World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i33.11743

World J Gastroenterol 2014 September 7; 20(33): 11743-11752
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Impacts of common factors of life style on serum liver enzymes

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Author contributions: Danielsson J analysed the data, drafted the manuscript; Kangastupa P analysed the data; Laatikainen T and Aalto M designed the study, performed data acquisition, revised the manuscript; Niemelä O designed the study and wrote the manuscript.
Supported by Competitive State Research Financing of the Expert Responsibility area of Seinäjoki Central Hospital and University of Tampere, VTR110
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Received: December 19, 2013 Revised: January 20, 2014
Accepted: May 19, 2014
Published online: September 7, 2014

Abstract

AIM: To investigate the impacts of gender, age and factors of life style (alcohol, overweight, coffee and smoking) on serum liver enzymes.

METHODS: Serum alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT) were measured from 6269 apparently healthy individuals (2851 men, 3418 women, mean age 45 ± 12 years, range 25-74 years) in a national cross-sectional health survey. All subjects underwent detailed clinical examinations and interviews including the amount and pattern of alcohol use, coffee consumption and smoking habits.

RESULTS: In this population with a mean ± SD alcohol consumption of 65 ± 105 g/wk and body mass index (BMI) of 26.1 ± 4.3 kg/m^2, both ALT and GGT were significantly influenced by alcohol use ($P < 0.001$) and BMI ($P < 0.001$), whereas smoking increased only GGT ($P < 0.001$). A significant effect of age on ALT was seen in men ($P < 0.001$) whereas not in women. Significant two-factor interactions of alcohol use in men were observed with age (ALT: $P < 0.01$; GGT: $P < 0.001$) and BMI (GGT: $P < 0.05$). For ALT, a significant interaction also occurred between BMI and age ($P < 0.005$). In contrast, women showed significant interactions of alcohol use with BMI (GGT: $P < 0.05$), smoking (GGT: $P < 0.001$), and coffee consumption (GGT: $P < 0.001$).

CONCLUSION: Life-style associated changes in liver enzymes may reflect health risks, which should be considered in the definition of normal limits for liver enzymes.

Key words: Alcohol; Obesity; Aging; Smoking; Liver enzymes; Oxidative stress

Core tip: The present study among 6269 apparently healthy individuals shows that the early changes in serum alanine aminotransferase and gamma-glutamyltransferase levels show distinct age- and gender-dependent variation according to the amount of alcohol drinking and the presence or absence of overweight. Coffee consumption and smoking also modulate the enzyme levels with different sensitivities between genders. The data should be implicated in the assessment of health risks associated with such factors of life style and when revisiting the concept of normal limits in the clinical use of liver enzymes.

Danielsson J, Kangastupa P, Laatikainen T, Aalto M, Niemelä O. Impacts of common factors of life style on serum liver en-

zymes. *World J Gastroenterol* 2014; 20(33): 11743-11752 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i33/11743.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i33.11743

INTRODUCTION

Since an increasing percentage of the general population consists of heavy drinkers[1,2], and over half suffer from overweight[3-7] adverse health effects resulting from such reasons constitute an inescapable problem in our society. Elevated serum liver enzymes and accumulation of fat in hepatic tissue are among the first manifestations in the sequence of events leading to morbidity and mortality due to alcohol drinking or excess body weight[8,9]. Consequently, there has been growing interest on the biological significance of the early-phase changes in serum liver enzyme activities and their clinical value as biomarkers of health and disease.

Recently, changes in serum alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT) have also attracted interest as prognostic parameters in a variety of extrahepatic conditions[10-15]. In both prospective and cross-sectional studies these enzymes have been observed to associate with diabetes, metabolic syndrome, and overall mortality[9,15-21]. Studies on the individual and joint impacts of various common factors of life style on ALT and GGT levels have, however, so far been limited. Similarly, the definitions of normal limits for these enzymes have remained as a matter of controversy and hampered the interpretation of the data in clinical trials.

In this work we measured serum ALT and GGT levels from a large age- and gender-stratified population of apparently healthy individuals with varying body mass index (BMI, kg/m^2) and with different levels of well-documented consumption of ethanol, coffee, and cigarette smoking. We also determined the normal limits for both enzymes based on the present sample of alcohol non-drinkers with normal body weight.

