Alcohol, High Blood Pressure, and Serum \( \gamma \)-Glutamyl Transpeptidase Level

Yuichi Yamada, Masao Ishizaki, Teruhiko Kido, Ryumon Honda, Ikiko Tsuritani, Eriko Ikai, and Haruki Yamaya

The influence of the level of serum \( \gamma \)-glutamyl transpeptidase, a biological marker of alcohol consumption, on elevations of blood pressure and on the development of hypertension related to increases in alcohol consumption was determined in a cross-sectional study of 1,492 middle-aged male workers and in a subsequent 5-year follow-up study of 1,393 workers. Blood pressure levels, as well as the prevalence and incidence of hypertension, were higher in the subjects with serum \( \gamma \)-glutamyl transpeptidase levels above 50 units/l than in those with normal levels. These differences were more marked in drinkers who consumed 30 ml or more of alcohol per day. Thus, elevated serum \( \gamma \)-glutamyl transpeptidase activity may identify drinkers at higher risk for the development of alcohol-related hypertension. (Hypertension 1991;18:819–826)

During the last 20 years, excessive alcohol consumption has been shown to be related to elevations in blood pressure and subsequently to the development of hypertension. Our previous studies\(^1,2\) demonstrated a significant correlation between the levels of serum \( \gamma \)-glutamyl transpeptidase (\( \gamma \)-GTP) activity, a biological marker of alcohol consumption, and blood pressure in a group of middle-aged male workers in a metal-products factory. The association of serum \( \gamma \)-GTP with blood pressure was shown to be independent of age, obesity, and the amount of alcohol consumed.

\( \gamma \)-GTP is an enzyme found in endothelial cell membranes in various organs where it appears to mediate peptide transport.\(^3\) However, the enzyme found to be elevated in serum is thought to originate mainly from hepatobiliary tract cells.\(^4\) Alcohol consumption is one of the major causes of elevated serum \( \gamma \)-GTP activity. The significance of the serum \( \gamma \)-GTP level as a biological marker of alcohol consumption has long been debated. Serum \( \gamma \)-GTP levels were shown to be elevated with increased alcohol consumption,\(^5-7\) but large variations in the response of \( \gamma \)-GTP activity to alcohol consumption have also been recognized.\(^8-10\) Thus, elevated serum \( \gamma \)-GTP activity in drinkers is probably related more closely to the biological effects of alcohol than to the amount consumed.\(^9-11\)

Therefore, the findings in our previous studies\(^1,2\) suggest that the elevation of serum \( \gamma \)-GTP activity in drinkers may reflect individual susceptibility to the pressor effect of alcohol. If excessive alcohol consumption, as has been demonstrated in many follow-up studies on drinkers, leads to elevated blood pressure and the development of hypertension,\(^12-17\) the differences in the levels of serum \( \gamma \)-GTP activity in drinkers may result in considerable differences in the relations between alcohol consumption, blood pressure, and hypertension in those persons. The present study was conducted to evaluate the influence of serum \( \gamma \)-GTP levels on the elevation of blood pressure and on the development of hypertension due to alcohol consumption in a cross-sectional group of middle-aged male workers in a metal-products factory. Subsequently, we conducted a 5-year follow-up study.

Methods

All workers above 35 years of age in the metal-products factory are required to receive annual health check-ups. There were 1,492 male workers aged 35–54 years who received a health check-up conducted in October and November 1983 and who were then followed to the end of March 1989. Workers older than 54 years were not included in this study because they are required to retire on their 60th birthday and so would not be available for examination during the entire 5-year follow-up period. The subjects comprised 96.1% of the workers of this age group in the factory.
Self-report questionnaires on alcohol and cigarette consumption were administered at the time of the health check-up. The questions on alcohol consumption related to the frequency of alcohol consumption during the preceding year and to the kind and volume of beverage consumed in a day. The volume of pure alcohol consumed was calculated from the volume concentration of alcohol in the beverages. The four categories of alcohol consumption were defined as follows. Nondrinkers consisted of abstainers and workers who drank only small amounts (less than 10 ml) of alcohol several times during the preceding year; light drinkers consumed up to 29 ml alcohol per day; moderate drinkers consumed 30–58 ml alcohol per day; and heavy drinkers consumed more than 58 ml alcohol per day. Workers were divided into non-smokers (including ex-smokers) and smokers. Smokers were further divided into three categories according to the number of cigarettes smoked in a day: light smokers smoked up to one pack (20 cigarettes), moderate smokers smoked up to two packs, and heavy smokers smoked more than two packs per day.

