ORIGINAL ARTICLE

Dose- and Gender-dependent Interactions between Coffee Consumption and Serum GGT Activity in Alcohol Consumers

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Abstract — Aims: Coffee consumption has been recently linked with decreased blood gamma-glutamyltransferase (GGT) activities and protection from alcoholic liver disease. To explore the relationship and dose response, we assessed the impacts of coffee and alcohol intake on serum GGT activity in apparently healthy men and women with varying levels of coffee and alcohol consumption.

Methods: Data on coffee, alcohol consumption and serum GGT activities were collected from 18,899 individuals (8807 men and 10,092 women), mean age 48 years, range 25–74 years, who participated in a large national cross-sectional health survey. Body mass index, smoking index and age were used as covariates in all analyses.

Results: Among the study population, 89.8% reported varying levels of coffee consumption; 6.9% were abstainers from alcohol, 86.1% moderate drinkers, 3.7% heavy drinkers and 3.3% former drinkers. In men, the elevation of GGT induced by heavy drinking (>280 g/week) was found to be significantly reduced by coffee consumption exceeding 4 cups per day. A similar trend was also observed among women, which however, did not reach statistical significance.

Conclusion: Coffee modulates the effect of ethanol on serum GGT activities in a dose- and gender-dependent manner. These observations should be implicated in studies on the possible hepatoprotective effects of coffee in alcohol consumers.

INTRODUCTION

Coffee is a widely consumed beverage, which is also a rich source of antioxidants and other bioactive compounds. The possible health effects of coffee intake have recently received increasing attention (Floegel et al., 2012; Freedman et al., 2012). Studies in liver diseases have indicated that the risk of fibrosis (Modi et al., 2010), alcoholic cirrhosis (Klatsky and Armstrong, 1992; Tverdal and Skurtveit, 2003), hepatitis (Freedman et al., 2009; Costentin et al., 2011) or hepatocellular carcinoma (Inoue et al., 2005; Shimazu et al., 2005; Hu et al., 2008) are decreased in persons who drink coffee. The causal relationships underlying such phenomena have, however, remained unclear.

Over the years, several studies have reported negative associations between coffee consumption and gamma-glutamyltransferase (GGT) enzyme activity (Amen et al., 1986; Casiglia et al., 1993; Poikolainen and Vartiainen, 1997; Tanaka et al., 1998; Ikeda et al., 2010). GGT enzyme is expressed in a wide variety of tissues including the liver, kidney, lung, pancreas and vascular endothelium. It plays an important role in the extracellular metabolism of glutathione (GSH) (Lança and Israel, 1991) and is closely related to the oxidant stress status in vivo (Lee et al., 2004; Zhang and Forman, 2009; Mistry and Stockley, 2010). Mean GGT activities in populations have been shown to change in parallel with alcohol consumption and the prevalence of obesity (Lee et al., 2006a; Alatalo et al., 2008). GGT levels may also be predictive of mortality associated with liver diseases, cardiovascular diseases or diabetes (Ruttmann et al., 2005; Lee et al., 2006b; Kazemi-Shirazi et al., 2007; Mason et al., 2010; Ryu et al., 2010; Targher, 2010).

Although coffee consumption seems to be inversely associated with GGT levels also in alcohol drinkers (Nilsson et al., 1990; Tanaka et al., 1998; Ikeda et al., 2010), the interactions and dose responses between coffee and alcohol intake and GGT levels have, however, remained largely unclear. The aim of this work was to analyse the impacts of alcohol and coffee consumption on serum GGT levels in a large population of apparently healthy individuals with a wide range of coffee and alcohol consumption.

SUBJECTS AND METHODS

Study protocol

Three independent, cross-sectional population health surveys (The National FINRISK studies) were carried out in six geographic areas in Finland in 1997, 2002 and 2007. In each year, an age- and a gender-stratified random sample was drawn from the population according to European Health Risk Monitoring project recommendations. The survey included detailed questionnaires on health status, medical history, alcohol and coffee intake, physical measurements and laboratory tests. The medical examinations were conducted using a standardized protocol, as previously described (The World Health Organization, 1988). Measurements of height and weight were carried out and body mass index (BMI, kg/m²) was subsequently calculated as a measure of relative body weight. Serum GGT (U/l) was measured by standard kinetic methods following the recommendation of the European Committee for Clinical Laboratory Standards (Leino et al., 1995). All surveys were conducted according to the ethical rules of the National Public Health Institute and all investigations were carried out in accordance with the Declaration of Helsinki.