MATERIALS AND METHODS

Study protocol

The present data was collected from a cross-sectional population health survey (The National FINRISK studies) carried out in six different geographic areas in Finland. An age- and gender stratified random sample of 13437 individuals was first drawn from the population register according to an international WHO MONICA (Monitoring trends and determinants in cardiovascular disease) protocol. The survey included physical measurements, laboratory tests and detailed questionnaires on health status and alcohol intake, covering also information on current health behaviour, medical history and socioeconomic factors. The medical examinations were conducted using a previously described standardized protocol[22,23]. Measurements of height and weight were carried out and BMI was calculated as a measure of relative body weight. Serum ALT and GGT were measured by standard kinetic methods following recommendations of the European Committee for Clinical Laboratory Standards (ECCLS)[24] on an Abbott Architect clinical chemistry analyser (Abbott Laboratories, Abbott Park, IL, United States). Measurements of serum lipids [total cholesterol, high density lipoprotein (HDL) cholesterol, Low Density Lipoprotein (LDL) cholesterol, triglycerides] were carried out by enzymatic methods (Thermo Electron Corporation, Waltham, Massachusetts, United States). Serum C-reactive protein was measured using a sensitive immunoturbidimetric method (Orion Diagnostica, Espoo, Finland). All surveys were conducted in accordance with the Declaration of Helsinki according to the ethical rules of the National Public Health Institute. The approval for this study was received from the Coordinating Ethics Committee of the Helsinki Hospital District.

The present sample included data from the subjects who both filled out the questionnaire and attended the medical examination. The response rate was 65.5%. All participants were devoid of any apparent clinical signs of liver disease. In order to obtain a representative sample of apparently healthy individuals, exclusions were made for the following reasons: diagnosis of myocardial infarction (n = 236), stroke, cerebral haemorrhage or embolism (n = 193), diabetes or glucose-intolerance (n = 476), hypertension (n = 985), use of statins or lipid lowering agents (n = 364) or signs of active infection at the time of the study (n = 342). In addition, exclusions were made due to missing variables (n = 866). The final population thus comprised 6269 individuals: 2851 men and 3418 women (mean age 45 ± 12 years, range 25-74 years).

Alcohol consumption was assessed with detailed questions on the type of beverage consumed, the frequency of consumption, and the amount of ethanol-containing drinks consumed regularly during the past weeks and one year prior to the data collection. The amount of ethanol in different beverages was quantitated as follows: beer 12 g (1/3 L), strong beer 15.5 g (1/3 L), long drink 15.5 g (1/3 L), spirit 12 g (4 cL), wine 12 g (12 cL) and cider 12 g (1/3 L). A dose of 12 g of pure ethanol was considered as one standard drink. The persons who reported no current alcohol consumption were referred to as non-drinkers (n = 2048), moderate drinkers (n = 3993) consumed less than 280 g of ethanol (men) or less than 190 g of ethanol (women) per week, heavy drinkers (n = 228) consumed > 280 g per week (men) or > 190 g per week (women). Smoking and coffee consumption were assessed with a set of standardized questions. The data on smoking was expressed as the amount of cigarettes per day and coffee consumption was recorded as the number of cups of coffee per day.

Statistical analysis

Values are expressed as mean ± SD or mean ± 95%CI. Significance tests were carried out using ANOVA for multiple factors, Bonferroni *post hoc* test and appropri-

Table 1 Distribution of study participants (n = 6269) in subgroups according to age and gender n (%)