Height (m) and weight (kg) were measured at the same time to obtain the body mass index (BMI, kg/m²). Blood pressure was measured with a sphygmomanometer with each subject in sitting position after resting in a chair for 5 minutes or longer. The cuff size was chosen according to the recommendations of the World Health Organization Expert Committee, 1978. Diastolic blood pressure was determined as the point at which the fifth Korotkoff sound disappeared. Blood samples were obtained by cubital vein puncture and were analyzed for serum γ-GTP activity following a modification of Orlowsky’s method using an automatic analyzer (SMAC III, Technicon, Tarrytown, N.Y.). Serum γ-GTP levels were divided into two categories; normal was defined as values below 50 units/l, and abnormal as values above 50 units/l.

Workers who were found to have health problems such as hypertension, diabetes mellitus, and liver diseases were registered in the health care center of the factory. Workers whose blood pressure was above 160/95 mm Hg in the annual health check-up were registered as hypertensive. After excluding these, the remaining 1,415 workers were then followed to the end of March 1989. Twenty-two workers dropped out during the follow-up period. Death due to malignancies and accidents occurred in three and two workers, respectively. The remaining 17 workers quit the factory for private reasons. Finally, 1,393 workers (98.4%) were observed during the 5-year follow-up period.

The contributions of alcohol consumption and serum γ-GTP level to the blood pressure level of the subjects and to the prevalence and incidence of hypertension were statistically analyzed. The effects of other variables known to be closely related to blood pressure, such as age, obesity, and cigarette consumption, were also considered. Statistical analyses in the present study were performed mainly by analysis of variance, a generalized linear model, the Cochran-Mantel-Haenszel test, and a multiple logistic model, using a Statistical Analysis System (SAS) program package (SAS Japan, Tokyo) for a personal computer PC-98 VX (NEC, Tokyo). Statistical significance was defined as less than 5% of probability.

The aim and design of the present study were approved by the ethical committee of Kanazawa Medical University. Informed consent was obtained from all subjects.

Results

The means and standard deviations of systolic and diastolic blood pressure, age, BMI, and serum γ-GTP activity in the 1,492 male workers at the beginning of the present study are summarized in Table 1 according to the four categories of alcohol consumption. The mean data for age and BMI did not differ among the subjects of the four groups with different alcohol consumption levels. On the other hand, blood pressure and serum γ-GTP levels showed statistically significant elevations of the mean values with increases in alcohol consumption. In comparison with nondrinkers, significant elevations were found in the systolic blood pressure of the heavy drinkers and in the diastolic blood pressure of the moderate and heavy drinkers. The elevations of serum γ-GTP activity with increases in alcohol consumption were more marked. The subjects of the four levels of alcohol consumption showed significant differences in the mean values of serum γ-GTP activity.

The relations between alcohol consumption and the means of blood pressure, age, BMI, and serum γ-GTP activity in the 1,492 male workers at the beginning of the present study are shown in Table 2. Differences in the four groups divided according to low or high serum γ-GTP level are shown in Table 2. Differences of the mean values in the levels of alcohol consumption and of serum γ-GTP were tested by two-way analysis of variance. The elevations of blood pressure with increased alcohol consumption were statistically significant. Comparison of the means of the two groups with different serum γ-GTP levels, taking alcohol consumption into consideration, showed that the subjects with elevated serum γ-GTP levels had higher blood pressure than the subjects with normal serum γ-GTP activity. The elevations of blood pressure with increasing alcohol consumption seemed more marked in the subjects with elevated serum γ-GTP levels. However, the interactions between alcohol consumption and serum γ-GTP related to blood pressure
levels were not statistically significant by analysis of variance. Significant differences in the mean values of age and BMI in the four alcohol consumption levels were not found. No differences were found in age in the two groups with different serum γ-GTP levels. However, the subjects with elevated serum γ-GTP levels had a higher BMI than the subjects with normal γ-GTP levels. The interactions between alcohol consumption and serum γ-GTP level related to BMI were significant, mainly due to the lower BMI ratio in the heavy drinkers with higher γ-GTP activity.

