Effect of moderate alcohol consumption on liver enzymes increases with increasing body mass index¹⁻³

Päivikki I Alatalo, Heidi M Koivisto, Johanna P Hietala, Katri S Puukka, Risto Bloigu, and Onni J Niemelä

ABSTRACT

Background: Although both ethanol consumption and overweight alter the activities of hepatic enzymes in circulation, the differentiation of an alcohol or nonalcohol basis for such changes remains problematic. The magnitude of alterations occurring among moderate drinkers has remained obscure.

Objective: We examined the links between moderate ethanol consumption, body mass index (BMI; in kg/m²), and liver enzymes.

Design: Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyltransferase (GGT) were recorded from 2164 apparently healthy participants (1028 men, 1136 women) reporting either no alcohol (abstainers) or <40 g ethanol consumption per day (moderate drinkers). The study population was further classified according to BMI as follows: <19 (underweight), ≥19 and <25 (normal weight), ≥25 and <30 (overweight), and ≥30 (obese).

Results: Serum ALT (P < 0.05) and GGT (P < 0.001) but not AST (P = 0.805) activities in moderate drinkers were higher than those in abstainers. For all enzymes, a significant main effect was observed of increasing BMI, which was more striking in moderate drinkers than in abstainers. Tests of between-subjects effects indicated significant interactions with sex and drinking status, although not with sex and BMI.

Conclusions: The effect of moderate alcohol consumption on liver enzymes increases with increasing BMI. These findings should be considered in the clinical assessment of overweight alcohol consumers and in the definition of normal ranges for liver enzymes. These results may also help to develop new approaches for examining patients with fatty liver induced by either ethanol or adiposity. Am J Clin Nutr 2008;88:1097–103.

INTRODUCTION

The rapidly increasing prevalence of obesity constitutes a major threat to modern health care. In most industrialized countries more than half of the population is currently overweight or obese (1, 2). Simultaneously, during the past decades the total per capita ethanol consumption and associated medical disorders have increased rapidly (3–5). Both excessive alcohol consumption and obesity are known to lead to accumulation of fat in hepatic tissue and to induce changes in serum liver-derived enzymes (6, 7).

Clinically, measurements of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyltransferase (GGT) are widely used as markers in establishing enzyme reference intervals in Nordic countries; therefore, they partially overlap with our previous study on GGT (12). The population included 2164 apparently healthy volunteers (1028 men, age 47 ± 18 y; 1136 women, age 46 ± 17 y), who were classified as either abstainers (n = 669: 250 men, age 49 ± 20 y; 419 women, age 49 ± 19 y) or moderate drinkers (n = 1495: 778 men, age 46 ± 17 y; 717 women, age 45 ± 16 y) and were further classified according to BMI as summarized in Table 1. The participants, who were not paid for their contribution, were primarily hospital personnel and their relatives or acquaintances.

The health status, the patterns and amounts of ethanol intake, and smoking habits were assessed with the use of specifically designed questionnaires. Participants who reported no alcohol intake during the past few months were classified as abstainers. Moderate drinkers were participants in whom the amount of alcohol consumed was <40 g of ethanol/d, and the maximum amount of alcohol during the past 24 h before sampling was 2 standard drinks (each providing 12 g of ethanol). The survey

