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Determinants of γ-Glutamyltransferase: Positive Interaction with Alcohol and Body Mass Index, Negative Association with Coffee

Kari Poikolainen and Erkki Vartiainen

γ-Glutamyltransferase is widely used as a marker of alcohol intake although its performance is poor. This might be related to other conditions influencing γ-glutamyltransferase activity. The authors studied determinants of γ-glutamyltransferase activity in a random sample (n = 6,010) drawn from the general population aged 25–64 years in Finland in 1992. In regression analysis, coffee intake and drinking boiled coffee were significantly ($p < 0.01$) negatively related to γ-glutamyltransferase, whereas age, male gender, the number of cigarettes per day, serum total cholesterol and high density lipoprotein cholesterol, heart rate, and diastolic blood pressure were significantly positively related to γ-glutamyltransferase. A significant ($p = 0.02$) positive interaction was observed between alcohol intake and body mass index. In logistic regression analysis, the proportion of elevated γ-glutamyltransferase values (≥50 U/liter) was significantly decreased, compared with lifelong abstainers, at the alcohol intake level of <40 g/week (odds ratio (OR) = 0.51, 95% confidence interval (CI) 0.29–0.92) and significantly increased at the level of ≥300 g/week (OR = 2.81, 95% CI 1.35–5.85) among nonobese subjects (body mass index < 27 kg/m^2). Among obese subjects, the respective proportion was significantly increased at the alcohol intake level of ≥40 g/week (OR = 2.02, 95% CI 1.11–3.68). The proportion of elevated γ-glutamyltransferase values was significantly decreased at the coffee intake levels of both four to six cups a day (OR = 0.44, 95% CI 0.31–0.62) and seven or more cups a day (OR = 0.36, 95% CI 0.24–0.53). In addition, drinkers of boiled coffee had elevated γ-glutamyltransferase values more often than drinkers of filtered or instant coffee (OR = 0.59, 95% CI 0.42–0.84). No effects of alcoholic beverage preference were observed. Elevated γ-glutamyltransferase activities appear to be related to heavy alcohol intake among the nonobese and to very light intake among obese subjects. Coffee appears to decrease γ-glutamyltransferase activity. *Am J Epidemiol* 1997;146:1019–24.

alcohol drinking; blood pressure; body mass index; cholesterol; coffee; gamma-glutamyltransferase; obesity; smoking

γ-Glutamyltransferase is widely used as a biologic marker of alcohol consumption in early detection of heavy drinkers and in monitoring the treatment success among problem drinkers. As a screening test for alcoholism and alcohol abuse, its sensitivity has been considered to be acceptable, but its specificity is poor (1, 2). In contrast to this, γ-glutamyltransferase has been found to have reasonable specificity but low sensitivity to changes in alcohol consumption (3). γ-Glutamyltransferase also correlates poorly with long-term average alcohol intake measured with daily diaries among nonalcoholic males (4). The poor screening performance of γ-glutamyltransferase is to a great extent due to other conditions influencing its levels. Knowledge of these other conditions would help the clinician to better evaluate the significance of increased γ-glutamyltransferase values both in screening and when helping the patient. Earlier studies have identified many of these conditions. Remarkably, γ-glutamyltransferase has been found to associate positively with alcohol intake and body mass index (BMI) but negatively with coffee (5–9). To our knowledge, possible interactions have not been examined previously. The present study examined both the relation between γ-glutamyltransferase and several potential covariates reported in earlier studies, especially BMI, alcohol and coffee intake, and the interactions between the covariates. In addition, we studied the possible role of the type of alcoholic beverage.

MATERIALS AND METHODS

A random sample was drawn from the general population aged 25–64 years in the following three areas in Finland in 1992: a region in southwestern Finland, the province of Kuopio, and the province of North

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Abbreviation: BMI, body mass index.

From the National Public Health Institute, Helsinki, Finland.
Reprint requests to Dr. Kari Poikolainen, National Public Health Institute, Mannerheimintie 166, 00300 Helsinki, Finland.