The interactions between alcohol consumption and serum γ-GTP to blood pressure levels were then evaluated by a generalized linear model, which was adjusted for other variables related to blood pressure. The primary model comprised age, BMI, cigarette consumption (four categories), and alcohol consumption (four categories) as independent variables, in addition to the interactions between alcohol consumption and serum γ-GTP levels (two categories) and between BMI and γ-GTP levels. γ-GTP levels themselves were not included in the independent variables, since its elevation undoubtedly depends on the increase in alcohol consumption or obesity in a general population. The interactions between BMI and γ-GTP levels were shown to be not statistically significant and thus were excluded in the final model. The final model itself, and all of the independent variables, including

### Table 1. Blood Pressure, Age, Body Mass Index, and Serum γ-Glutamyl Transpeptidase Activity in 1,492 Male Workers by Level of Alcohol Consumption

<table>
<thead>
<tr>
<th>Variables</th>
<th>Nondrinker (n=463)</th>
<th>Light drinker (n=637)</th>
<th>Moderate drinker (n=331)</th>
<th>Heavy drinker (n=61)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Light drinker</td>
<td>118.1±12.5</td>
<td>118.6±12.5</td>
<td>121.3±13.3</td>
<td>123.0±15.9†</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>72.2±9.0</td>
<td>73.0±9.2</td>
<td>75.6±10.3†</td>
<td>76.1±10.9†</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>42.7±5.3</td>
<td>42.0±4.9</td>
<td>42.6±5.0</td>
<td>43.0±5.1</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.4±2.7</td>
<td>22.3±2.3</td>
<td>22.4±2.6</td>
<td>22.8±2.8</td>
<td>NS</td>
</tr>
<tr>
<td>γ-GTP (units/l)</td>
<td>18.1±1.7</td>
<td>24.4±1.9†</td>
<td>31.5±2.0†‡</td>
<td>41.4±2.2†‡</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Nondrinkers were abstainers and subjects who drank less than 10 ml alcohol several times during the preceding year; light drinkers consumed up to 29 ml alcohol per day; moderate drinkers consumed 30–58 ml alcohol per day; heavy drinkers consumed more than 58 ml alcohol per day; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; γ-GTP, serum γ-glutamyl transpeptidase activity.

*p<0.05 by Scheffe’s method in comparison with nondrinkers.
†p<0.05 by Scheffe’s method in comparison with light drinkers.
‡p<0.05 by Scheffe’s method in comparison with moderate drinkers.
§Geometric means and geometric standard deviations were obtained. The upper 97.5 percentile and lower 2.5 percentile distribution values were obtained as $M_x$($SD)^2$ and $M_-$($SD)^2$, respectively.

### Table 2. Means of Blood Pressure and Related Variables by Levels of Alcohol Consumption in Male Workers With or Without Elevated Serum γ-Glutamyl Transpeptidase Levels