¹ From the Department of Laboratory Medicine and Medical Research Unit, Seinäjoki Central Hospital and University of Tampere, Seinäjoki, Finland (PIA, HMK, JPH, KSP, and OJN), and the Medical Informatics Group, University of Oulu, Finland (RB).
² Supported by a grant from the Finnish Foundation for Alcohol Studies (to OJN).
³ Address reprint requests to OJ Niemelä, Seinäjoki Central Hospital, Laboratory, FIN-60220 Seinäjoki, Finland. E-mail: onni.niemela@epshp.fi. Received February 25, 2008. Accepted for publication June 26, 2008.
TABLE 1
Main characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>BMI &lt; 19</th>
<th>BMI ≥ 19 and &lt; 25</th>
<th>BMI ≥ 25 and &lt; 30</th>
<th>BMI ≥ 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>(underweight)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(normal weight)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(overweight)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(obese)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>13/58</td>
<td>553/784</td>
<td>417/256</td>
<td>40/37</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>38 ± 18</td>
<td>45 ± 17</td>
<td>50 ± 18</td>
<td>49 ± 17</td>
</tr>
<tr>
<td>Men</td>
<td>37 ± 17</td>
<td>45 ± 17</td>
<td>49 ± 17</td>
<td>49 ± 16</td>
</tr>
<tr>
<td>Women</td>
<td>38 ± 18</td>
<td>45 ± 17</td>
<td>53 ± 18</td>
<td>48 ± 18</td>
</tr>
<tr>
<td>Abstainers [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>5 (2)</td>
<td>136 (55)</td>
<td>98 (39)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Women</td>
<td>20 (5)</td>
<td>257 (61)</td>
<td>116 (28)</td>
<td>25 (6)</td>
</tr>
<tr>
<td>Moderate drinkers [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>8 (1)</td>
<td>417 (54)</td>
<td>319 (41)</td>
<td>30 (4)</td>
</tr>
<tr>
<td>Women</td>
<td>38 (5)</td>
<td>527 (73)</td>
<td>140 (20)</td>
<td>12 (2)</td>
</tr>
</tbody>
</table>

1 Significantly different between subgroups with BMI < 25 and ≥ 25, P < 0.001 (chi-square test).
2 ± SD (all such values).
3 Significantly different from the other groups, P < 0.01 (Kruskal-Wallis test).
4 Significantly different from overweight participants, P < 0.05 (Kruskal-Wallis test).
5 Significantly different from normal-weight participants, P < 0.05 (Kruskal-Wallis test).

excluded persons who had clinical or laboratory evidence of any current or recent illnesses or infections, were pregnant, had donated blood during the past 5 mo, or had used any prescription drugs during the preceding 1 wk. None of the abstainers or moderate drinkers was a former alcoholic or had any social or medical records of heavy drinking or associated medical disorders. In this population, 81% of the participants were nonsmokers, 6% smoked 1–5 cigarettes/d, and 11% smoked >5 cigarettes/d. No smoking was allowed for 1 h before sampling. Serum ALT, AST, and GGT measurements were carried out with measuring systems compatible with the International Federation of Clinical Chemistry.

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 the Kruskal-Wallis test or the Mann-Whitney test when comparing 2 groups. Correlations were calculated with Pearson’s product-moment correlation coefficients or with Spearman’s rank correlation, as required. The differences between correlations were analyzed with the z test for correlation coefficients. The 2- and 3-factor analyses were carried out with the use of SPSS 13.0 FOR WINDOWS statistical software (SPSS Inc, Chicago, IL) after logarithmic transformation of the raw data to obtain symmetrical distributions. The chi-square test was used for comparison of frequency data. A P value < 0.05 was considered statistically significant.

RESULTS

The main clinical characteristics of the study population according to weight status are presented in Table 1. Overweight and obesity were more common in men than in women (P < 0.001). The participants with underweight were younger (38 ± 18 y) than were participants in the other BMI groups (P < 0.01). The mean age of participants with normal weight (45 ± 17 y) was also younger than of participants with overweight (50 ± 18 y) (P < 0.01).

Serum ALT (P < 0.05) and GGT (P < 0.001), but not AST (P = 0.805), activities in moderate drinkers were significantly higher than that in abstainers (Figure 1). When the study population was further classified to subpopulations according to BMI, the enzyme activities were found to increase as a function of increasing BMI (Figure 2). The subgroups from low to high BMI differed from one another in an additive manner, the highest values occurring in participants with moderate drinking combined with obesity, especially in men. In the analyses on the interactions between BMI, drinking status, and sex by tests of between-subject effects with each enzyme as the dependent variable, significant main effects of BMI (P < 0.0001) and sex (P < 0.0001) were noted for all enzymes, whereas drinking status was associated with GGT (P < 0.0001) and ALT (P < 0.05) only. Significant 2-factor interactions were observed between sex and drinking status for ALT (P = 0.034), AST (P = 0.016), and GGT (P < 0.001). The interactions between sex and BMI or between drinking and BMI or the 3-factor interaction (sex × drinking × BMI) were not significant. ALT was positively correlated with

FIGURE 1. Mean (±SD) alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyltransferase (GGT) values in the study population reporting either no alcohol consumption (abstainers; n = 669) or moderate drinking (n = 1495). Significantly different from abstainers (Mann-Whitney test): aP < 0.05; bP < 0.001.
AST ($r = 0.647$, $P < 0.001$) and GGT ($r = 0.492$, $P < 0.001$), and AST was correlated with GGT ($r = 0.401$, $P < 0.001$).

