SBP (mmHg)	123.3 (15.1)	127.7 (15.9)	119.9 (15.6)	123.0 (16.6)
DBP (mmHg)	77.7 (10.1)	81.1 (10.4)	74.3 (10.2)	76.4 (10.5)

*   Drinking habit - ND: nondrinkers, including persons who consume no alcohol or small volumes of alcohol only or several social occasions. DD: daily drinkers, persons who consume alcoholic beverages almost every day.

†   Geometric means (GM) and geometric standard deviations (GSD). The 95% confidence limits are calculated as GM÷(GSD)² to GM×(GSD)².

Methods

Male and female subjects, who were between 40 to 59 years of age and either consumed alcohol or did not, were recruited from among all participants in this age group, (21,873 men and 10,449 women) who underwent a health screening program conducted by an occupational health service facility during the one-year period of 1992. The participants who stated in a self-report questionnaire that they had not drunk at all, or had drunk only a small volume (< 10 ml) of alcohol not more often than once a month during the preceding one-year period, were regarded as essentially nondrinkers.

On the other hand, the participants who had drunk alcoholic beverages almost every day were defined as daily drinkers. The male nondrinkers and daily drinkers numbered 4,920 and 9,390, respectively, and the female nondrinkers and daily drinkers 8,081 and 278, respectively. The remaining 9,653 male and female participants who had drunk alcoholic beverages sometimes but not every day, and thus had consumed a smaller volume than the daily drinkers, were excluded from the present study to facilitate comparison between the nondrinkers and daily drinkers.

In the health screening program, body weight was measured with only the jacket removed, and the value of body weight was determined as the measured weight minus 1 kg. Blood pressure was measured once using an automatic oscillometric monitor, BP-103N (Nippon Colin, Japan), following the recommendations of the Japanese Association for Cerebro-cardiovascular Disease Control for the mass screening of hypertension using automatic equipment (*24, 25*). Namely, blood pressure was measured after the subjects had rested on a chair for five minutes or longer, using cuffs 13 cm wide and 24 cm long. After the measurement of blood pressure, fasting venous blood was obtained from the cubital vein, and serum γ-GTP level was determined using an automatic analyzer, Hitachi 7250 (Hitachi, Japan).

The subjects were divided into four categories of body mass index (BMI: kg/m²): slender (BMI < 20 kg/m²), medium (20-24 kg/m²), overweight (25-27 kg/m²), and obese (BMI ≥ 28 kg/m²). The subjects were then divided into five categories of serum γ-GTP levels: less than 15, 15 to 29, 30 to 59, 60 to 119, and above 120 U/l. This categorization of serum γ-GTP level was based on the fact that the geometric mean value of serum γ-GTP in the male participants aged 40 to 59 years in the health check-ups was around 30 U/l, and the geometric standard deviation was 2.0.

The prevalence of hypertension was calculated in each of the categories, and compared among the different categories of serum γ-GTP levels for each category of BMI in both drinkers and nondrinkers, and in both men and women. Hypertension was defined here as being present in persons who showed blood pressure levels above 160/95 mmHg at the health check-ups or those being treated with hypotensive agents. After excluding the subjects receiving hypotensive agents, the means of blood pressure were then compared among the categories.

The differences in the relationships of serum γ-GTP to the prevalence of hypertension or to blood pressure levels between drinkers and nondrinkers, and between men and women, after adjusting for age and BMI, were statistically evaluated by a multiple logistic regression analysis and a generalized linear model analysis. These statistical analyses were performed using an SAS program package distributed by SAS Japan for a personal computer, PC-98 RL (NEC, Japan). Statistical significance was defined as $p < 0.05$.

Results

Means and standard deviations of age, BMI, serum γ-GTP, and blood pressure in the male and female subjects with or without alcohol consumption are shown in Table 1. Geometric means and geometric standard deviations were obtained for serum γ-GTP levels. The means of all these variables were significantly higher in the men than in the women. Mean age and BMI were 1.3 year and 0.3 kg/m² respectively higher in the men than in the women.

