AGE-RELATED CHANGES ON SERUM GGT ACTIVITY AND THE ASSESSMENT OF ETHANOL INTAKE

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Abstract — Aims: Gamma-glutamyl transferase (GGT) is a commonly used marker of ethanol abuse. However, although increasing age has also been suggested to elevate serum GGT activities, the magnitude of such effects on GGT in the assessment of ethanol intake have remained poorly defined. Methods: GGT activities from 208 heavy drinkers were compared with those from a reference population including 1330 moderate drinkers and 1160 abstainers, who were further classified to following age intervals: 18–30, 30–50, 50–70, and >70 years. Results: GGT activities increased with increasing age until after 70 years decreasing values were noted in male abstainers. The heavy drinkers belonging to age groups 18–30, 30–50, and 50–70 years showed 2.7-, 8.0-, and 6.9-fold higher mean GGT activities than those in the corresponding groups of abstainers, respectively. The values in the group of moderate drinkers also exceeded those of abstainers in all age groups of men, whereas in women the difference was significant only among those aged 18–30 years. Conclusions: The data indicate that GGT activities respond to ethanol intake in an age-dependent manner, which should be considered in the clinical use of GGT measurements for detecting alcohol use disorders.

INTRODUCTION

Gamma-glutamyl transferase (GGT) is a membrane-bound glycoprotein enzyme, which catalyses the transfer of the gamma-glutamyl moiety of glutathione to various peptide acceptors. Chronic ethanol consumption is known to induce a rise in serum GGT and therefore it is also a widely used index of excessive ethanol intake (Zein and Discombe, 1970; Reyes and Miller, 1980; Anton et al., 2002; Niemelä, 2002; Conigrave et al., 2003). Although several studies have reported a positive correlation between ethanol intake and serum GGT activity, the sensitivities and specificities of GGT as a clinical marker of heavy drinking has, however, shown notable variation (Bagrel et al., 1979; Chick et al., 1981; Papoz et al., 1981; Persson et al., 1990; Hietala et al., 2005). Recent studies by several groups of investigators have also emphasized obesity as an important factor, which can increase serum GGT activities (Daeppen et al., 1998; Peters and Cook, 2002; Lam and Mobaran, 2004; Colicchio et al., 2005; Lawlor et al., 2005; Puukka et al., 2006). In addition, age has been suggested to affect GGT activities (Daeppen et al., 1998; Sillanaukee et al., 1998; Conigrave et al., 2002; Stromme et al., 2004; Lee et al., 2004b). However, the possible age-related effects on serum GGT activities in the assessment of hazardous drinking practices have remained poorly defined.

This work was initiated to gain further insight on GGT as a marker of alcohol abuse by comparing GGT activities among heavy drinkers with those of either moderate drinkers or abstainers classified into different age cohorts.

Study protocol

Serum GGT activities were measured from 208 heavy drinkers (174 men, mean age 43 ± 10 years; 34 women, mean age 42 ± 10 years, range 19–67 years), who had been admitted for detoxification in a consecutive manner. The clinical assessments included detailed personal interviews on the patterns and amounts of ethanol consumption using a time-line follow-back technique. All patients showed a history of chronic ethanol consumption or binge drinking, the mean recent consumption from the period of 4 weeks prior to sampling being 128 g ethanol/day (range 40–540 g).

For comparisons, data from a survey of 2490 apparently healthy individuals (1184 men and 1306 women, mean age 47 ± 18 years, range 18–90 years), which were collected for establishing reference intervals in Nordic countries, were also used as kindly provided by the project coordinator, professor Pål Rustad, Fürt Medical Laboratory, Oslo, Norway. These subjects were classified based on self-reports to either moderate drinkers (n = 1330: 705 men; 625 women) or abstainers (n = 1160: 479 men; 681 women). Those, whose current alcohol consumption had been 0 drinks per week for the past few months were categorized as abstainers. Moderate drinkers were individuals who were devoid of any history of alcohol abuse and who consumed alcohol in amounts, which had ranged from 1 to 21 standard drinks per week corresponding to a range of 1–40 g ethanol/day. The maximum amount during the past 24 h prior to sampling had been 24 g (two standard drinks). The population was further grouped according to age as follows: 18–30 years: 291 men, 318 women; 30–50 years: 343 men, 407 women; 50–70 years: 343 men, 362 women; age >70 years: 207 men, 219 women. The mean body mass index (BMI) was not found to be significantly different between these subgroups (Table 1). The survey excluded individuals who had clinical or laboratory evidence of current or recent illnesses or infections, who were pregnant,
had donated blood during the past 5 months or had used any prescription drugs during the preceding 1 week. Smoking had not been allowed for 1 h prior to sampling. All GGT measurements were carried out with International Federation of Clinical Chemistry (IFCC) compatible measuring systems and standard clinical chemical methods. The procedure was approved by the institutional review board. Informed consent was obtained from the participants and the study was carried out according to the provisions of the Declaration of Helsinki.