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group of γ-GTP level</th>
<th>n</th>
<th>Nondrinker</th>
<th>Light drinker</th>
<th>Moderate drinker</th>
<th>Heavy drinker</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>I</td>
<td>438</td>
<td>118.0±12.6</td>
<td>118.2±12.4</td>
<td>120.2±12.8</td>
<td>120.7±13.3</td>
<td>†</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>25</td>
<td>119.1±9.2</td>
<td>121.9±13.0</td>
<td>125.1±14.6</td>
<td>126.9±19.2</td>
<td></td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>I</td>
<td>72.2±9.0</td>
<td>72.7±9.1</td>
<td>74.5±10.0</td>
<td>74.8±10.6</td>
<td>†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>72.7±8.2</td>
<td>76.0±9.5</td>
<td>79.9±10.4</td>
<td>78.3±11.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>I</td>
<td>42.7±5.3</td>
<td>41.9±4.9</td>
<td>42.3±4.9</td>
<td>43.1±5.5</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>43.8±5.1</td>
<td>42.6±5.2</td>
<td>43.3±5.0</td>
<td>42.8±4.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>I</td>
<td>22.1±2.7</td>
<td>22.3±2.3</td>
<td>21.9±2.4</td>
<td>23.1±2.5</td>
<td>†‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>24.3±2.7</td>
<td>23.4±2.2</td>
<td>24.1±2.4</td>
<td>22.5±3.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>γ-GTP (units/l)</td>
<td>I</td>
<td>16.8±1.5</td>
<td>20.8±1.6</td>
<td>23.6±1.5</td>
<td>25.7±1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>72.3±1.5</td>
<td>88.1±1.7</td>
<td>88.1±1.6</td>
<td>91.5±1.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SD. Differences of means among subjects of four alcohol consumption levels and two serum γ-GTP levels tested by two-way analysis of variance. Nondrinkers were abstainers and subjects who drank less than 10 ml alcohol several times during the preceding year; light drinkers consumed up to 29 ml alcohol per day; moderate drinkers consumed 30–58 ml alcohol per day; heavy drinkers consumed more than 58 ml alcohol per day; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; γ-GTP, serum γ-glutamyl transpeptidase activity.

* †p<0.05 significantly different in alcohol consumption.
†‡p<0.05 significantly different in serum γ-GTP levels.
§Geometric means and geometric standard deviations were obtained. The upper 97.5 percentile and lower 2.5 percentile distribution values were obtained as $M_x$($SD)^2$ and $M_-$($SD)^2$, respectively.
the interactions between alcohol consumption and γ-GTP levels, were shown to be significant.

The adjusted mean values of blood pressure in the eight groups with the four different alcohol consumption levels and two different serum γ-GTP levels are shown in Figure 1. In comparison with nondrinkers, statistically significant elevations were found in the systolic blood pressure of the heavy drinkers and in the diastolic blood pressure of the moderate and heavy drinkers in the subjects with elevated serum γ-GTP activity. On the other hand, no significant differences in blood pressure among the four different alcohol consumption levels were found in the subjects with normal serum γ-GTP activity.

As shown in Table 3, the 77 workers with hypertension (77 of 1,492 workers, 5.2%) at the beginning of the study were distributed according to alcohol consumption as follows: 21 of 463 nondrinkers (4.5%), 26 of 637 light drinkers (4.1%), 24 of 331 moderate drinkers (7.3%), and six of 61 heavy drinkers (9.8%). Thus, the prevalence of hypertension appeared to increase gradually with increases in alcohol consumption, but the difference in the prevalence of hypertension among the four levels of alcohol consumption did not reach a statistically significant level ($x^2=7.56, p=0.056$). No increase in hypertension prevalence with increase in alcohol consumption was evident in the subjects with normal serum γ-GTP activity. Hypertension seemed more marked in the subjects with elevated serum γ-GTP activity but not significantly so (by Fisher's exact test, $p=0.136$). The difference in the prevalence of hypertension between the two groups with different serum γ-GTP levels was shown to be highly significant ($x^2=12.9$ by the Cochran-Mantel-Haenszel test, $p<0.001$), when the different alcohol consumption levels were taken into consideration. Results of the Breslow-Day test for the homogeneity of the odds ratios in the four levels of alcohol consumption were not significant ($x^2=2.43, p>0.10$).

The interactions between alcohol consumption and serum γ-GTP level compared with the prevalence of hypertension were then evaluated by a multiple logistic model, where age, BMI, and cigarette consumption were included as independent variables, in addition to alcohol consumption and the interactions between alcohol consumption and γ-GTP level. The interactions, as well as age, BMI, and alcohol consumption separately, were significantly related to the prevalence of hypertension.

In comparison with nondrinkers with normal serum γ-GTP activity, the odds ratios of the prevalence of hypertension in 1,492 male workers consuming different volumes of alcohol by level of serum γ-glutamyl transpeptidase activity are shown in Table 3. The 77 workers with hypertension among the four levels of alcohol consumption were not significant in either group I or II. The difference between the two groups of serum γ-GTP level was highly significant, taking alcohol consumption into consideration. (Cochran-Mantel-Haenszel, $x^2=12.94, p<0.001$). Homogeneity of the odds ratios between the two groups in the four levels of alcohol consumption was not excluded statistically (Breslow-Day, $x^2=2.425, p>0.10$).