Table 2. Numbers of Middle-Aged Men and Women with or without Alcohol Consumption According to Body Mass Size and Serum γ-GTP Levels

Serum γ-GTP levels (U/l)	SEX	Slender*		Medium		Overweight		Obese	
		ND[†]	DD	ND	DD	ND	DD	ND	DD
I: -14	M	390	285	1,232	883	173	101	46	11
	F	1,083	31	4,251	99	770	14	235	2
II: 15-29	M	208	481	1,186	2,238	386	489	145	121
	F	145	18	700	57	240	7	187	10
III: 30-59	M	50	219	406	1,624	214	585	119	186
	F	16	4	152	15	57	3	70	4
IV: 60-119	M	11	121	133	846	85	347	36	132
	F	6	0	36	7	20	1	15	2
V: 120-	M	11	94	58	434	20	136	11	47
	F	0	1	3	3	2	0	2	0

* Body mass size - slender: BMI<20 kg/m², medium: BMI 20-24, overweight: BMI 25-27, obese: BMI ≥28.
† Drinking habit - ND: nondrinkers, including persons who consume no alcohol or small volumes of alcohol only on several social occasions. DD: daily drinkers, persons who consume alcoholic beverages almost every day.

The geometric mean of serum γ-GTP was 1.5 times higher in the men than in the women. Differences in systolic and diastolic blood pressure between the men and women were 5.9 and 4.8 mmHg, respectively.

On the other hand, there were no significant differences in age and BMI between the drinkers and nondrinkers, either in the men or women. However, geometric means of serum γ-GTP in the men and women with alcohol consumption were 1.7 and 1.5 times, respectively, higher than in those without alcohol consumption. Mean systolic and diastolic blood pressure levels in the male drinkers were 4.4 and 3.4 mmHg, respectively, higher than those in the male nondrinkers. Respective differences between the female drinkers and nondrinkers were 3.1 and 2.1 mmHg.

Although not shown in the table, the prevalence of hypertension in the combined total of male and female subjects was 16.6 and 10.6%, respectively, *i.e.* 1.6 times more prevalent in men as compared to women. Hypertension was found in 626 of 4,920 male nondrinkers (12.7%) but in 1,748 of 9,390 male drinkers (18.6%), and in 844 of 8,081 female nondrinkers (10.4%) and 38 of 278 female drinkers (13.7%). Thus, hypertension in men and women with alcohol consumption was 1.5 and 1.3 times, respectively, more frequent than in those without it.

The numbers of male and female subjects with or without alcohol consumption in each category of BMI and serum γ-GTP are shown in Table 2. In women, the numbers of subjects with higher serum γ-GTP levels were small in both nondrinkers and drinkers. Thus, the prevalences of hypertension in each of the categories are summarized in Table 3, excluding the categories with numbers less than ten in women. The prevalences of hypertension were increased with increased BMI, but were higher at higher serum γ-GTP levels at all levels of body

mass size, in both drinkers and nondrinkers, and in both men and women.

The mean of blood pressure was then calculated in each of the categories, after excluding the subjects being treated with hypotensive agents. Table 4 shows the mean systolic blood pressure levels in the male and female subjects with or without alcohol consumption according to body mass size and serum γ-GTP levels. The mean values were elevated with increased BMI, but were also higher at higher serum γ-GTP levels. Similar results were obtained for diastolic blood pressure, although not shown in the table.

Multiple logistic regression analysis was performed to evaluate the association of hypertension with the variables of age, BMI, and serum γ-GTP levels, separately in the male and female drinkers and nondrinkers. All three variables were significantly related to the prevalence of hypertension in both sexes and in both drinkers and nondrinkers. The results of the analysis including sex and the difference in alcohol consumption as independent variables are shown in Table 5. Among daily drinkers the odds ratio of hypertension was 1.24 as compared with nondrinkers; and among female daily drinkers the odds ratio of hypertension was 1.24 as compared with male daily drinkers, which meant that the prevalence of hypertension among male daily drinkers was 0.81 times that among female daily drinkers.