### Statistical methods

Values are expressed as mean ± SD. Comparisons were made with Kruskal–Wallis test and Dunn’s multiple comparison test or Mann–Whitney test when comparing two groups. Correlations were calculated with Pearson product-moment correlation coefficients or with the Spearman’s rank correlation, as required. Reference intervals were calculated as mean ± 2 SD after logarithmic transformation of the GGT raw data to obtain symmetrical distributions (Horn and Pesce, 2003). A P-value <0.05 was considered statistically significant.

### RESULTS

Serum GGT activity (177 ± 309 U/l, mean ± SD) in the heavy drinkers significantly exceeded the levels of both moderate drinkers (29 ± 23 U/l) (P < 0.001) and abstainers (24 ± 17 U/l) (P < 0.001). The difference between the latter two groups was also significant (P < 0.001). Figure 1 demonstrates the GGT activities in the heavy drinkers, moderate drinkers, and abstainers as further grouped according to age. The heavy drinkers (aged 18–70 years) showed significantly higher values than the reference population, the mean values in age groups 18–30, 30–50, and 50–70 years being 2.7-, 8.0-, and 6.9-fold higher than those of abstainers, respectively. The GGT activities among moderate drinkers also exceeded those of abstainers in all age groups. While in the alcohol-consuming individuals, there was a continuing increase in GGT activities with increasing age, the abstainers were found to show decreased GGT activities in those >70 years.

When the reference population was subsequently divided according to both age and gender, moderate drinkers were found to show higher GGT activities than the abstainers in all age categories among men, whereas in women a statistically significant difference occurred only in those aged 18–30 years (Fig. 2). In men, the youngest age group (18–30 years) showed significantly lower GGT activities than the other age groups both in moderate drinkers and abstainers (P < 0.001). In women, the GGT activities remained essentially similar between 18 and 50 years and significantly lower than the values in those >50 years (P < 0.001) (Fig. 2).

Table 1 summarizes the lower and upper normal limits for GGT activities, defined as mean ± 2SD, in the different age groups and their relative changes as a function of moderate drinking. The upper normal limits (mean ± 2SD) were found to be up to 10–42% (men) and 8–27% (women) higher, when the normal ranges were based on the data of moderate drinkers instead of abstainers. The percentages of elevated GGT activities among heavy and moderate drinkers in these comparisons are shown in Table 2. The GGT sensitivities in correctly classifying heavy drinkers in age-matched comparisons were found to vary between 49 and 74% (men), and 41 and 56% (women), the highest sensitivities being found in the youngest age group. In contrast, in comparisons without age-matching, the youngest age group of heavy drinkers was detected with poor sensitivity. Moderate drinkers were found to show a 5–9% incidence of elevated values without age-matching, whereas in age-matched comparisons, the incidence of elevated GGT activities was found to be up to 21% in men and 10% in women (Table 2).

In the analysis of the data controlling for the effect of BMI, no significant interaction was observed. Correlation between GGT activities and age between 18 and 70 years was positive and significant for all study subgroups, as follows: heavy drinkers (r = 0.21, P < 0.01), moderate drinkers (r = 0.22, P < 0.0001), and abstainers (r = 0.24, P < 0.0001). However, in those >70 years, the correlation between GGT and age turned negative both in moderate drinkers (r = –0.18, P < 0.01) and abstainers (r = –0.16, P < 0.001).

### DISCUSSION

The present data in a large population of individuals representing a wide range of ethanol consumption indicate distinct age- and gender-related effects on GGT activities, which could create significant population variability in studies on GGT.
activities in the assessment of excessive ethanol consumption and liver induction. The activities increased with increasing age until after 70 years decreasing activities were noted in men who did not consume alcohol. While previous studies have also reported increased GGT activities with increasing age (Daeppen et al., 1998; Sillanaukee et al., 1998; Conigrave et al., 2002; Stromme et al., 2004; Lee et al., 2004) the decreasing activities specifically among male abstainers in old age have not been previously acknowledged. The correlation between age and GGT values appears to in fact turn negative in those >70 years. The incidence of heavy alcohol consumption is also known to naturally decline with increasing age (Karlamangla et al., 2006), as also reflected in the present material containing no heavy drinkers above the age 70 among over 200 consecutive admissions for detoxification.