		Age group (yr)					
		25-29	30-39	40-49	50-59	60-69	70-74
Men							
n		325	714	727	671	345	69
Alcohol, g/wk							
	0	86 (26.5)	166 (23.2)	169 (23.2)	156 (23.2)	108 (31.3)	27 (39.1)
	< 280	222 (68.3)	510 (71.4)	515 (70.8)	466 (69.4)	219 (63.5)	39 (56.5)
	⩾ 280	17 (5.2)	38 (5.3)	43 (5.9)	49 (7.3)	18 (5.2)	3 (4.3)
BMI, kg/m^2							
	< 18.5	4 (1.2)	1 (0.1)	2 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)
	⩾ 18.5 and < 25	171 (52.6)	260 (36.4)	236 (32.5)	208 (31.0)	101 (29.3)	20 (29.0)
	⩾ 25 and < 30	113 (34.8)	331 (46.4)	375 (51.6)	322 (48.0)	162 (47.0)	37 (53.6)
	⩾ 30	37 (11.4)	122 (17.1)	114 (15.7)	140 (20.9)	82 (23.8)	12 (17.4)
Smoking, cigarettes/d							
	0	189 (58.2)	446 (62.5)	476 (65.5)	469 (69.9)	274 (79.4)	65 (94.2)
	1-10	68 (20.9)	94 (13.2)	67 (9.2)	49 (7.3)	22 (6.4)	3 (4.3)
	⩾ 11	68 (20.9)	174 (24.4)	184 (25.3)	153 (22.8)	49 (14.2)	1 (1.4)
Coffee, cups/d							
	0	62 (19.1)	81 (11.3)	55 (7.6)	59 (8.8)	24 (7.0)	5 (7.2)
	1-4	143 (44.0)	248 (34.7)	239 (32.9)	246 (36.7)	180 (52.2)	39 (56.5)
	⩾ 5	120 (36.9)	385 (53.9)	433 (59.6)	366 (54.5)	141 (40.9)	25 (36.2)
Women							
n		461	861	860	795	365	76
Alcohol, g/wk							
	0	190 (41.2)	356 (41.3)	308 (35.8)	289 (36.4)	155 (42.5)	38 (50.0)
	< 190	267 (57.9)	492 (57.1)	533 (62.0)	489 (61.5)	203 (55.6)	38 (50.0)
	⩾ 190	4 (0.9)	13 (1.5)	19 (2.2)	17 (2.1)	7 (1.9)	0 (0.0)
BMI, kg/m^2							
	< 18.5	23 (5.0)	12 (1.4)	7 (0.8)	1 (0.1)	0 (0.0)	1 (1.3)
	⩾ 18.5 and < 25	305 (66.2)	508 (59.0)	488 (56.7)	311 (39.1)	126 (34.5)	25 (32.9)
	⩾ 25 and < 30	92 (20.0)	245 (28.5)	245 (28.5)	325 (40.9)	153 (41.9)	31 (40.8)
	⩾ 30	41 (8.9)	96 (11.1)	120 (14.0)	158 (19.9)	86 (23.6)	19 (25.0)
Smoking, cigarettes/d							
	0	314 (68.1)	616 (71.5)	616 (71.6)	652 (82.0)	326 (89.3)	71 (93.4)
	1-10	109 (23.6)	157 (18.2)	141 (16.4)	75 (9.4)	21 (5.8)	2 (2.6)
	⩾ 11	38 (8.2)	88 (10.2)	103 (12.0)	68 (8.6)	18 (4.9)	3 (3.9)
Coffee, cups/d							
	0	145 (31.5)	152 (17.7)	71 (8.3)	62 (7.8)	22 (6.0)	5 (6.6)
	1-4	235 (51.0)	440 (51.1)	409 (47.6)	445 (56.0)	240 (65.8)	59 (77.6)
	⩾ 5	81 (17.6)	269 (31.2)	380 (44.2)	288 (36.2)	103 (28.2)	12 (15.8)

ate covariates as indicated. Logarithmic transformations of ALT and GGT data were used to obtain non-skewed distributions with homogeneity of variance. Correlations were calculated using Pearson product-moment correlation coefficients. The differences in partial correlations were analyzed with the *Z*-test for correlation coefficients. Calculations of reference limits based on the population of normal-weight non-drinkers were carried out according to previously described nonparametric methods and Dixon's test for detection and exclusion of outliers[25,26]. Age of 40 years was used as a cut-off for group stratification based on previous findings showing an increase in the 97.5 percentile of GGT in both genders at the age of about 40 years[26]. The analyses were carried out with the use of Analyse-it v 2.21 for Microsoft Excel (Leeds, United Kingdom) and SPSS 21.0 (SPSS Inc., Chicago, IL) for Windows statistical software. A P value < 0.05 was considered statistically significant.

RESULTS

This study cohort of apparently healthy individuals consisted of 2851 men and 3418 women, who participated in a national cross-sectional health survey. The data on alcohol consumption indicated that 32.7% of the population were non-drinkers, 63.7% were moderate drinkers and 3.6% were heavy drinkers. The mean ± SD alcohol consumption was 65 ± 105 g/wk: men 99 ± 137 g/wk, women 37 ± 53 g/wk. In this material with a mean BMI of 26.1 ± 4.3 kg/m^2 (men 26.7 ± 3.9 kg/m^2; women 25.6 ± 4.5 kg/m^2), 16.4% of the subjects were obese (BMI > 30 kg/m^2) and 38.8% showed BMI levels between 25 and 30 kg/m^2 indicating overweight. Smokers comprised 28.0% of the population. The demographic characteristics of the study participants, as further classified according to age and gender, are summarized in Table 1.