### Table 3. Prevalence of Hypertension in 1,492 Male Workers Consuming Different Volumes of Alcohol by Level of Serum γ-Glutamyl Transpeptidase Levels

<table>
<thead>
<tr>
<th>Alcohol consumption</th>
<th>All subjects</th>
<th>Group I* (γ-GTP&lt;50 units/l)</th>
<th>Group II* (γ-GTP≥50 units/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>Hypertension (%)</td>
<td>$n$</td>
</tr>
<tr>
<td>Nondrinker</td>
<td>463</td>
<td>21 (4.5)</td>
<td>438</td>
</tr>
<tr>
<td>Light drinker</td>
<td>637</td>
<td>26 (4.1)</td>
<td>567</td>
</tr>
<tr>
<td>Moderate drinker</td>
<td>331</td>
<td>24 (7.3)</td>
<td>259</td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>61</td>
<td>6 (9.8)</td>
<td>38</td>
</tr>
<tr>
<td>Total</td>
<td>1,492</td>
<td>77 (5.2)</td>
<td>1,302</td>
</tr>
</tbody>
</table>

Hypertension indicates all hypertensive subjects given antihypertensive therapy irrespective of blood pressure level. Nondrinkers were abstainers and subjects who drank less than 10 ml alcohol several times during the preceding year; light drinkers consumed up to 29 ml alcohol per day; moderate drinkers consumed 30–58 ml alcohol per day; heavy drinkers consumed more than 58 ml alcohol per day; γ-GTP, serum γ-glutamyl transpeptidase activity.

* Differences in the prevalence of hypertension among the four levels of alcohol consumption were not significant in either group I or II. The difference between the two groups of serum γ-GTP level was highly significant, taking alcohol consumption into consideration. (Cochran-Mantel-Haenszel, $x^2=12.94, p<0.001$). Homogeneity of the odds ratios between the two groups in the four levels of alcohol consumption was not excluded statistically (Breslow-Day, $x^2=2.425, p>0.10$).
of hypertension among the remaining seven groups were calculated after adjustment for age, BMI, and cigarette consumption. Light drinkers with normal γ-GTP activity, moderate drinkers with normal γ-GTP activity, heavy drinkers with normal γ-GTP activity, nondrinkers with high γ-GTP activity, light drinkers with high γ-GTP activity, moderate drinkers with high γ-GTP activity, and heavy drinkers with high γ-GTP activity showed odds ratios of 0.947, 1.252, 1.168, 1.425, 1.307, 4.078, and 5.570, respectively. A significantly higher prevalence of hypertension, in comparison with the nondrinkers with normal serum γ-GTP activity, was found in the moderate and heavy drinkers with elevated serum γ-GTP levels but not in those with normal serum γ-GTP. These results are illustrated in Figure 2, together with the 95% confidence limits of the odds ratios (obtained by Bonferroni's method for multiple comparisons).

For the 1,393 workers who were examined in the subsequent 5-year follow-up study, the mean blood pressure values at the beginning of the study are shown in Table 4, together with the mean rises in blood pressure during the 5-year period. The mean values of age and BMI were almost equal to those found in the 1,492 workers overall, and thus these data were omitted from the table. In the mean values of the rises in blood pressure during the 5-year period, no significant differences were found either among the subjects at the four drinking levels or in the subjects with the two different serum γ-GTP levels. The mean values were also analyzed with a generalized linear model for the adjustments of age, BMI, and cigarette consumption; however, no significant differences were found in the adjusted mean values. Thus, these data are not shown.

During the 5-year period, 29 of the 1,393 workers (1.9%) became hypertensive: seven of 436 nondrinkers (1.6%), 10 of 602 light drinkers (1.7%), 10 of 300 moderate drinkers (3.3%), and two of 54 heavy drinkers (3.7%). The differences in the incidence of hypertension among the subjects of the four different alcohol consumption groups were not statistically significant. The increase in the incidence of hypertension with increases in alcohol consumption was more marked in the subjects with elevated serum γ-GTP levels, but this association was also not significant. The difference in the incidence of hypertension between the subjects with the two different serum γ-GTP levels was shown to be highly significant ($\chi^2=14.5$ by the Cochran-Mantel-Haenszel test).