Karelia. The participation rate was 76 percent. Sampling and measurements have been described earlier in detail (10, 11). The number of subjects in the data set was 6,051. We excluded 41 cases because of missing γ-glutamyltransferase values, and so the total number of subjects analyzed was 6,010.

A self-administered questionnaire was mailed to the sample participants, who returned the questionnaires while attending a medical examination. Blood was drawn from the antecubital vein for the measurement of γ-glutamyltransferase.

The following variables were based on self-reports of physician-diagnosed diseases: diabetes mellitus, hypertension, heart failure, angina pectoris, and myocardial infarction. Strenuous exercise was defined as leisure-time exercise resulting in sweating and shortness of breath at least two to three times a week.

The cutoff point for BMI was ≥27 kg/m^2. Earlier findings have suggested no additional increase in γ-glutamyltransferase after this level of BMI (9). Systolic and diastolic blood pressures were averages of two measurements during the medical examination.

Alcohol intake was assessed by a self-administered questionnaire that included questions about the usual frequency and amount of consuming beer, wine, and spirits during the 12 months before the survey. Earlier studies have shown that in populations in which alcohol intake varies greatly over time, this approach gives more reliable estimates on long-term intake than relying on shorter recall periods (12, 13). Estimates of mean alcohol intake were based on the following alcohol content: beer, 4.8 percent; wine, 14.5 percent; and spirits, 37.0 percent. The alcohol content percentages were based on the average amount of alcohol in various beverage types sold by the State Alcohol Monopoly in Finland. Lifelong abstainers reported consuming no alcohol during their lifetime. Those who had abstained the previous year or more were defined as former drinkers.

The numbers of cases with missing values were as follows: coffee intake, 11; tea intake, 42; smoking, four; alcohol intake (including lifelong abstainers and former drinkers), 24; BMI, one; diastolic blood pressure, four; heart rate, two. In multivariate analyses, these cases were always assigned the value of the lowest category—for example, cases with a missing value on smoking were assumed to be never smokers.

In the first series of multivariate regression analyses with the logarithm of γ-glutamyltransferase as the dependent variable, the following were entered as continuous independent variables: age, intake of alcohol, coffee and tea, number of cigarettes per day, serum total cholesterol, BMI, serum high density lipoprotein cholesterol, time spent fasting before the blood sample, systolic and diastolic blood pressure, and heart rate. The following were entered as dichotomous variables (categorization of "yes/no" variables in parentheses, if not evident): sex, marital status (married, single, divorced, widowed), years of education (≤8, 9–10, ≥11), strenuous exercise, former smoker, frequent alcohol intoxication (once a week or more often), type of coffee (boiled, filtered, instant), history of physician-diagnosed myocardial infarction, angina pectoris, heart failure, diabetes mellitus, and hypertension during the past 12 months. A constant of 0.1 was added before taking natural logarithms to variables with zero values. Interactions were tested by introducing product terms to models with the original variables. Logistic regression analyses were applied to estimate odds ratios of elevated γ-glutamyltransferase for various categories of covariates. Percentages of the 6,010 persons with high and low γ-glutamyltransferase activity in categories of independent variables in the latter analysis are shown in table 1.

RESULTS

In multivariate regression analysis, variables not significantly associated with γ-glutamyltransferase were removed from the final model. These were marital status, years of education, tea intake, frequent alcohol intoxication, fasting time before the blood sample, preferences of beer, wine and spirits, and a history of myocardial infarction, angina pectoris, heart failure, diabetes mellitus, or hypertension. In the final model, coffee intake, and drinking boiled coffee, were significantly negatively related to γ-glutamyltransferase. Strenuous exercise was close to a significant negative association with γ-glutamyltransferase (p = 0.056). Age, the number of cigarettes smoked per day, serum total cholesterol and high density lipoprotein cholesterol, heart rate, and diastolic blood pressure were all significantly positively related to γ-glutamyltransferase, with males having higher γ-glutamyltransferase values than females. A significant positive interaction was observed between alcohol intake and BMI (table 2).

