Serum γ-Glutamyl Transpeptidase Levels and Hypertension in Non-drinkers: A Possible Role of Fatty Liver in the Pathogenesis of Obesity Related Hypertension

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Abstract

The relationships between increases in body mass index (BMI) and increases in hypertension were compared between non-drinkers with elevated serum γ-glutamyl transpeptidase (γ-GTP) levels (≥50 U/l) and those with normal levels, who comprised 10,952 men and 22,107 women aged 40-59 years recruited from an occupational health clinic. Hypertension was found in 16.1% and 13.5% of the men and women, and elevated serum g-GTP was found in 10.8% and 2.8% of the men and women, respectively. The prevalences of hypertension and elevated serum γ-GTP levels were both increased with increased BMI. Hypertension was, however, shown to be 1.5 times more prevalent in the persons with elevated serum γ-GTP levels than in those with normal levels in both sexes, even after adjusting for BMI by a multiple logistic analysis. It can be concluded that elevations of serum γ-GTP, which are probably a reflection of fatty liver in the non-drinkers, are closely related to the development of hypertension associated with increased obesity.

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Introduction

Obesity is often accompanied by hypertension. However, the exact mechanisms involved in the development of hypertension in obese persons remain unclear, including the question of why only some obese persons develop hypertension and others do not (3,11). During the last decade, much attention has been paid to the role of dominant distribution of adipose tissue in the abdominal cavity of some obese persons, i.e., visceral type obesity (1,2,13), in the development of obesity-related complications including hypertension. The development of hypertension in visceral type obesity is attributed to insulin resistance or hyperinsulinemia (5). The details of the associations between visceral type obesity, insulin resistance or hyperinsulinemia, and hypertension, however, remain to be elucidated by further investigations.

On the other hand, we have found a linear association between serum γ-glutamyl transpeptidase (γ-GTP) levels and blood pressure, not only in drinkers (15,17) but also in non-drinkers (16). Since the elevations of serum γ-GTP levels in non-drinkers mainly depend on increased obesity (8,16), these findings suggest that the rise in blood pressure in obese persons is closely related to the elevations of serum γ-GTP levels. The rise in blood pressure may result in hypertension. However, the relationship between serum γ-GTP levels and the development of hypertension could not be determined in our previous study of non-drinkers (16) because of the limited size of the study population. The aim of the present study is, therefore, to elucidate the relationship in a large-scale male and female non-drinker population.

Subjects and Methods

The study population was recruited from workers who had undergone health check ups conducted during a one-year period at an occupational health check-up service facility. The total number of the participants was around 100,000 (60,000 men and 40,000 women) at the facility. Workers aged between 40-59 years who stated that they had not drunk at all, or had drunk a small volume (< 10 ml) of alcohol not more often than once a month during the one-year period, were regarded as essentially non-drinkers. The present study population, 10,952 men and 22,112 women, comprised about 20%

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Table 1 Frequencies of hypertension and elevated serum γ-GTP according to body mass index in male and female non-drinkers aged 40-59 years

BMI(kg/m^2)	Men Number	HT[a] (%)	γ-GTP↑[b] (%)	Women Number	HT (%)	γ-GTP↑ (%)
-17.4	135	7 (5.2)	5 (3.7)	294	16 (5.4)	7 (2.4)
17.5-19.9	1,383	99 (7.2)	59 (4.3)	3,077	185 (6.0)	36 (1.2)
20.0-22.4	3,143	348 (11.1)	209 (6.6)	7,538	676 (9.0)	126 (1.7)
22.5-24.9	3,543	577 (16.3)	389 (11.0)	6,455	967 (15.0)	207 (3.2)
25.0-27.4	1,946	472 (24.3)	333 (17.1)	3,109	679 (21.8)	127 (4.1)
27.5-29.9	609	173 (28.4)	122 (20.0)	1,125	260 (23.1)	63 (5.6)
30.0-32.4	131	50 (38.2)	38 (29.0)	367	141 (38.4)	34 (9.3)
32.5	63	32 (50.8)	26 (41.3)	147	72 (49.0)	17 (11.6)
Total	10,952	1,758 (16.1)	1,181 (10.8)	22,107	2,996 (13.5)	612 (2.8)

a) HT:Hypertensives include subjects being treated with anti-hypertensive medicines and those showing blood pressure above 160/95 mmHg.

b) γ-GTP↑: Elevated serum γ-GTP levels were defined as above 50 U/l.

and 80%, respectively, of the total male and female participants aged between 40-59 years.