The relative differences in the enzyme activities in the different study subgroups with the population of abstainers with normal weight as baseline are shown in Figure 3. In the group of abstainers with obesity the mean ALT, AST, and GGT activities were 52%, 18%, and 36% above the baseline, respectively, whereas in moderate drinkers with obesity the corresponding activities were 105%, 41%, and 123% higher. ALT activities exceeding $\geq 2$-fold the upper normal activity for each enzyme, which signal high risks of tissue injury, were found in 6% of the obese abstainers and in 10% of the obese moderate drinkers. For GGT the corresponding percentages were 0% and 5%, respectively. In the present study population the median ratio of AST to ALT (AST:ALT) was 1.049; 55% of the participants had AST:ALT $> 1$. The distribution of values of AST:ALT above or below 1 in the total population was also found to vary according to drinking status ($P < 0.002$ for lower portion of higher ratios among moderate drinkers) or the presence or absence of overweight ($P < 0.001$ for lower portion of higher ratios among overweight participants). Among the BMI subgroups, the distributions showed significant differences according to drinking status in participants with underweight ($P < 0.05$ for higher portion of higher ratios among moderate drinkers) and overweight ($P < 0.001$ for lower portion of higher ratios among moderate drinkers) but not in participants with normal weight (Figure 4).

The strongest correlations between the liver enzymes and BMI in the total study population were noted for ALT and GGT among moderate drinkers, whereas in abstainers the corresponding correlations were lower and rather similar with each other (Table 2). The partial correlation coefficients indicated that GGT activities depended more on ethanol intake, whereas ALT was most strongly associated with BMI. Correlations between BMI and liver enzymes in analyses controlling for drinking status were $r = 0.31$ for ALT, $r = 0.23$ for AST, and $r = 0.23$ for GGT ($P < 0.01$ for all), the difference in correlations being significant both between ALT and AST and between ALT and GGT ($P < 0.02$). Because increasing age may also affect the concentrations of the liver enzymes, multiple regression analyses on the effect of age were also carried out (GGT: $R^2$ for women = 0.018, $R^2$ for men = 0.032; ALT: $R^2$ for women < 0.001, $R^2$ for men < 0.001; AST: $R^2$ for women = 0.018, $R^2$ for men = 0.039), indicating that age accounts for <3%, 0.1%, and 4% of the variation in this population, respectively.
DISCUSSION

Both ethanol consumption and obesity are increasingly common causes of metabolic aberrations and steatosis in the liver. Although it is well established that not all alcohol consumers or obese patients go on to develop advanced liver disease, the factors determining a benign or progressive course of hepatic disease have, however, remained poorly known.

The present data indicate that increased BMI increases the effect of moderate drinking on enzymes reflecting hepatocellular health. Conversely, it may well be assumed that increased drinking increases the effect of adiposity on liver function. Although the hepatic effects of ethanol or obesity were addressed in several previous studies (13–16), the early phase interactions between ethanol consumption, BMI, and the biochemical variables reflecting liver status have received less attention. We previously reported that alcohol drinking and obesity may increase serum GGT in an additive manner (12). Similarly, Ruhl and Everhart (7) showed that overweight and obesity increase the risk of alcohol-related abnormal aminotransferase activity. The present data also show a joint action of effects and compare the relative differences in the enzyme activities with the use of a large number of normal-weight abstainers as a reference population. Although GGT seems to be most sensitive to ethanol intake, ALT seems to be the predominant responder to increasing BMI. Our findings suggest that, on establishing appropriate baseline concentrations for each enzyme, it may become possible to develop more accurate models to evaluate the early phase hepatic responses and the alcohol or nonalcohol basis for obesity-associated fatty change in the liver.