### TABLE 4. Rise in Blood Pressure During 5-Year Period by Levels of Alcohol Consumption in 1,393 Male Workers With or Without Elevated Serum γ-Glutamyl Transpeptidase Levels

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group of γ-GTP level</th>
<th>n</th>
<th>Nondrinker</th>
<th>n</th>
<th>Light drinker</th>
<th>n</th>
<th>Moderate drinker</th>
<th>n</th>
<th>Heavy drinker</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP (mm Hg)</td>
<td>I</td>
<td>414</td>
<td>117.0±11.7</td>
<td>536</td>
<td>117.1±11.0</td>
<td>241</td>
<td>118.9±11.0</td>
<td>36</td>
<td>118.9±11.1</td>
</tr>
<tr>
<td></td>
<td>DBP (mm Hg)</td>
<td>I</td>
<td>414</td>
<td>71.8±8.0</td>
<td>75.0±8.2</td>
<td>122.7±13.1</td>
<td>19</td>
<td>122.2±17.0</td>
<td>241</td>
<td>117.1±11.0</td>
</tr>
<tr>
<td></td>
<td>ΔSBP (mm Hg)</td>
<td>I</td>
<td>414</td>
<td>0.5±9.0</td>
<td>1.5±9.4</td>
<td>1.2±9.7</td>
<td>2.4±10.3</td>
<td>NS</td>
<td></td>
<td>2.5±11.9</td>
</tr>
<tr>
<td></td>
<td>ΔDBP (mm Hg)</td>
<td>I</td>
<td>414</td>
<td>0.5±9.0</td>
<td>1.5±9.4</td>
<td>1.2±9.7</td>
<td>2.4±10.3</td>
<td>NS</td>
<td></td>
<td>2.5±11.9</td>
</tr>
</tbody>
</table>

Values are mean±SD. Differences of means among subjects of four alcohol consumption levels and two serum γ-GTP levels tested by two-way analysis of variance. Nondrinkers were abstainers and subjects who drank less than 10 ml alcohol several times during the preceding year; light drinkers consumed up to 29 ml alcohol per day; moderate drinkers consumed 30–38 ml alcohol per day; heavy drinkers consumed more than 38 ml alcohol per day; SBP, systolic blood pressure; DBP, diastolic blood pressure; γ-GTP, serum γ-glutamyl transpeptidase activity. Δ = rise during the 5-year period. Group I, serum γ-GTP level <50 units/l; group II, serum γ-GTP level ≥50 units/l. *p<0.05 significantly different in alcohol consumption levels. †p<0.05 significantly different in serum γ-GTP levels.
TABLE 5. Incidence of Hypertension in 1,393 Male Workers Consuming Different Volumes of Alcohol and of Different Serum γ-Glutamyl Transpeptidase Levels

<table>
<thead>
<tr>
<th>Alcohol consumption</th>
<th>All subjects</th>
<th>Group I* (γ-GTP&lt;50 units/l)</th>
<th>Group II* (γ-GTP≥50 units/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondrinker</td>
<td>n</td>
<td>Hypertension (%)</td>
<td>n</td>
</tr>
<tr>
<td>Light drinker</td>
<td>436</td>
<td>7 (1.6)</td>
<td>414</td>
</tr>
<tr>
<td>Moderate drinker</td>
<td>602</td>
<td>10 (1.7)</td>
<td>536</td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>300</td>
<td>10 (3.3)</td>
<td>241</td>
</tr>
<tr>
<td>Total</td>
<td>1,393</td>
<td>29 (2.1)</td>
<td>1,227</td>
</tr>
</tbody>
</table>

Hypertension indicates all hypertensive subjects given antihypertensive therapy irrespective of blood pressure level. Nondrinkers were abstainers and subjects who drank less than 10 ml alcohol several times during the preceding year; light drinkers consumed up to 29 ml alcohol per day; moderate drinkers consumed 30–58 ml alcohol per day; heavy drinkers consumed more than 58 ml alcohol per day; γ-GTP, serum γ-glutamyl transpeptidase activity.