In logistic regression analysis, the cutoff point of γ-glutamyltransferase was set at ≥50 U/liter. High density lipoprotein cholesterol was not significant and was therefore removed from the final model. To study the above-mentioned interaction, the model was parametrized to include 13 combined categories of alcohol (seven levels) and BMI (two levels), leaving nonobese abstainers (BMI < 27 kg/m^2) as the comparison group.

The interaction is shown in figure 1. Among the nonobese subjects, elevated γ-glutamyltransferase activities were found significantly less often at the alco-

TABLE 1. Characteristics (%) of 6,010 persons with high and low γ-glutamyltransferase (GGT) activity, Finland, 1992

Characteristic	GGT (units/liter) <50 (*n* = 5,355) (%)	GGT (units/liter) ≥50 (*n* = 655) (%)
Male	43.7	76.0
Age (years)		
25–34	23.9	9.9
35–44	25.0	22.6
45–54	25.0	34.1
55–64	26.0	33.4
Coffee intake (cups/day)		
0	7.8	9.3
1–3	30.6	34.5
4–6	46.0	41.2
≥7	15.6	15.0
Boiled coffee	9.1	7.3
Strenuous exercise	49.4	37.4
Alcohol intake (g/week) among subjects with BMI* < 27 kg/m²		
Lifelong abstainer	4.5	2.4
Former drinker	3.2	1.5
≤39	36.9	10.1
40–99	13.2	7.8
100–199	5.6	6.7
200–299	2.0	2.6
≥300	1.3	4.1
Alcohol intake (g/week) among subjects with BMI ≥ 27 kg/m²		
Lifelong abstainer	4.2	2.8
Former drinker	2.7	3.5
≤39	16.8	21.2
40–99	5.7	13.4
100–199	2.7	10.7
200–299	0.8	7.8
≥300	0.6	5.3
Former smoker	18.5	27.5
Regular smoker	26.2	38.8
Diastolic blood pressure (mmHg)		
≤84	64.5	34.2
85–104	33.0	57.7
≥105	2.5	8.1
Heart rate (beats/minute)		
≤79	82.2	71.0
80–89	12.5	17.7
90–99	3.8	7.3
≥100	1.5	4.0
Total cholesterol (mmol/liter)		
≤3.9	5.4	2.1
4.0–4.9	26.4	11.8
5.0–5.9	35.6	28.2
6.0–6.9	22.5	34.2
≥7.0	10.1	23.7

* BMI, body mass index.

TABLE 2. Linear regression analysis of γ-glutamyltransferase activity on covariates of 6,010 persons in Finland, 1992

Covariate	Regression coefficient ± SE*	*p* value
Age (years)	0.00470 ± 0.00148	0.002
Sex (male vs. female)	0.40562 ± 0.03283	<0.0001
Strenuous exercise (yes vs. no)	−0.05391 ± 0.02818	0.056
Heart rate (beats/minute)	0.01330 ± 0.00242	<0.0001
Diastolic blood pressure (mmHg)	0.00655 ± 0.00131	<0.0001
Total cholesterol (mmol/liter)	0.09259 ± 0.01359	<0.0001
HDL* cholesterol (mmol/liter)	0.11984 ± 0.04450	0.007
Regular smoking (yes vs. no)	0.00681 ± 0.00159	<0.0001
BMI* (kg/m²)	0.02995 ± 0.00559	<0.0001
Former drinker (yes vs. no)	0.25192 ± 0.08714	0.004
Alcohol intake (g/week)	−0.00486 ± 0.03931	0.9
Interaction between alcohol intake and BMI	0.00330 ± 0.00145	0.02
Coffee intake (cups/day)	−0.02812 ± 0.00428	<0.0001
Boiled coffee (yes vs. no)	−0.15488 ± 0.04880	0.002
Constant	0.07709 ± 0.20010	0.7

* SE, standard error; HDL, high density lipoprotein; BMI, body mass index.