In the health checkups conducted at the occupational clinic, body weight was measured with only any jacket removed, and the value of body weight was determined as the measured weight minus 1 kg. Blood pressure was determined using automatic equipment, following the recommendations of the Japanese Association for Cerebro-cardiovascular Disease Control (JACD) for the mass screening of hypertension using automatic manometers (9,10). Namely, blood pressure was measured after the subject had rested on a chair for five minutes or longer, using cuffs 13 cm wide and 24 cm long. Serum γ-GTP levels were determined using an automatic analyzer, Hitachi 7250.

The subjects were divided into eight categories of body mass index (BMI) by 2.5 kg/m^2 each, and further divided into two categories of elevated serum γ-GTP levels. Elevated serum γ-GTP levels were defined as above 50 U/l, which was settled as the upper normal limit value at the facility. The prevalences of hypertension in the sixteen categories were calculated. Hypertension was defined as being present in persons showing blood pressure levels above 160/95 mmHg at the health checkups or those being treated with anti-hypertensive medicines.

The relationships between the increases in BMI and the increase in hypertension were then statistically compared between the subjects with or without elevated serum γ-GTP levels by a multiple logistic analysis. The logistic analysis was performed using an SAS program package distributed by SAS Japan, for a personal computer, PC 98 VX, NEC. Statistical significance was defined as $p<0.05$.

Results

The prevalences of hypertension and those of persons with elevated serum γ-GTP levels according to the levels of BMI in the male and female non-drinkers are shown in Table 1. Both the prevalences of hypertension and persons with elevated serum γ-GTP levels were increased parallel with increases in BMI, in both sexes.

The prevalences of hypertension in the sixteen categories are shown in Table 2a for men and 2b for women. The prevalences of hypertension were increased with increases in BMI in both the subjects with elevated serum γ-GTP levels and those with normal levels. However, hypertension was generally more prevalent in the persons with elevated serum γ-GTP levels at all levels of BMI, which was also common in both sexes.

The differences in the relationships of the increase in hypertensive persons to increases in BMI between the subjects with elevated serum γ-GTP levels and those with normal levels were tested statistically by a multiple logistic analysis. The logistic model was formulated as follows:

$\mathrm{Log}_e\,(pX/qX)=ß_0 + \Sigma ßiXi$; where pX means the probability of hypertension, qX=1-pX, pX/qX means the odds of the probability, X1 was BMI (kg/m^2), X2 was sex: coded 0 (women) or 1 (man), and X3 was serum γ-GTP level: coded 0 (normal) or 1 (elevated).

Table 2A Relationships between body mass index and hypertension according to serum γ-GTP levels in male non-drinkers aged 40-59 years

BMI(kg/m^2)	Normal γ-GTP Number	HT[b]	(%)	Elevated γ-GTP[a] Number	HT	(%)
-17.4	130	7	(5.4)	5	0	(0.0)
17.5-19.9	1,324	92	(6.9)	59	7	(11.9)
20.0-22.4	2,934	313	(10.7)	209	35	(16.7)
22.5-24.9	3,154	487	(15.4)	389	90	(23.1)
25.0-27.4	1,613	377	(23.4)	333	95	(28.5)
27.5-29.9	487	127	(26.1)	122	46	(37.7)
30.0-32.4	93	32	(34.0)	38	18	(47.4)
32.5-	37	17	(45.9)	26	15	(57.7)
Total	9,771	1,452	(14.9)	1,181	306	(25.9)

a) Elevated serum γ-GTP levels were defined as above 50 U/l.
b) HT:Hypertensives include subjects being treated with anti-hypertensive medicines and those showing blood pressure above 160/95 mmHg.