*Differences in prevalence of hypertension among the four levels of alcohol consumption not significant in Groups I or II. Difference between two groups of serum γ-GTP level was highly significant, taking alcohol consumption into consideration (Cochran-Mantel-Haenszel \( \chi^2 = 14.55, p < 0.001 \)). Homogeneity of the odds ratios between the two groups in the four levels of alcohol consumption was not excluded statistically (Breslow-Day, \( \chi^2 = 7.40, p > 0.10 \)).

Multiple logistic analysis, however, showed statistically significant interactions between alcohol consumption and γ-GTP levels to the incidence of hypertension. The odds ratios of the incidence of hypertension, in comparison with nondrinkers with normal γ-GTP activity, were then calculated among the remaining groups. The nondrinkers with high γ-GTP levels and the heavy drinkers with normal γ-GTP levels did not include any men with hypertension. Thus, the calculations were performed after the nondrinkers with high γ-GTP levels were added to the light drinkers with high γ-GTP levels, and after the heavy drinkers with normal γ-GTP levels were added to the moderate drinkers with normal γ-GTP levels.

The odds ratios of the incidence of hypertension in light drinkers with normal γ-GTP levels, in moderate and heavy drinkers with normal γ-GTP levels, in nondrinkers and light drinkers with high γ-GTP levels, in moderate drinkers with high γ-GTP levels, and in heavy drinkers with high γ-GTP levels were 0.623, 1.167, 2.631, 5.731, and 8.799, respectively. The results are illustrated in Figure 3, together with the 95% confidence limits of the odds ratios. A significantly higher incidence of hypertension, compared with the nondrinkers with normal serum γ-GTP levels, was found in the moderate drinkers with elevated serum γ-GTP levels.

**Discussion**

According to the review of MacMahon on a large number of epidemiological studies concerning the relation between alcohol consumption and blood pressure, the rises in systolic and diastolic blood pressure in subjects consuming 24–30 g alcohol per day, in comparison with nondrinkers, amount to 3–4 mm Hg and 1–2 mm Hg, respectively. In subjects consuming 40–60 g alcohol per day, the rises in systolic and diastolic blood pressure are 5–6 mm Hg and 2–4 mm Hg, respectively. In the present study, systolic and diastolic blood pressure differences in the moderate drinkers consuming 30–58 ml (i.e., about 24–46 g alcohol per day) were both 3 mm Hg higher than those in the nondrinkers. In the heavy drinkers consuming 59 ml or more (i.e., about 47 g or more alcohol per day), the elevations of systolic and diastolic blood pressure were 5 mm Hg and 4 mm Hg.

**FIGURE 3.** Plot shows relation between alcohol consumption and incidence of hypertension during 5-year follow-up period in subjects with or without elevated serum γ-glutamyl transpeptidase (γ-GTP) levels after adjustment for age, body mass index, and alcohol consumption. See text for definitions of alcohol consumption. Odds ratios (bars) and the 95% confidence limits obtained by Bonferroni's method (width of column), are shown compared with nondrinkers with normal serum γ-GTP levels (<50 units/l). Light columns denote subjects with normal serum γ-GTP levels and dark columns those with elevated serum γ-GTP levels (≥50 units/l). Column A represents nondrinkers and light drinkers with high γ-GTP levels, and column B represents moderate and heavy drinkers with normal γ-GTP levels.
respectively. Thus, the relation between alcohol consumption and blood pressure observed in the present study is basically in accordance with the results of previous studies.

The mean values of serum γ-GTP were significantly different at each of the four different alcohol consumption levels in the present study. However, the mean value of serum γ-GTP even in the heavy drinkers was 41.4 units/l, which means that a majority of the heavy drinkers did not show elevated serum γ-GTP activity. These findings support the contention that elevated serum γ-GTP activity in drinkers is related more closely to the biological effects of alcohol consumption than to the amount of alcohol consumed.9–11

In addition to several studies showing a positive correlation between increases in alcohol consumption and rise in blood pressure,13,14,21 positive correlations between elevated serum γ-GTP levels and increases in blood pressure have also been reported.22,23 If the assumption that serum γ-GTP level reflects the individual susceptibility to the pressor effect of alcohol is correct, the alcohol–blood pressure relation should be different in the subjects with different serum γ-GTP levels.