The study included data from the subjects who both filled out the questionnaire and attended the medical examination.

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The response rates obtained in the present sample ranged from 64 to 71%. Exclusion criteria were pregnancy (n = 137), diagnosis of myocardial infarction (n = 627), stroke, cerebral haemorrhage or cerebral embolism (n = 517), diabetes or glucose-intolerance (n = 1137) or signs of active infection at the time of the study (n = 837). In addition, exclusions were made because of missing variables (n = 1780). The final population comprised 18,899 individuals; 8807 men and 10,092 women; mean age 48 years, range 25–74 years.

Coffee and alcohol consumption and smoking status at baseline were assessed with a set of standardized questions. The participants were asked to quantify the frequency and quantity of their coffee consumption, and the data were recorded as the number of cups of coffee per day. Alcohol consumption was assessed with detailed questions on the amounts and patterns of alcohol intake including questions on the type of alcoholic beverage consumed, the frequency of consumption and the amount of drinks consumed during the previous weeks and 1 year prior to sampling. In this study, the amount of drinks consumed during the past 1 week prior to sampling was used as an estimate of the numbers of drinks consumed currently. The amount of ethanol in different beverages was assessed as follows: beer 12 g (1/3 l), strong beer 15.5 g (1/3 l), wine 12 g (12 cl) and cider 12 g (1/3 l), long drink 15.5 g (1/3 l), wine 12 g (12 cl) and cider 12 g (1/3 l) (Tynjälä et al., 2012). A dose of 12 g of pure ethanol was considered as one standard drink. The subjects were also classified into subgroups as follows: persons who reported no alcohol consumption and had been life-long abstainers were referred to as abstainers (n = 1298), persons who reported no alcohol consumption and had decided to stop drinking completely although they had used to drink earlier were referred to as former drinkers (n = 629), moderate drinkers consumed ≤24 doses (men) and ≤16 doses (women) per week (n = 16,232), heavy drinkers (n = 740) consumed >24 doses per week (men) or >16 doses per week (women). Smoking was quantified as the amount of cigarettes smoked per day. The main characteristics of the study population are summarized in Table 1.

### Table 1. The main characteristics of the study population, as classified by daily intake of coffee

<table>
<thead>
<tr>
<th>Daily coffee intake, cups</th>
<th>0</th>
<th>1–2</th>
<th>3–4</th>
<th>5–6</th>
<th>&gt;6</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1937</td>
<td>3483</td>
<td>6198</td>
<td>4626</td>
<td>2655</td>
</tr>
<tr>
<td>Percentage of total population</td>
<td>10.2</td>
<td>18.4</td>
<td>32.8</td>
<td>24.5</td>
<td>14.0</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>814/1123</td>
<td>1379/2104</td>
<td>2550/3648</td>
<td>2357/2269</td>
<td>1707/948</td>
</tr>
<tr>
<td>Age</td>
<td>men</td>
<td>45.3 ± 14.0</td>
<td>50.9 ± 14.6</td>
<td>50.3 ± 13.6</td>
<td>48.0 ± 12.3</td>
</tr>
<tr>
<td></td>
<td>women</td>
<td>40.6 ± 13.3</td>
<td>48.6 ± 14.5</td>
<td>49.3 ± 13.0</td>
<td>48.1 ± 11.5</td>
</tr>
<tr>
<td>BMI</td>
<td>men</td>
<td>26.4 ± 3.9</td>
<td>27.0 ± 4.0</td>
<td>26.9 ± 3.9</td>
<td>27.0 ± 3.8</td>
</tr>
<tr>
<td></td>
<td>women</td>
<td>25.1 ± 5.0</td>
<td>26.0 ± 4.9</td>
<td>26.3 ± 4.8</td>
<td>26.4 ± 4.6</td>
</tr>
<tr>
<td>Smoking</td>
<td>men</td>
<td>2.4 ± 7.0</td>
<td>2.2 ± 6.1</td>
<td>3.3 ± 7.4</td>
<td>5.0 ± 8.9</td>
</tr>
<tr>
<td></td>
<td>women</td>
<td>1.0 ± 3.7</td>
<td>1.2 ± 4.0</td>
<td>1.8 ± 4.6</td>
<td>3.2 ± 6.3</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>abstainers (men/women)</td>
<td>81/124</td>
<td>51/187</td>
<td>90/322</td>
<td>87/211</td>
</tr>
<tr>
<td></td>
<td>former drinkers (men/women)</td>
<td>40/52</td>
<td>28/57</td>
<td>82/97</td>
<td>96/62</td>
</tr>
<tr>
<td></td>
<td>moderate drinkers (men/women)</td>
<td>643/935</td>
<td>1175/1818</td>
<td>2234/3162</td>
<td>2070/1958</td>
</tr>
<tr>
<td></td>
<td>heavy drinkers (men/women)</td>
<td>50/12</td>
<td>125/42</td>
<td>144/67</td>
<td>104/38</td>
</tr>
</tbody>
</table>