Generalized linear model analysis of systolic blood pressure and related variables in the male and female drinkers and nondrinkers also showed that age, BMI, and serum γ-GTP levels, were all significantly related to blood pressure in both sexes and in both drinkers and nondrinkers. Table 6 shows the results of the analysis including sex and the difference in alcohol consumption as independent variable. The daily drinkers showed a systolic

Table 3.   Prevalence of Hypertenion in Middle-Aged Men and Women with or without Alcohol Consumption Accordming to Body Mass Size and Serum γ-GTP Levels

Serum γ-GTP levels (U/l)	Sex	Slender		Medium		Overweight		Obese	
		ND[≠]	DD	ND	DD	ND	DD	ND	DD
I: -14	M	5%	9	8	11	15	12	17	18
	F	6	0	7	8	15	29	18	—[§]
II: 15-29	M	7	14	12	13	15	20	23	28
	F	10	0	13	18	20	—	30	30
III: 30-59	M	20	16	16	17	24	27	23	30
	F	19	—	15	20	25	—	34	—
IV: 60-119	M	18	21	20	24	28	27	33	37
	F	—	—	11	—	20	—	53	—
V: 120-	M	27	26	22	33	25	29	18	47
	F	—	—	—	—	—	—	—	—

*   Hypertension was defined as BP≥160/95 mmHg or being treated with antihypertensive agents.

†   Body mass size - slender: BMI<20 kg/m², medium: BMI 20-24, overweight: BMI 25-27, obese: BMI≥28.

≠   Drinking habit - ND: nondrinkers, including persons who consume no alcohol or small volumes of alcohol only on several social occasions. DD: daily drinkers, persons who consume alcoholic beverages almost every day.

§   Because of the small number of subjects (<10), the prevalence is not shown.

Table 4.   Means of Systolic Blood Pressure (mmHg) in Middle-Aged Men and Women with or without Alcohol Consumption According to Body Mass Size and Serum γ-GTP Levels

Serum γ-GTP levels (U/l)	Sex	Slender[*]		Medium		Overweight		Obese	
		ND[†]	DD	ND	DD	ND	DD	ND	DD
I: -14	M	111	121	121	123	125	126	128	129
	F	117	115	119	120	122	125	125	—[≠]
II: 15-29	M	120	124	123	125	126	129	129	131
	F	117	122	121	124	126	—	127	132
III: 30-59	M	127	129	125	129	126	130	129	132
	F	114	—	123	127	121	—	129	—
IV: 60-119	M	127	131	128	130	130	133	135	135
	F	—	—	121	—	123	—	136	—
V: 120-	M	136	130	131	134	135	134	133	133
	F	—	—	—	—	—	—	—	—

*   Body mass size - slender: BMI<20 kg/m², medium: BMI 20-24, overweight: BMI 25-27, obese: BMI≥28.

†   Drinking habit - ND: nondrinkers, including persons who consume no alcohol or small volumes of alcohol only on several social occasions. DD: daily drinkers, persons who consume alcoholic beverages almost every day.

≠   Because of the small number of subjects (<10), the mean value is not shown.

blood pressure 2.7 mmHg higher than the nondrinkers, and this difference was statistically significant. On the other hand, systolic blood pressure was shown to be 0.4 mmHg higher in the men than in the women, but this difference not statistically significant.

The results of multiple logistic regression analysis indicated that an increased prevalence of hypertension was associated with increased BMI in both male and female subjects with or without alcohol consumption, for the three levels of serum γ-GTP of 20, 50 and 100 U/l (Fig. 1; age fixed at 50 years).