Table 2B Relationships between body mass index and hypertension according to serum γ-GTP levels in female non-drinkers aged 40-59 years

BMI(kg/m^2)	Normal γ-GTP Number	HT[b]	(%)	Elevated γ-GTP[a] Number	HT	(%)
-17.4	287	15	(5.2)	7	1	(14.3)
17.5-19.9	3,041	181	(6.0)	36	4	(11.1)
20.0-22.4	7,412	657	(8.9)	126	19	(15.1)
22.5-24.9	6,248	927	(14.8)	207	40	(19.3)
25.0-27.4	2,982	641	(21.5)	127	38	(29.9)
27.5-29.9-	1,062	244	(23.0)	63	16	(25.4)
30.0-32.4	333	124	(37.2)	34	17	(50.0)
32.5-	130	65	(50.0)	17	7	(41.2)
Total	21,495	2,854	(13.3)	612	142	(23.0)

a) Elevated serum γ-GTP levels were defined as above 50 U/l.
b) HT:Hypertensives include subjects being treated with anti-hypertensive medicines and those showing blood pressure above 160/95 mmHg.

The results are summarized in Table 3. All of the variables, i.e., BMI, sex, and serum γ-GTP levels, were significantly related to the probability of hypertension, and the odds ratios of hypertension were shown to be 1.13 in sex difference (men/women), and 1.51 in different serum γ-GTP levels (elevated/normal). The logistic curves of the increase in hypertension with increased BMI obtained in the statistical results, for the men and women with or without elevated serum γ-GTP levels, are illustrated in Figure 1.

Discussion

Increases in the prevalence of hypertension with increases in BMI were observed in non-drinkers, both in those with and without elevated serum γ-GTP levels, but were higher at all levels of BMI in the persons with elevated serum γ-GTP levels. These findings were basically common to both men and women, although men showed a slightly higher prevalence of hypertension than women. It can be said from these results that the levels of serum γ-GTP are closely related to the devel-

Table 3 Results of a multiple logistic analysis for body mass index, sex, and serum γ-GTP levels in relation to hypertension in 10,952 male and 22,107 female non-drinkers aged 40-59 years

Variable	Parameter	Estimate	SE(bi)	χ^2 value[b]	Odds[c](95% confidence)
Intercept	β_0	-5.7031	0.1243	2106.6**	
X_1:BMI (kg/m^2)	β_1	0.1689	0.0051	1113.7**	
X2:Sex (0 or 1)[d]	β_2	0.1226	0.0340	13.0*	1.13(1.06-1.21)
X_3:γ-GTP (0 or 1)[e]	β_3	0.4121	0.0602	46.8**	1.51(1.34-1.70)

a) Logistic model:Log_e (pX/qX)=β_0 + $\Sigma\beta iXi$; pX:the probability of hypertension, qX=1-pX, pX/qX:the odds of the probability, βi:paramater estimate, Xi:variable, SE(βi):standard error of estimate.

b) *:p<0.001, **:p<0.0001

c) Odds ratio was calculated only for sex and γ-GTP, which were coded 0 or 1.

d) Sex: coded 0 (women) or 1 (man)

e) γ-GTP: coded 0 (normal; <50 U/l) or 1 (elevated; ≥ 50 U/l)

opment of hypertension associated with increased obesity. However, some possible biases involved in the present study should be discussed.

The present non-drinkers included occasional drinkers who consumed a small volume of alcohol, not more often than once a month. In a previous study (14), we found no differences between teetotalers and occasional drinkers who consumed alcohol less than once a month with respect to serum hepatic enzymes and blood pressure levels. On the other hand, we cannot exclude the possibility that our non-drinker group contained some drinkers who consumed more alcohol, because the selections were made by self-reported alcohol consumption data. However, we found a significant correlation between serum γ-GTP and blood pressure in the previous study on a smaller size non-drinker population (16), where the subjects showing higher serum γ-GTP levels were carefully evaluated for alcohol consumption by interviews.

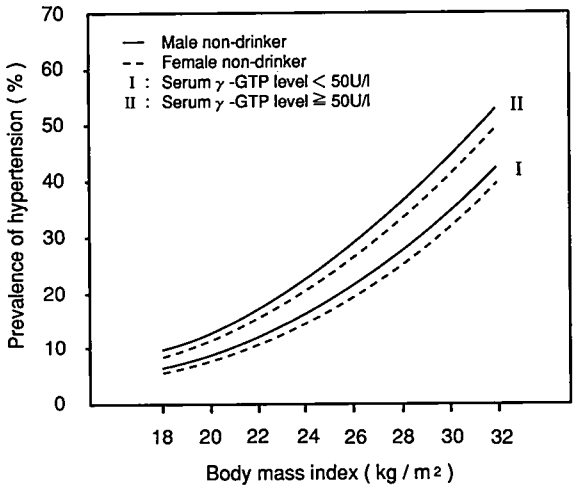

Figure 1: Logistic curves of prevalence of hypertension with increases in body mass index in non-drinkers with elevated serum γ-GTP levels (II:≥50 U/l) and those with normal levels (I). Solid lines denote men and dashed lines denote women.