The data on age, BMI and smoking (number of cigarettes/day) are expressed as mean ± SD.

### STATISTICAL METHODS

Results are expressed as means (SD) and 95% confidence intervals, as appropriate. Differences between groups were determined with ANOVA using the Bonferroni post hoc test for multiple comparisons following logarithmic transformation of GGT data to obtain non-skewed distributions with homogeneity of variance. Age, BMI and smoking were used as covariates in all analyses. The statistical analyses were carried out using SPSS for Windows 19.0 (Chicago, IL, USA). P-values <0.05 were considered statistically significant.

### RESULTS

Among the 18,899 study participants, 89.8% of the population were coffee consumers, whereas 10.2% reported no coffee intake. Table 1 summarizes the demographic characteristics of the study population as further classified into subgroups as follows: no coffee consumption, 1–2 cups per day, 3–4 cups per day, 5–6 cups per day or more than 6 cups per day.

The data on the distribution of alcohol consumption in this population indicated that 6.9% were abstainers, 3.3% were former drinkers, 86.1% were moderate drinkers and 3.7% were heavy drinkers. As expected, the highest GGT activities in both men and women occurred in heavy drinkers (56.9 ± 2.3; 30.8 ± 2.3 U/l, respectively). These values were significantly higher than those in moderate drinkers (31.8 ± 1.8; 20.1 ± 1.7 U/l), abstainers (27.7 ± 1.6; 18.4 ± 1.7 U/l) or former drinkers (27.0 ± 1.8; 17.5 ± 1.7 U/l) (P < 0.001 for all comparisons, respectively). The values in moderate drinkers also significantly exceeded those of abstainers (P < 0.001) or former drinkers (P < 0.001).

GGT levels in the different subgroups of coffee and alcohol consumers as further classified according to the gender are demonstrated in Fig. 1. In men, the highest GGT levels were found in heavy drinkers consuming no coffee (Fig. 1A). In the heavy drinkers reporting ≥5 cups of coffee per day, the activities were significantly lower than in the corresponding group with no coffee consumption (P < 0.05 by post hoc test). GGT levels also significantly exceeded those in former drinkers (P < 0.001).
for those consuming 5–6 cups, $P < 0.01$ for those consuming >6 cups). In women, a similar trend was also observed, which, however, did not reach statistical significance (Fig. 1B). In male moderate drinkers, the increase in GGT levels was most pronounced among the groups consuming 1–6 cups of coffee, whereas not in abstainers or in those consuming >6 cups. In women, a slight GGT increase was seen in moderate drinkers reporting 1–2 cups of coffee per day. Analyses showed that how coffee was prepared (espresso, boiled or filtered) did not affect the above associations (data not shown).

**DISCUSSION**

The present findings among a population of apparently healthy Finnish individuals indicate that coffee consumption modulates GGT activities induced by alcohol drinking in a...
dose- and gender-dependent manner. Because Finland tops the world in annual coffee consumption (~12 kg per person being consumed each year), the present large and well-characterized cross-sectional survey should offer an excellent basis for examining the biological responses of coffee in individuals with a wide range of coffee and ethanol intake.