Discussion

Hypertension was more prevalent in male and female daily drinkers than in the nondrinkers of similar age and body mass index, *i.e.*, 1.5 times more prevalent in male drinkers than in male nondrinkers and 1.3 times more prevalent in female drinkers than in female nondrinkers. Also, systolic blood pressure was higher in the daily drinkers than in the nondrinkers in both sexes, *i.e.*, 4.4 mmHg higher in male drinkers than in male nondrinkers and 3.1 mmHg higher in female drinkers than in

Table 5. Results of Multiple Logistic Regression Analysis for Variables Related to Hypertension in Middle-Aged 14,310 Men and 8,359 Women

Variable	Parameter	Estimate	SE (β)	Probability	Odds ratio (95% range)[†]
Intercept	β_0	-10.82	0.289		
X_1: Age (y. o)	β_1	0.083	0.003	<0.0001	
X_2: BMI (kg/m^2)	β_2	0.113	0.007	<0.0001	
X_3: γ-GTP (U/l)[≠]	β_3	1.182	0.061	<0.0001	
X_4: Alcohol[§]	β_4	0.217	0.052	<0.0001	1.24 (1.12–1.38)
X_5: Sex[¶]	β_5	0.216	0.058	<0.0002	1.24 (1.11–1.39)

* Log $_e$ $(pX/qX) = \beta_0 + \Sigma\beta_iX_i$. p$X$: probability of hypertension, q$X = 1 - pX$, p$X/$qX means the odds of the probability, β_i: parameter estimate, SE (β): standard error of estimate.

[†] Odds ratios were calculated only for differences in sex (women/men) and in alcohol consumption (drinkers/nondrinkers).

[≠] Logarithmically transformed.

[§] "Nondrinker" was coded as 0 and "daily drinker" as 1.

[¶] "Man" was coded as 0 and "woman" as 1.

Table 6. Results of Generalized Linear Model Analysis for Variables Related to Systolic Blood Pressure in Middle-Aged 13,118 Men and 7,753 Women

Variables	Parameter	Estimate	SE(β)	Probability
Intercept	β_0	75.79	1.223	
X_1: Age (y. o)	β_1	0.473	0.017	<0.0001
X_2: BMI (kg/m^2)	β_2	0.693	0.038	<0.0001
X_3: γ-GTP (U/l)[†]	β_3	7.927	0.362	<0.0001
X_4: Alcohol[≠]	β_4	2.671	0.277	<0.0001
X_5: Sex[§]	β_5	-0.413	0.288	0.1510

* $Y = \beta_0 + \Sigma\beta_iX_i$. Y=systolic blood pressure (mmHg), β_i: parameter estimate, SE (β): standard error of estimate.

[†] Logarithmically transformed.

[≠] "Nondrinker" was coded as 0 and "daily drinker" as 1.
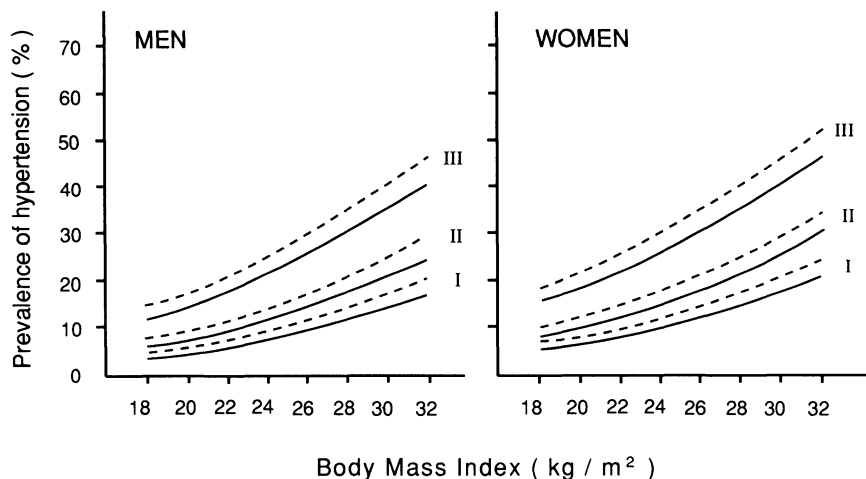
[§] "Man" was coded as 0 and "woman" as 1.