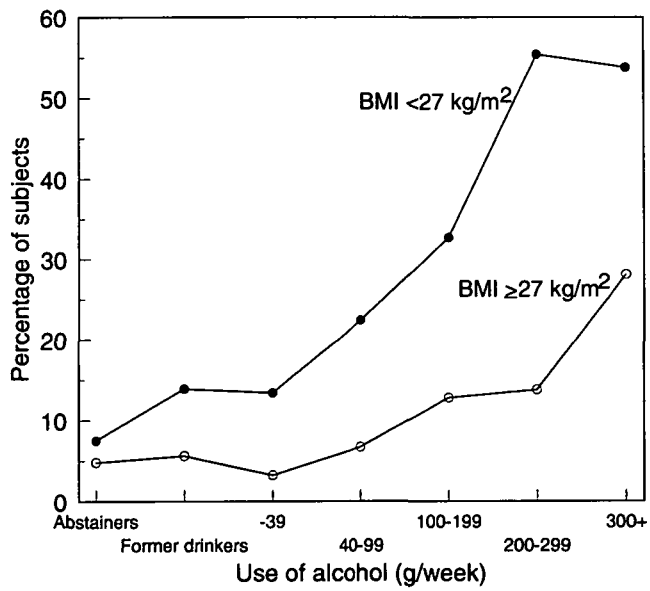

FIGURE 1. Unadjusted percentages of subjects with gamma-glutamyltransferase activity of ≥50 U/liter by alcohol intake and body mass index (BMI).

hol intake level of <40 g/week and significantly more often at the level of ≥300 g/week. Among the obese subjects, elevated γ-glutamyltransferase values were found significantly more often at the alcohol intake level of ≥40 g/week compared with abstainers (table 3). Elevated γ-glutamyltransferase activities were found significantly less often at coffee intake levels of both four to six cups a day and seven or more cups a day compared with nondrinkers of coffee. In addition, drinkers of boiled coffee had elevated γ-glutamyltransferase values less often compared with drinkers of filtered or instant coffee. When males and females were analyzed separately, the results remained similar to those described above.

TABLE 3. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for elevated (≥50 units/liter) γ-glutamyltransferase activity in categories of covariates of 6,010 persons in Finland, 1992

Covariate	OR	95% CI	Reference category*
Male sex	2.54	2.03–3.17	Female
Age (years)			25–34
35–44	1.69	1.21–2.37	
45–54	1.88	1.35–2.62	
55–64	1.83	1.31–2.56	
Coffee intake (cups/day)			0
1–3	0.75	0.53–1.06	
4–6	0.44	0.31–0.62	
≥7	0.36	0.24–0.53	
Boiled coffee (yes)	0.59	0.42–0.84	No
Strenuous exercise (yes)	0.72	0.60–0.87	No
Alcohol intake (g/week) among subjects with BMI† < 27 kg/m²			
Lifelong abstainer	1		
Former drinker	0.68	0.29–1.58	
≤39	0.51	0.29–0.92	
40–99	0.77	0.42–1.43	
100–199	1.19	0.63–2.26	
200–299	1.23	0.57–2.67	
≥300	2.81	1.35–5.85	
Alcohol intake (g/week) among subjects with BMI ≥ 27 kg/m²			
Lifelong abstainer	1.21	0.59–2.49	
Former drinker	1.46	0.72–2.96	
≤39	1.59	0.91–2.80	
40–99	2.02	1.11–3.68	
100–199	3.06	1.63–5.75	
200–299	7.96	3.96–16.0	
≥300	5.95	2.77–12.8	
Former smoker (yes)	1.45	1.14–1.85	No
Regular smoker (yes)	1.90	1.50–2.41	No
Diastolic blood pressure (mmHg)			≤84
85–104	1.70	1.39–2.08	
≥105	1.84	1.24–2.75	
Heart rate (beats/minute)			≤79
80–89	1.35	1.05–1.73	
90–99	1.58	1.08–2.32	
≥100	2.39	1.40–4.07	
Total cholesterol (mmol/liter)			≤3.9
4.0–4.9	0.77	0.42–1.41	
5.0–5.9	1.01	0.56–1.83	
6.0–6.9	1.62	0.89–2.93	
≥7.0	2.50	1.36–4.60	

* For dichotomous variables, the reference category is usually "no"; for other variables, it is the lowest category in table 1.
† BMI, body mass index.