The present subjects may include some persons with elevated serum γ-GTP due to causes other than alcohol consumption, such as hepatobiliary diseases or barbiturate use. However, the presence of these conditions, at least, could not exaggerate the association between elevated serum γ-GTP and hypertension. Some possible artificial effects associated with the manner of measurement of body weight and blood pressure also were not thought to have influenced critically the present results showing a higher prevalence of hypertension in the subjects with higher serum γ-GTP levels at all levels of BMI. Therefore, the present findings were thought to be basically valid.

As shown in Table 2 and Figure 1, the prevalences of hypertension were also elevated with increased BMI even in the subjects with normal serum γ-GTP levels. The difference in the prevalence of hypertension between the two serum γ-GTP levels seemed small, the ratio being around 1.3 in obese subjects with BMI of 30 kg/m^2. However, it should be noted that the mean value of serum γ-GTP levels in the obese subjects must be also higher even though the levels remained within normal limits. Miura reported in a ten-year follow-up study

in a Japanese rural population (6), that the subjects with serum γ-GTP levels above 10 U/l showed an incidence of hypertension 2.3 times higher than that of the subjects with lower γ-GTP levels, independent of alcohol consumption. Thus, if the persons with normal serum γ-GTP were divided further into different levels of serum γ-GTP, it can be expected that some differences in the relationship between hypertension and increased BMI would be apparent among the subjects with the different γ-GTP levels.

The significance of the association between the elevation of serum γ-GTP levels and the development of hypertension in non-drinkers, however, remains unclear, i.e., whether it is a biological association or a mere statistical association, and whether it is a causal or non-causal one. The levels of serum γ-GTP in non-drinkers correlated not only with BMI but also with other serum hepatic enzyme levels, such as alanine aminotransferase and aspartate aminotransferase (16). Therefore, the elevations of serum γ-GTP levels in non-drinkers must be closely related to the progress in fatty change in the liver cells, i.e., fatty liver (8,16), and the association between serum γ-GTP levels and hypertension is probably a reflection of an association between fatty liver and hypertension in obese persons.

Although confirming evidence has not yet been provided, fatty liver, as suggested by Kissebah (5), may have a close association with proliferated adipose tissue in the abdominal cavity, and may play an important role in the development of insulin resistance or hyperinsulinemia, i.e., hepatic insulin resistance, in visceral type obesity. Hypertension is known to be induced by hyperinsulinemia.

Unfortunately, no parameters indicating dominant adipose tissue distribution in the abdominal cavity, such as waist/hip (W/H) ratio, were determined in the present occupational population. A significant correlation between serum γ-GTP levels and W/H ratios was, however, reported in a study of Dutch men (18). Alcohol consumption was not fully evaluated in the Dutch study, and the researchers mentioned that it remained unclear whether or not elevated serum γ-GTP levels should be regarded as an indicator of increased alcohol consumption, or were due to hepatic steatosis in the subjects. Since alcohol consumption is also a major cause of hepatic steatosis, the results of the Dutch study may be interpreted as suggesting an association between fatty liver and visceral type obesity.

It was also noted from the present results that the prevalences of hypertension were different between the two levels of serum γ-GTP even in the persons with BMI of less than 25 kg/m^2, who were not obese, even in slender persons. This means that some non-drinkers, even if they are not obese, have higher serum γ-GTP levels, probably reflecting fatty change in the liver-cells, and tend to have hypertension more frequently. Patients with essential hypertension, even if not obese, often show insulin resistance or hyperinsulinemia (4,7,12). Some relation may exist between the disturbances in insulin metabolism found in non-obese hypertensives and the presence of fatty liver in them.

Although further studies are needed to elucidate the relationships between visceral type obesity, fatty liver and insulin metabolism, especially the question of which one is the primary problem, the present results suggest a possible pathogenetic role of fatty liver in the more frequent development of hypertension in visceral type obese persons. At least, more attention should be paid to the role of fatty liver in further investigations.

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