As recently indicated, GGT activities here started to show distinct changes when mean regular alcohol consumption exceeded 100 g (men) or 50 g (women) per week (Tynjälä et al., 2012). Consumption of over 24 drinks per week (corresponding to 280 g of ethanol) was found to lead to an ~3-fold increase in GGT activities when compared with the corresponding group of abstainers. Regular consumption of ≥5 cups of coffee per day in this subpopulation was in turn associated with an ~50% reduction in GGT activities. The levels of alcohol intake exceeding 280 g per week among men correspond to the widely accepted limits, which also associate with increased risks for ethanol-induced medical problems (Corrao et al., 2004; Gunzerath et al., 2004). Thus, the present data also support the possibility of hepatoprotective effects of coffee in heavy drinkers (Klatsky and Armstrong, 1992; Tverdal and Skurtveit, 2003; Klatsky et al., 2006; Kendrick and Day, 2007; Ikeda et al., 2010). Indeed, previous studies have indicated that the risks for both alcoholic cirrhosis (Klatsky and Armstrong, 1992; Tverdal and Skurtveit, 2003; Modi et al., 2010) and hepatitis (Freedman et al., 2009; Costentin et al., 2011) are decreased in coffee drinkers, although as yet the doses of coffee required to produce such effects have remained unclear.

The causal mechanistic explanations by which coffee exerts its health effects are also still pending. Coffee contains over 1000 chemically distinct compounds and the beneficial liver effects have been thought to be largely related to their antioxidative potential (Bidell et al., 2006; Gressner, 2009; Freedman et al., 2012). In alcohol consumers, enhanced oxidative stress is a key mechanism in the initiation of hepatotoxicity (Lee et al., 2003; Dey and Cederbaum, 2006; Floegel et al., 2012). GGT enzyme is involved in the metabolism of GSH, which, upon alcohol drinking, is lost into the circulation (Speisky et al., 1985; Lanaça and Israel, 1991). Components of coffee (kahweol and cafestol) in turn can induce gamma-glutamyl cysteine synthetase, the rate-limiting enzyme in GSH synthesis (Huber et al., 2002). The levels of GGT activities in circulation appear to be closely linked with the processes of free radical species development and proinflammation and could, thus, also serve as biomarkers reflecting the oxidative stress status in the body (Lee et al., 2004; Emdin et al., 2005; Alatalo et al., 2008).

Based on the present findings, it appears that the protective actions of coffee may not be activated until a particular oxidative stress level has been reached and may not be seen with low doses of coffee. Here, the most significant effects of coffee on GGT activities were seen in male heavy drinkers of alcohol who drank ≥5 cups of coffee/day. A previous follow-up study by Ruhl and Everhart (2005) showed clinically significant hepatoprotective effects of coffee consumption in consumers of ≥2 cups per day, which were, however, restricted to high-risk persons with heavy alcohol intake, overweight, diabetes and excess iron burden. Interestingly, low or moderate intake of coffee in moderate drinkers here were associated with slightly elevated GGT activities, suggesting possible hormetic effects of coffee and alcohol on liver enzymes. Previously, either positive or J-shaped associations between coffee and risk of coronary vascular disease have also been reported (Higdon and Frei, 2006; Floegel et al., 2012).

Beneficial health effects of coffee have also been reported among patients with type 2 diabetes possibly through mechanisms involving improved insulin sensitivity and biological responses to insulin (Agardh et al., 2004; Bidell et al., 2008). Studies in experimental animals have also demonstrated that coffee consumption protects from liver damage caused by a high-fat diet (Vitaglione et al., 2010). Interestingly, recent studies have also suggested a close link between hepatic effects and atherosclerosis and that GGT may represent a link between fatty liver and the development of early atherosclerosis (Kozakova et al., 2012).

In addition to alcohol consumption, increased GGT activities in apparently healthy individuals have been shown to result from obesity (Alatalo et al., 2008), smoking (Breitling et al., 2009) or advanced age (Tynjälä et al., 2012). These were all used as covariates in the present analysis and, thus, should not confound the associations reported. The present data suggest, however, gender differences in GGT responses to alcohol and coffee. While this may be due to a lower number of women among heavy drinkers and a consequent lack of statistical power in the present analyses, it should be noted that sex steroids may play a role in the regulation of oxidant stress status in vivo (Grassi et al., 2007; Alatalo et al., 2009). Women are known to have a greater propensity than men for ethanol-induced tissue damage at more than moderate drinking levels.

Taken together, our findings suggest that high intake of coffee leads to lower GGT levels in heavy alcohol consumers, particularly, among men. The present data should be implicated in the comprehensive assessment and the treatment of patients with excessive alcohol consumption and in studies evaluating GGT as a biomarker of liver dysfunction.

Conflict of interest statement — None declared.

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