Fig. 1. *Relationships between body mass index, serum γ-glutamyl transpeptidase levels and hypertension in men and women aged 50 years with or without alcohol consumption. Illustrated from the results of a multiple logistic analysis. Serum γ-GTP levels - I: 20 U/l, II: 50 U/l, III: 100 U/l. Solid lines denote nondrinkers, and dashed lines denote daily drinkers.*

female nondrinkers. Since about 75 percent of the male daily drinkers consumed 30 to 60 ml of alcohol per day, and most of the female daily drinkers consumed up to 30 ml of alcohol per day, these differences in the prevalence of hypertension and blood pressure levels between the male and female drinkers and nondrinkers were consistent with the dose-response relation observed in previous epidemiological studies (1, 2).

Prevalences of hypertension and levels of blood pressure were positively correlated with the levels of serum γ-GTP in both male and female drinkers and nondrinkers, as shown in Tables 3 and 4, although the numbers of female drinkers and nondrinkers who had high serum γ-GTP levels were small. These findings were also consistent with those in our previous studies conducted separately in drinkers (5, 6) and nondrinkers (17-19).

When adjustments were done for serum γ-GTP levels, in addition to age and BMI, the difference in the prevalence of hypertension between daily drinkers and nondrinkers was decreased to 1.2 times, and that in systolic blood pressure was decreased to 2.7 mmHg. These differences were still statistically significant, suggesting that the relationship of serum γ-GTP with blood pressure and hypertension may differ in drinkers and nondrinkers.

However, as shown in Fig. 1, these differences were very small, and it remains open to question whether these differences were truly related to the pressor effects of alcohol itself. Other factors might have influenced the results in drinkers and nondrinkers. For example, alcohol consumers may be detected to be hypertensive more often than nonconsumers, either because physicians may pay more attention to hypertension in alcohol consumers, or because alcohol consumers may visit physicians more often. Further, lifestyle and behavioral factors other than alcohol consumption in daily drinkers, such as psychological stress, may contribute to blood pressure elevation. The effects of these possible confounding factors, however, were not analyzed in the present study.

It is difficult to draw definite conclusions from the present cross-sectional observations owing in part to limitations in the study design. For example, we cannot deny a possible bias in this study associated with the selection of subjects based on a self-administered questionnaire of alcohol consumption. Our nondrinker group might have included many alcohol consumers who had elevated blood pressure and serum γ-GTP, although a significant association between serum γ-GTP and blood pressure has been observed in a smaller nondrinker population (17) in which the subjects were carefully evaluated for alcohol consumption by interviews.

At present, however, the small differences in the prevalence of hypertension and the levels of blood pressure between drinkers and nondrinkers after adjusting for serum γ-GTP levels indicate that the relationship between serum γ-GTP and blood pressure and hypertension is very similar in both drinkers and nondrinkers. This similar relation suggests a pathogenetic role of elevated serum γ-GTP, which

may reflect hepatic steatosis (20, 21, 23), in the development of hypertension in middle-aged people, regardless of alcohol consumption.

Decreases in serum γ-GTP have been observed to precede those in blood pressure in interventional studies of alcohol moderation. This is consistent with the contention that elevated levels of serum γ-GTP may be causally related to blood pressure elevations and the development of hypertension in drinkers. A close association between changes in serum γ-GTP and those in blood pressure during alcohol moderation has been detected by some researchers (26-29). A similar association was also observed in obese men during weight reduction by dieting (30).

The exact biological link between elevations of serum γ-GTP and those of blood pressure and the development of hypertension in drinkers and nondrinkers remains unknown and should be elucidated by further studies.

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