The lower and upper normal limits for ALT and

Table 2 Lower and upper normal limits for alanine aminotransferase and gamma-glutamyltransferase based on non-drinkers with normal weight

	Normal weight non-drinkers			Reference[1]	
	n	Lower limit U/L	Upper limit U/L	Lower limit U/L	Upper limit U/L
ALT					
Men	162	10	47	10	70
Women	523	8	37	10	45
GGT					
Men	162	11	52		
< 40 yr	55	10	48	10	80
⩾ 40 yr	107	12	53	15	115
Women	522	8	42		
< 40 yr	228	8	34	10	45
⩾ 40 yr	294	9	47	10	75

[1]Commonly used values in Nordic countries based on NORIP data[26].

GGT as defined here by calculating 2.5th and 97.5th percentiles of the data based on normal weight non-drinkers are shown in Table 2. The observed upper normal limits for both enzymes were found to be significantly lower than the currently used limits in Nordic countries used as reference in the present comparisons[26].

In the total study material, significant effects of alcohol consumption ($P < 0.001$), BMI ($P < 0.001$), and age ($P < 0.001$) were noted for both ALT and GGT. In the analyses for main effects and interactions between the study variables, the levels of ALT and GGT in both genders were found to be significantly influenced by alcohol use (ALT: $P < 0.05$ for men; $P < 0.001$ for all other comparisons) and BMI ($P < 0.001$) (Table 3). There was also a significant main effect of age on GGT ($P < 0.001$) and on ALT in men ($P < 0.001$), whereas not in women (Figure 1, Table 3). Highest ALT levels in men occurred in those aged 25-50 years whereas in women such age-dependent variation was not observed (Figure 1). The highest GGT values were observed in age groups 50-60 years (men) and 60-70 years (women) (Figure 1). Smoking significantly influenced GGT levels in both genders ($P < 0.001$) (Table 3).

The impact of ethanol intake in men was found to become significantly more pronounced upon increasing age (Figure 2, Table 3). In men over 40 years alcohol consumption exceeding 16 drinks per week was a stronger determinant of GGT activities than in those below 40 (Figure 2). In women, such interaction was not observed.

The effects of increasing body weight on ALT and GGT levels in the different age-categories are shown in Figure 3. Interestingly, in men below 40 years, overweight was found to be a stronger inducer of ALT activities than in those above 40 years. In contrast such interaction between BMI and age was not found among women (Table 3). The analysis of the effect of alcohol drinking in the different BMI-based subgroups showed that the presence of overweight or obesity significantly potentiates GGT activities both in men and women who consume alcohol (Figure 4). Analyses of two-factor interactions between

Table 3 Summary of main effects and two-factor interaction statistics for alanine aminotransferase and gamma-glutamyltransferase

	Men		Women	
	ALT	GGT	ALT	GGT
Main effects				
Ethanol	< 0.050	< 0.001	< 0.001	< 0.001
BMI	< 0.001	< 0.001	< 0.001	< 0.001
Age	< 0.001	< 0.001	NS	< 0.001
Smoking	NS	< 0.001	NS	< 0.001
Coffee	NS	NS	NS	< 0.050
Two-factor interaction				
Ethanol × age	0.008	0.001	0.295	0.197
Ethanol × BMI	0.301	0.038	0.537	0.048
Ethanol × smoking	0.398	0.094	0.794	0.001
Ethanol × coffee	0.534	0.260	0.138	0.001
BMI × age	0.003	0.067	0.502	0.788
BMI × smoking	0.878	0.342	0.904	0.690
BMI × coffee	0.430	0.653	0.261	0.090
Age × smoking	0.831	0.089	0.558	0.342
Age × coffee	0.095	0.117	0.018	0.061

The analyses of main effects and two-factor interactions were carried out using ANOVA on SPSS 21.0 for Windows statistical software. Alcohol use, BMI, smoking and coffee consumption were used as covariates, as appropriate. NS: Not significant; LT: Alanine aminotransferase; GGT: Gamma-glutamyltransferase; BMI: Body mass index.

the study variables also showed statistically significant interactions of alcohol use and smoking (GGT: $P < 0.001$) as well as between alcohol use and coffee consumption especially among women (GGT: $P < 0.001$).

The correlations between ALT, GGT and various metabolic and inflammatory markers are summarized in Table 4. Significant correlations emerged between the liver enzymes and the lipid profile, C-reactive protein and indices of overweight. However, there were also distinct differences in the correlation coefficients observed between the liver enzymes and the other biomarkers when comparing men and women or subjects below or above 40 years of age. Stronger correlations between liver enzymes and indices of lipid status (cholesterol, triglycerides) were found in men. Significant correlations also occurred between the liver enzyme levels and waist circumference, which especially in case of GGT among men over 40 years was slightly stronger than the corresponding correlation with BMI (Table 4).