In the subgroup of 5,169 alcohol drinkers, subjects who reported consuming 67 percent or more of their total alcohol intake as a certain beverage type were considered to be beverage preferrers. Defined this way, 27 percent of the total sample preferred beer, 13 percent wine, and 15 percent spirits. After adding the beverage preference variables into the final multivariate logistic regression models described above, no effects of beverage preference were observed.

DISCUSSION

Finding a positive association between γ-glutamyltransferase and age, smoking, serum cholesterol, heart rate, and blood pressure broadly agrees with earlier studies (5, 7, 14). Earlier studies have also found that γ-glutamyltransferase associates positively with both alcohol intake and BMI; however, interactions have not been examined. We found a positive interaction between alcohol and BMI. Among nonobese subjects, only heavy alcohol intake was significantly related to elevated γ-glutamyltransferase values whereas among obese subjects, very light intake was associated with a higher proportion of elevated levels. These associations persisted after controlling for several confounders. We were not able to control for sugar intake, a factor that has been found earlier to relate negatively with γ-glutamyltransferase activity in a Japanese population study that found no significant association between γ-glutamyltransferase and BMI (15). If there is an association between BMI and sugar intake, controlling for the latter might, however, dilute the association between γ-glutamyltransferase and BMI.

The interaction between alcohol and BMI is a new finding. Our findings suggest that moderate alcohol intake does not significantly increase γ-glutamyltransferase at the moderate level of consuming <300 g of alcohol per week among nonobese subjects. Among obese subjects, however, a significant increase in γ-glutamyltransferase was observed at the ≥40-g level of alcohol intake. The lack of significant differences between nonobese and obese lifelong abstainers (and former drinkers) suggests that obesity as such is not strongly related to high γ-glutamyltransferase, although the point estimates of odds ratios are consistent with a weak effect. This effect is supported by a 5-year follow-up study of nondrinkers, wherein increases in γ-glutamyltransferase were found to be positively related to blood pressure, BMI, and the progression in fatty change in the liver (16). However, an intervention study among obese, nontreated mildly hypertensive patients found no significant change in γ-glutamyltransferase after a substantial (mean 7.8 kg) weight loss, although γ-glutamyltransferase correlated with alcohol consumption (17).

Moderate amounts of alcohol are metabolized to acetaldehyde and subsequently to acetate, the latter

mainly by aldehyde dehydrogenase. Overload of ethyl alcohol induces the microsomal ethanol oxidizing system in the liver and results in accumulation of acetaldehyde, of which the production is more than available aldehyde dehydrogenase can handle. Acetaldehyde promotes reduced glutathione depletion, free radical-mediated toxicity, and lipid peroxidation (18). Depletion of glutathione may induce hepatic γ-glutamyltransferase activity through and increased synthesis of its mRNA (19). Raised γ-glutamyltransferase has been thought to indicate increased oxidative stress (14). If γ-glutamyltransferase reflects closely the degree of oxidative stress, then lower levels of γ-glutamyltransferase should be associated with antioxidant intake. However, we found no significant association between γ-glutamyltransferase and tea intake or wine preference. Unfortunately, we could not make a distinction between red wine, known for its higher antioxidant potential (20–22), and other types of wine.

The association between smoking and γ-glutamyltransferase is inconsistent. One study has found an association (14), but another has not (9). Among Japanese men, a positive association was found only among men who drank coffee infrequently or not at all. This might be ascribed to a residual confounding effect of alcohol (6).