Interestingly, even moderate drinking seems to increase GGT activities to higher levels than those in abstainers, most strikingly in men and in women <30 years, suggesting that these age groups may also show more sensitive liver induction. While the biological mechanisms underlying these observations remain obscure at this time, it may be assumed that the enhanced activities could be regarded as signs of metabolic induction and activation of body’s defence mechanisms towards the ethanol-induced metabolic burden (Speisky et al., 1990; Nakanishi et al., 2000b; Kevil et al., 2004). There may also be both age- and gender-dependent susceptibility to ethanol-induced hepatotoxicity. Young adults may be more resistant to the damaging effects of alcohol (Chan et al., 1989). On the other hand, women are known to be more vulnerable to the development of alcoholic liver disease (Ashley et al., 1977; Schenker, 1997). It is possible that GGT enzyme induction could play a hepatoprotective role in the early phase of the toxic stimuli due to the fact that the enzyme, which occurs on the sinusoidal side of the hepatocytes, may break glutathione into cysteine, which plays a key role in the regulation of the cellular redox status (Speisky et al., 1990; Shoveller et al., 2005). Recently, serum GGT has also been shown to readily respond to overweight and obesity, especially in the individuals with moderate drinking practices (Puukka et al., 2006). Thus, increasing age together with ethanol and/or obesity could create an interaction triad, which synergistically increases the metabolic burden and the risk of liver injury. GGT enzyme induction has also been recently linked with the generation of reactive oxygen species possibly serving also as a marker of oxidative stress (Browning and Horton, 2004; Furukawa et al., 2004; Lee et al., 2004a; Lim et al., 2004). It is also of interest to note that recent studies have suggested that coffee consumption may be inversely related to serum GGT and that coffee could inhibit the inducing effects of aging on serum GGT activities (Nakanishi et al., 2000a).

It appears that the clinical value of serum GGT measurements in the assessment of excessive ethanol intake could be further improved if long-term biological influences of...
moderate drinking (Hietala et al., 2005) and factors unrelated to alcohol yet affecting GGT levels could be more efficiently controlled when defining assay normal ranges. Here, depending on the age group, GGT upper normal limits would be up to 40% higher if moderate drinkers would be included into the reference population. Since the mean alcohol consumption is continuously increasing in our society (Room et al., 2005), there may also be a trend towards increases in mean GGT activities at population level. Consequently, an increasing percentage of alcoholics may escape detection in clinical settings. In accordance with this view the recent NORIP survey on enzyme determinations in Nordic countries concluded that in middle-aged (>40 years) men GGT activities up to 110 U/I might be considered normal (Stromme et al., 2004). In previous studies, the diagnostic sensitivity of GGT in detecting alcohol use disorders has usually been shown to be lower for...
women than for men (Anton and Moak, 1994; Yersin et al., 1995; Mundle et al., 2000). The sensitivity of GGT as a clinical marker of alcohol abuse has also been shown to be especially disappointing in studies dealing with young adults (<30 years) (Chan et al., 1989; Nyström et al., 1993; Sillanaukee et al., 1998; Conigrave et al., 2002), even when they have alcohol dependence (Bisson and Milford-Ward, 1994). It is therefore noteworthy that in the present work the reference populations with or without age-matching provided markedly different views on GGT sensitivities.

Taken together, the present data supports the concept that the diagnostic potential of GGT measurements could be improved by establishing specific age-categorized reference intervals based on healthy individuals who abstain from ethanol. These findings should also be considered in studies on the pathogenesis of ethanol-induced oxidative stress and liver induction.

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REFERENCES


Table 2. The incidence of elevated GGT values (%) in heavy drinkers and moderate drinkers

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Men (n = 174) (%)</th>
<th>Women (n = 34) (%)</th>
<th>Men (n = 705) (%)</th>
<th>Women (n = 625) (%)</th>
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<td>A. Age-matched comparisons</td>
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<td>18–30</td>
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Data when compared with the reference data obtained from abstainers with or without age-matching.