DISCUSSION

Our data among a large cross-sectional sample of apparently healthy individuals shows age- and gender-dependent interactions between alcohol use, BMI, smoking and serum liver enzymes, which have recently been suggested as important disease risk markers in both hepatic and extrahepatic conditions[12,27]. The data also suggests distinct differences in the reactivities of ALT and GGT towards the metabolic burdens created by the various factors of life style.

In current societies, alcohol and obesity-related health

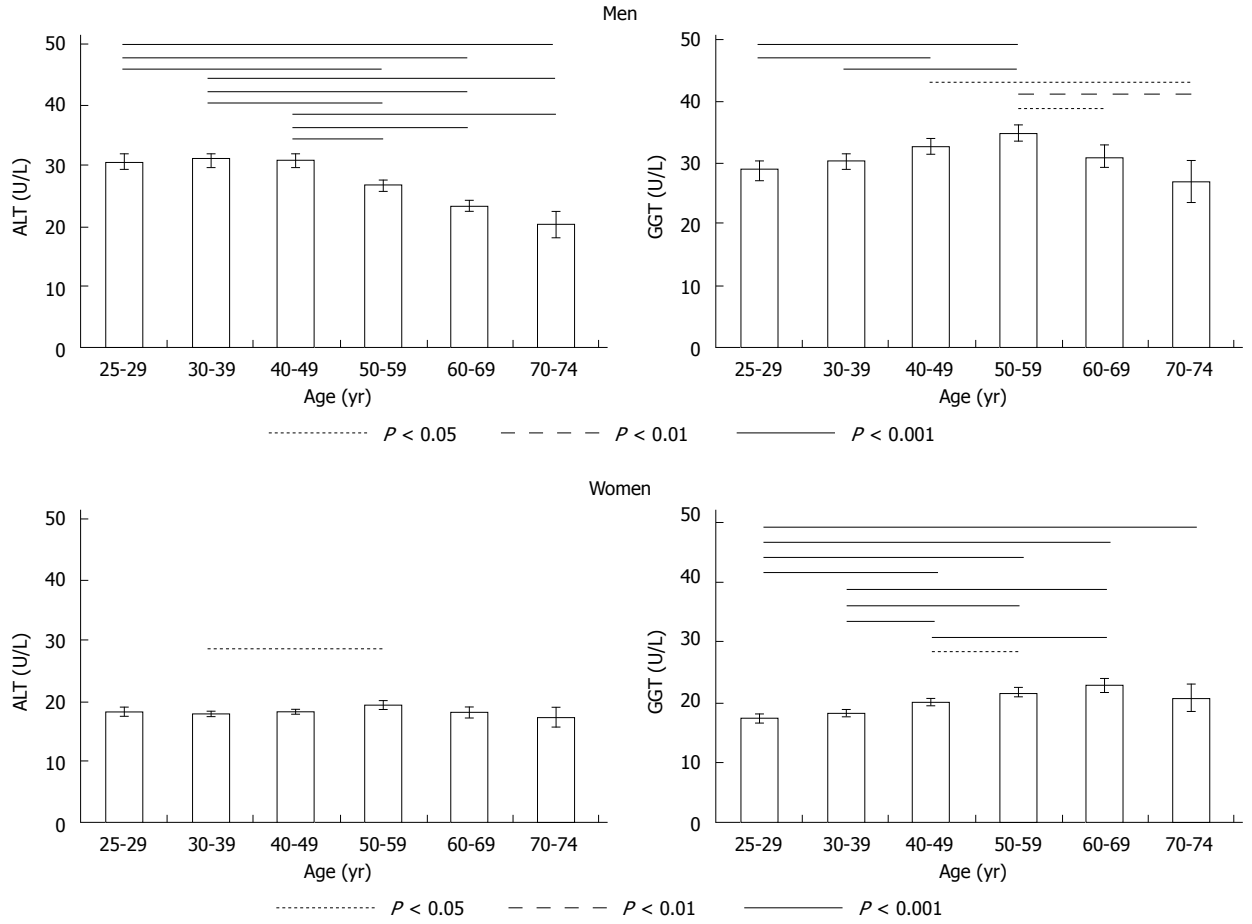

Figure 1 Alanine aminotransferase and gamma-glutamyltransferase levels (geometric mean ± 95%CI) in men and women classified to subgroups according to age. Horizontal lines indicate significant differences between groups, as assessed by ANOVA with Bonferroni *post hoc* test. Alcohol intake (drinks/wk), BMI (kg/m^2), smoking (cigarettes/d), and coffee consumption (cups/d) were used as covariates. ALT: Alanine aminotransferase; GGT: Gamma-glutamyltransferase.