In the present cross-sectional study in 1,492 middle-aged male workers, significantly higher blood pressures and a higher prevalence of hypertension were found in the subjects with elevated serum γ-GTP levels in comparison with those with normal γ-GTP levels. In the follow-up study of 1,393 subjects, although the rises in blood pressure during the 5-year period did not differ among the groups of subjects with or without elevated serum γ-GTP levels, the incidence of hypertension was significantly higher in the subjects with elevated serum γ-GTP levels than in those with normal γ-GTP levels.

After adjustment for age, BMI, and cigarette consumption, the interactions between alcohol consumption and serum γ-GTP levels related to the elevation of blood pressure and the development of hypertension were shown to be statistically significant by a generalized linear model and multiple logistic models. The adjusted blood pressure levels and prevalence and incidence of hypertension were significantly higher in drinkers with elevated serum γ-GTP levels who consumed 30 ml or more of alcohol per day than in nondrinkers with normal γ-GTP activity.

Also, as shown in our previous study,24 serum γ-GTP levels weakly but significantly correlated with blood pressure even in the nondrinkers in the present study. In nondrinkers, however, elevations of serum γ-GTP are mainly related to obesity. Thus, the differences in blood pressure and the prevalence and incidence of hypertension between the subjects with or without elevated serum γ-GTP levels might have become smaller in the nondrinkers than those in the drinkers when the results were adjusted for BMI. It might also have resulted in the significant interactions between alcohol consumption and γ-GTP to blood pressure levels in the present study.

On the other hand, a significant elevation of serum γ-GTP levels with an increase in alcohol consumption and a weak but significant correlation between serum γ-GTP and blood pressure were found in the present subjects with normal serum γ-GTP levels. Weill et al25 reported a significant decrease in serum γ-GTP levels in drinkers with normal levels after the cessation of alcohol consumption. Thus, serum γ-GTP activity within the normal range, at least in some of the drinkers, might have been elevated by alcohol. The slight elevations of blood pressure with increases in alcohol consumption observed in the present subjects with normal γ-GTP levels, therefore, do not entirely exclude a possible association between elevated serum γ-GTP levels and elevated blood pressure in them.

The present type of epidemiological study, based on self-reports of alcohol consumption data and the detection of cases by a physician, may be subject to various sources of bias. The subjects with elevated serum γ-GTP levels might have reported their alcohol consumption as being less than that of the subjects with normal γ-GTP levels. This may result in higher blood pressure and higher prevalence and incidence of hypertension at a given alcohol consumption level in the subjects with elevated serum γ-GTP activity. The subjects with elevated serum γ-GTP activity might have visited their physician more often than the subjects with normal γ-GTP activity, resulting in more frequent detection of hypertension in the former than the latter group.

In addition to these possible biases, the results of the present 5-year follow-up study failed to show any differences in the rise in blood pressure between the subjects with elevated serum γ-GTP levels and those with normal serum γ-GTP levels. The higher incidence of hypertension during the 5-year period observed in the subjects with elevated γ-GTP levels is attributable in large part to their higher blood pressure at the beginning of the follow-up study. Therefore, a longer observation period or some type of interventional study is needed to confirm the assumption that levels of serum γ-GTP activity reflect individual susceptibility to the pressor effect of alcohol.

The results of the present study, in which higher blood pressure and higher prevalence and incidence of hypertension were shown in the subjects with serum γ-GTP levels above 50 units/l (especially in drinkers consuming 30 ml or more alcohol per day), suggest that elevated serum γ-GTP activity may identify drinkers at higher risk for the development of alcohol-related hypertension. The possible mechanisms involved in the association between the elevation of serum γ-GTP and high blood pressure have been discussed elsewhere.23,26

References

Key Words: alcohol • alcohol-related hypertension • γ-glutamyltransferase
Alcohol, high blood pressure, and serum gamma-glutamyl transpeptidase level.
Y Yamada, M Ishizaki, T Kido, R Honda, I Tsuritani, E Ikai and H Yamaya

Hypertension. 1991;18:819-826
doi: 10.1161/01.HYP.18.6.819

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/18/6/819

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/