In agreement with earlier studies (5–9), we found a negative association between γ-glutamyltransferase and coffee intake. Moreover, boiled coffee associated negatively with γ-glutamyltransferase even after controlling for the number of cups of coffee consumed. This suggests that boiled coffee may decrease high γ-glutamyltransferase more than filtered or instant coffee. Similar results have been reported previously from Norway (5). It is unclear whether the association is due to boiled coffee being on the average more strongly brewed than filtered coffee, to some unknown beneficial constituent in the filterable fraction of the brew, or to some other factor.

The mechanisms of the possible decreasing effect of coffee on γ-glutamyltransferase activity are unknown. The cholesterol-elevating effect of boiled coffee has been shown to be due to cafestol and possibly, to a lesser extent, to kahweol and some minor coffee diterpenes (23). These lipids are removed from coffee by filtering. Cafestol also has been shown to decrease γ-glutamyltransferase (23). Cafestol-containing boiled coffee drinking does not, however, fully explain the negative associations between coffee and γ-glutamyltransferase. This association has also been found in populations drinking filtered coffee (8). The same applies to the association between coffee and liver cirrhosis (24).

The association might also be due to some extent to caffeine. Although coffee is the most concentrated source of caffeine, the latter is found also in tea and cola drinks. Tea, however, has not been found to be inversely related to alcoholic cirrhosis risk (25), and earlier studies have not found a negative association between γ-glutamyltransferase and tea (6, 25). It is noteworthy that our point estimates of regression coefficients for coffee and tea intake in the present study were both negative, although the latter were of smaller magnitude and not significant (data not shown). Moreover, one study has found an association between serum caffeine and γ-glutamyltransferase (9).

Coffee contains significant quantities of magnesium. A 177-ml cup of ground regular coffee contains 9 mg of magnesium (approximately 3 percent of the recommended dietary allowance). The same-sized cup of espresso also has 9 mg of magnesium, Turkish coffee has 8.1 mg, and decaffeinated instant coffee has 5.2 mg (26). Magnesium is essential in the maintenance of membrane integrity and energy production and in the function of the sodium potassium adenosine triphosphatase (27). In rabbit erythrocytes, calcium load and magnesium have been found to be related to a reduction in adenosine triphosphate and a decrease in glutathione regeneration (28). Animal experiments suggest that magnesium may protect against cardiac damage caused by cathecholamine-induced formation of free radicals (29). In the rat, magnesium deficiency aggravates the hepatic damage caused by alcohol (30). Magnesium supplementation appears to speed up the normalization of γ-glutamyltransferase among alcoholics (27). The above suggests that caffeine, cafestol, and magnesium all might have a role in the decrease of γ-glutamyltransferase activity brought about by coffee drinking. Experimental studies would be helpful to further clarify this question.

The coffee-γ-glutamyltransferase association implies that coffee drinking protects the liver from the adverse effects of alcohol. The risk of liver cirrhosis has been found to be increased among heavy drinkers but to be lower among coffee drinkers than nondrinkers (24, 25, 31). In an Italian case-control study, the risk of liver cirrhosis was found to be significantly increased at the level of $\geq$100 g of alcohol per day, and coffee drinking appeared to halve the relative risk from 10.8 to 5.5 (24). In contrast to this, cigarette smoking and coffee consumption were not consistently related to risk of hospitalization or death for nonalcoholic cirrhosis (25). Usual choice of alcoholic beverage had no independent relation (25). That the apparent protective effect of coffee is specific for alcoholic cirrhosis speaks for a causal association. So does the dose-response relation. Should coffee then be

recommended for health reasons? Although some nonsignificant results suggest that coffee intake at the level of four or more cups per day might be related to myocardial infarction (31), coffee or tea intake does not appear to have any notable adverse effects on health in large population studies. A study based on data from the Kaiser Permanente Medical Care Program found, after adjustment for several covariates, no increased risk of death from all causes (31). However, coffee intake is known to increase the risk of many adverse effects, including arrhythmias and anxiety in sensitive individuals (32). Thus, a general recommendation cannot be given without reservations.

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