In this series, participants who had >2-fold the upper normal limit of the enzyme activity, indicating a high risk of tissue injury, were restricted to the groups of moderate drinkers and obesity. Previous studies have further shown that changes in the ratios of the transaminase enzymes may be helpful in the differential diagnosis of alcoholic compared with nonalcoholic liver damage (9) or in predicting fibrosis in nonalcoholic steatohepatitis (NASH) (17). Elevated AST:ALT occur both in patients with alcoholic liver disease and NASH with a high risk of fibrosis (17). The present work indicates that there may be specific changes in the enzyme ratios also among apparently healthy persons with only mild changes in ALT and AST activities, suggesting that the enzyme ratios may depend on drinking status and BMI. In the early phase of hepatic involvement as a result of obesity there may be a shift to low AST:ALT, whereas progression to more advanced liver disease both in NASH and alcoholic liver disease is typically characterized by elevated AST:ALT. Although the primary mechanisms underlying such changes remain obscure at this time, it should be noted that, although ALT is cytosolic and rather liver specific, AST has both cytosolic and mitochondrial forms and is found in several tissues. In advanced liver disease there may also be disturbances in the hepatic clearance of AST through sinusoidal liver cells (17).

In addition to obesity-induced fatty liver, high ALT activities were previously found in patients with diabetes (14, 18). In obesity, high values probably mark fatty change in the liver (19, 20), and the values usually decline with weight loss (21). Serum ALT activities may be linked with hepatic insulin resistance and the biochemical changes occurring during hepatic gluconeogenesis, inflammation, or both (22, 23). Obesity-related steatosis causes increased production of inflammatory cytokines that result from nuclear transcription factor κB activation and lead to Kupffer cell activation and hepatic and systemic insulin resistance (24). Similarly, excessive ethanol intake, even in the absence of significant hepatic pathology, induces cytokine production (25).

Recently, Chang et al (26) suggested the possibility of using small changes in ALT as predictors of nonalcoholic fatty liver disease. The present findings emphasize, however, the importance of a careful consideration of drinking habits in the assessment of such patients. Apparently, even moderate drinking in combination with excess caloric intake can induce the enzyme activities. Although obesity was previously shown to aggravate the severity of liver disease also in advanced alcoholsics, the mechanisms of such interactions have remained unknown (6, 24, 27, 28). In experimental animals, high-fat diets reproduce many

**FIGURE 3.** Relative differences (%) in mean serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyltransferase (GGT) activities in the different study groups. The mean activity obtained from the corresponding group of abstainers with normal weight is used as baseline. For weight group BMIs, see the legend to Figure 2.
of the features found in nonalcoholic steatohepatitis, and administration of high-fat diets together with ethanol results in enhanced oxidative stress and more severe liver injury (29).

Ethanol-inducible cytochrome enzyme, CYP2E1, may also be induced by obesity, because of free fatty acids serving as substrates. Thus, ethanol and obesity could work in concert to aggravate cellular injury and fat accumulation (27, 30–35). GGT, present in serum and on the cell surfaces of most cell types, is responsible for extracellular metabolism of glutathione, the main antioxidant in mammalian cells, and, apparently, GGT enzyme induction is specifically associated with the generation of reactive oxygen species (12, 36–39). Interestingly, changes in GGT were recently linked with cardiovascular mortality (40–42).

From the present data it also appears that some of the changes on hepatic enzymes occur in a sex-dependent manner. In general, women have a greater propensity than men to develop liver damage at more than moderate drinking levels (43). Women also show lower thresholds for moderate drinking limits. Sex steroids may play a role in cytochrome enzyme expression and in the regulation of hepatic oxidant stress status (44, 45). Interestingly, recent studies have suggested a protective effect of coffee consumption on ethanol-induced liver damage and cellular oxidative

![Figure 4](https://example.com/figure4.png)

**FIGURE 4.** The distributions of ratios of aspartate aminotransferase to alanine aminotransferase (AST:ALT) in the different study subgroups are shown. The difference in distribution was significant for participants with underweight ($P < 0.05$) and for participants with overweight ($P < 0.001$), although not for participants with normal weight or obesity (chi-square test). The interaction of drinking status by weight status was also significant ($P < 0.01$). For weight group BMIs, see the legend to Figure 2.