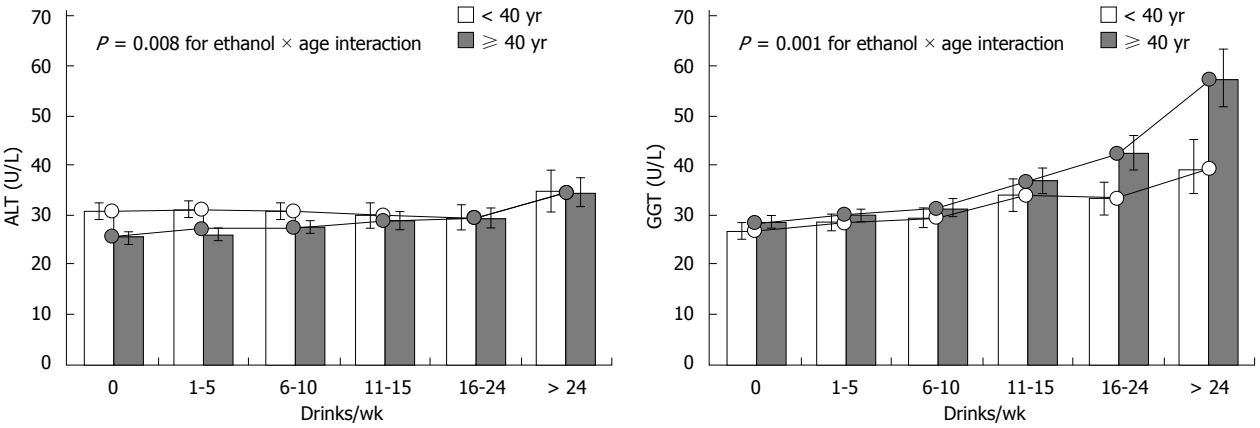

Figure 2 Interactions of ethanol intake with age on alanine aminotransferase and gamma-glutamyltransferase levels in men. An aggravated effect of ethanol was seen in those who were over 40 years of age and consumed over 16 drinks of alcohol per week. In women, the interaction between alcohol use and age was not significant (Table 3). Smoking and coffee consumption were used as covariates. ALT: Alanine aminotransferase; GGT: Gamma-glutamyltransferase.

problems are often co-existing and may function in a synergistic manner[9,16,21,28]. GGT has previously been shown to readily increase among alcohol consumers with obesity[16] as well as in heavily smoking alcohol users[17], which may be related with the pivotal role of GGT in the metabolism of glutathione (GSH)[29-34]. Mild GGT elevations may be considered a sign of a need to maintain intracellular GSH levels under conditions of oxidative stress[14,29,30,32-34]. In turn, alterations in ALT activities likely reflect disturbed liver cell integrity[27].

According to the present data the upper normal limits of ALT and GGT enzymes in their clinical use as disease

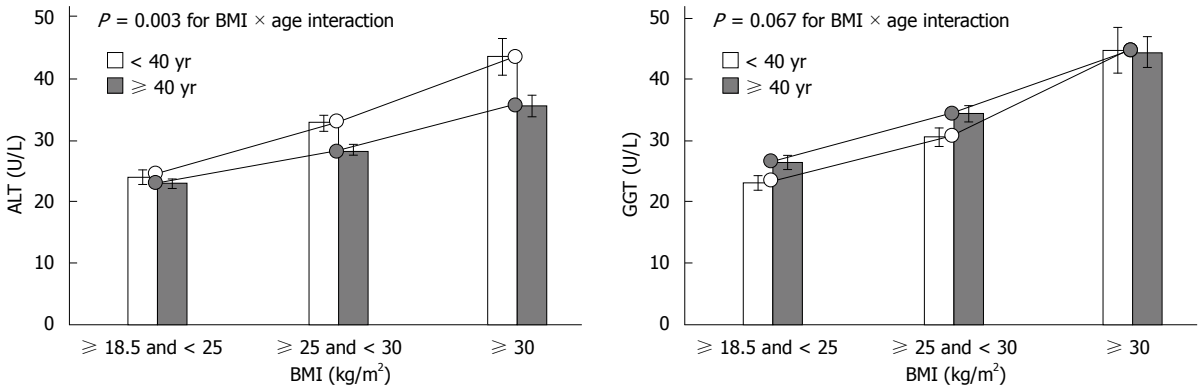

Figure 3 Interactions of body mass index with age on alanine aminotransferase and gamma-glutamyltransferase levels. A significant interaction was noted only on alanine aminotransferase (ALT) levels in men below 40 years of age. Alcohol intake, smoking and coffee consumption were used as covariates. BMI: Body mass index.

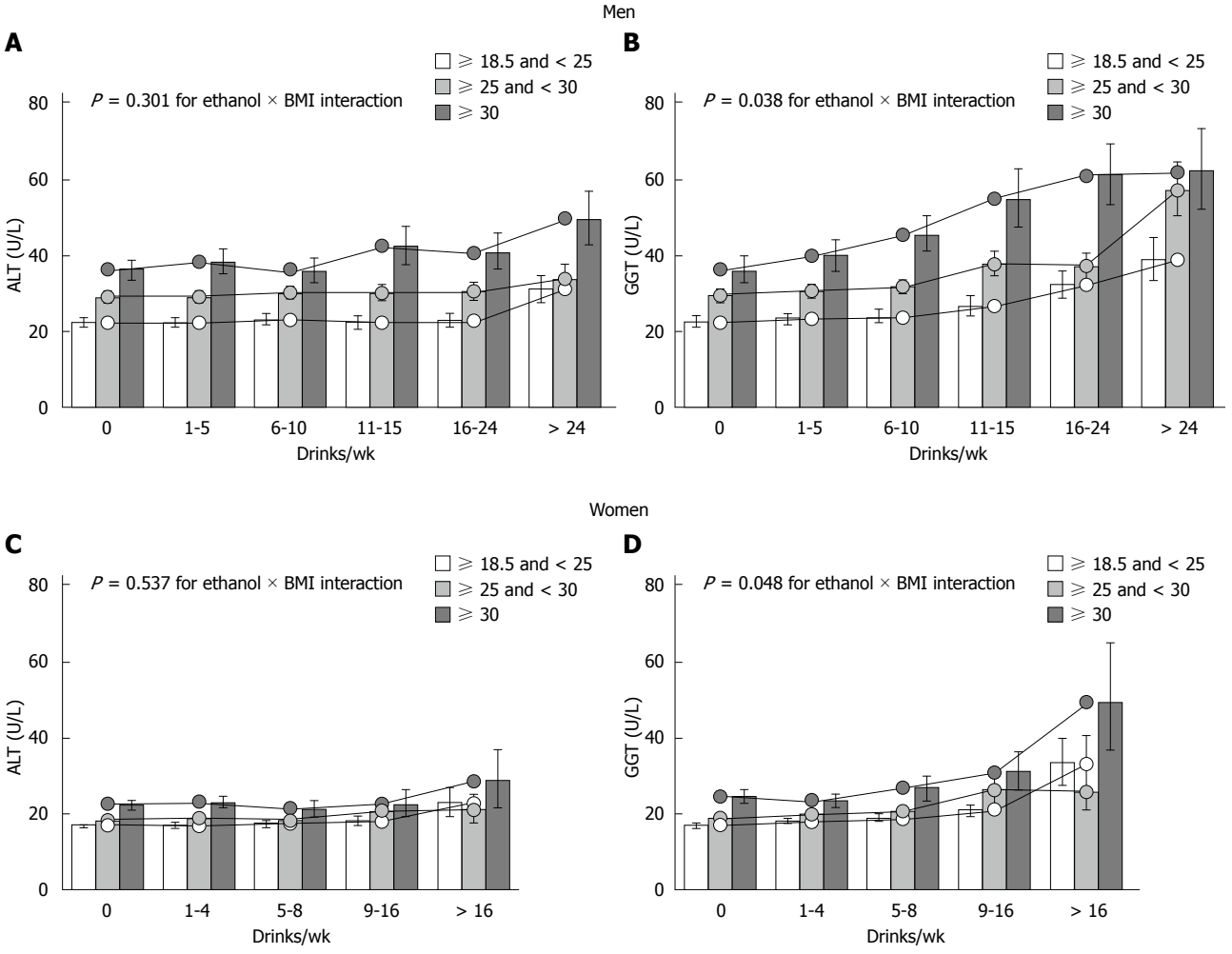

Figure 4 Interactions of ethanol intake with body mass index on alanine aminotransferase and gamma-glutamyltransferase levels. Significant interactions in both men and women were noted for gamma-glutamyltransferase (GGT), whereas not for alanine aminotransferase (ALT). Covariates used were age (years), smoking, and coffee consumption. BMI: Body mass index.