**TABLE 2**

<table>
<thead>
<tr>
<th></th>
<th>Abstainers</th>
<th>Moderate drinkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.24$^2$ [244]</td>
<td>0.32$^2$ [766]</td>
</tr>
<tr>
<td>Women</td>
<td>0.16$^2$ [411]</td>
<td>0.19$^2$ [705]</td>
</tr>
<tr>
<td>All</td>
<td>0.21$^2$ [655]</td>
<td>0.33$^2$ [1471]</td>
</tr>
<tr>
<td>AST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.14$^4$ [218]</td>
<td>0.15$^2$ [658]</td>
</tr>
<tr>
<td>Women</td>
<td>0.20$^3$ [369]</td>
<td>0.08 [581]</td>
</tr>
<tr>
<td>All</td>
<td>0.21$^2$ [587]</td>
<td>0.22$^2$ [1239]</td>
</tr>
<tr>
<td>GGT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.22$^3$ [231]</td>
<td>0.32$^2$ [698]</td>
</tr>
<tr>
<td>Women</td>
<td>0.18$^2$ [383]</td>
<td>0.22$^2$ [621]</td>
</tr>
<tr>
<td>All</td>
<td>0.23$^2$ [614]</td>
<td>0.37$^2$ [1319]</td>
</tr>
</tbody>
</table>

$^1$ $n$ in brackets. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, y-glutamyltransferase.

$^2$ $P < 0.001$.

$^3$ $P < 0.05$.

$^4$ $P < 0.01$. 

Downloaded from https://academic.oup.com/ajcn/article-abstract/88/4/1097/4650058 by guest on 18 April 2018
stress, which is also sex dependent and associated with a lower prevalence of high aminotransferases (46). Thus, further studies on the interactions between coffee consumption, alcohol drinking, and the prevalence of elevated aminotransferases appear clearly warranted.

Currently, patients with unexplained aminotransferase elevations constitute an increasingly common cause for referral to liver clinics (18). Our findings indicate that the clinical interpretation of hepatic enzymes as disease biomarkers could be sharpened if the effects of obesity and ethanol intake would be more carefully controlled in the definition of enzyme normal ranges. When establishing true baseline values, it may be recommended to use databases of abnormals with normal weight as reference. Alternatively, BMI-based reference intervals could be used, and the upper limits of normal could be set higher for more obese persons. Although the mean values for serum transaminases are usually considered similar from one population to another, the level of elevation that is regarded as abnormal varies widely, and the values usually follow skewed distributions characterized by a long tail at the high end of the scale (47). On the basis of the present data such findings in the earlier literature could be explained by a high prevalence of alcohol consumption and excess body weight in the reference materials. It should, however, be noted that at this time we cannot rule out the possibility of underreporting of alcohol intake, which commonly occurs in any alcohol-health study and could lead to higher thresholds than it seems in the present data.

In summary, the present study indicates that the effect of moderate alcohol consumption on serum liver enzyme activities increases with increasing BMI. Future population studies appear warranted addressing the prognostic implications of such responses and whether it might be necessary to formulate BMI-based recommendations for safe levels of alcohol consumption (27). More exact definitions of baseline values and normal ranges for hepatic enzymes are also needed to help the clinical assessment of patients with fatty liver induced by either alcohol or adiposity.

We thank Professor Pål Rustad, Furst Medical Laboratory, Oslo, Norway, for providing data on the Nordic NORIP Survey on reference intervals.

The author’s responsibilities were as follows—PIA: analyzed data and drafted the manuscript; HMK, JPH, and KSP: participated in the study design and material collection; RB: involved in the statistical analyses of the data; OJN: involved in the study design and writing the manuscript. None of the authors had a personal or financial conflict of interest.

REFERENCES