biomarkers should be markedly lower than those currently used in most countries[35,36]. Despite of the fact that biomarker reference intervals are crucial tools to differentiate between healthy and diseased subjects, as yet we share no widely accepted upper normal limits even for these most common liver enzymes. This may have been due to lack of knowledge on dose responses between ethanol intake and biomarker levels, inconsistencies regarding the definition of safe levels of ethanol intake and ignorance of excess body weight in different sample populations. For successful implementation of early treatment programs to reduce alcohol- and obesity-induced morbidity, correct definitions of reference intervals and greater harmonization of analytical goals for biomarkers

Table 4 Correlations between study variables

	Men (n = 2851)		Women (n = 3418)	
	ALT	GGT	ALT	GGT
ALT		0.543[a]		0.483[a]
Total cholesterol	0.182[1,a]	0.347[1,a]	0.105[1,a]	0.193[1,a]
HDL	-0.163[a]	-0.017	-0.098[a]	-0.045[b]
LDL	0.151[a]	0.252[1,a]	0.118[a]	0.182[1,a]
Triglycerides	0.266[1,a]	0.327[1,a]	0.178[1,a]	0.229[1,a]
CRP	0.142[a]	0.280[a]	0.104[a]	0.238[a]
BMI	0.378[1,a]	0.351[1,a]	0.256[1,a]	0.284[1,a]
Waist circumference	0.367[1,a]	0.395[1,a]	0.253[1,a]	0.303[1,a]
	Men < 40 yr (n = 1039)		Men ⩾ 40 yr (n = 1812)	
	ALT	GGT	ALT	GGT
ALT		0.592[a]		0.538[a]
Total cholesterol	0.297[1,a]	0.391[1,a]	0.164[1,a]	0.298[1,a]
HDL	-0.201[a]	-0.083[b]	-0.139[a]	0.003
LDL	0.282[1,a]	0.332[1,a]	0.110[1,a]	0.178[1,a]
Triglycerides	0.322[a]	0.373[1,a]	0.256[a]	0.301[1,a]
CRP	0.180[a]	0.267[a]	0.137[a]	0.273[a]
BMI	0.451[1,a]	0.446[1,a]	0.351[1,a]	0.284[1,a]
Waist circumference	0.459[1,a]	0.463[1,a]	0.352[1,a]	0.336[1,a]
	Women < 40 yr (n = 1322)		Women ⩾ 40 yr (n = 2096)	
	ALT	GGT	ALT	GGT
ALT		0.450[d]		0.495[d]
Total cholesterol	0.050	0.087[b]	0.099[d]	0.154[d]
HDL	-0.114[d]	-0.054[a]	-0.096[d]	-0.057[b]
LDL	0.082[b]	0.104[d]	0.106[d]	0.139[d]
Triglycerides	0.083[1,b]	0.115[1,d]	0.217[1,d]	0.249[1,d]
CRP	0.044[1]	0.154[1,d]	0.148[1,d]	0.302[1,d]
BMI	0.267[d]	0.291[d]	0.231[d]	0.236[d]
Waist circumference	0.242[d]	0.292[d]	0.244[d]	0.267[d]

[a]P < 0.05 *vs* Control, [b]P < 0.01 *vs* Control, [d]P < 0.001 *vs* Control. [1]Statistically significant differences (P < 0.05) in correlation coefficients between men and women or those below or above 40 years of age (Z-test). ALT: Alanine aminotransferase; GGT: Gamma-glutamyltransferase; HDL: High density lipoprotein; LDL: Low density lipoprotein; CRP: C-Reactive protein; BMI: Body mass index.

with predictive value should be of utmost importance.

In the present study population, 40 years of age was used as a cut-off for group stratification based on previous findings, which have shown an increase in GGT levels in both genders at this age point[26]. Among men over 40 years, alcohol consumption even in amounts which were below the current limits of heavy drinking appeared to pose a risk towards elevated ALT and GGT levels, suggesting an increased susceptibility to ethanol-induced adverse health effects upon increasing age[31,37]. Intriguingly, a recent large United States population-based study also suggested relatively high mortality rates among older men consuming ethanol[38]. Although women in general are known to be more susceptible to ethanol-induced morbidity, the concept of safe limits for ethanol intake in different age categories of men also appears to need further attention.

The present findings also underscore the impact of excess body weight in the biological interactions influencing liver enzyme status. Young men presenting with overweight or obesity were found to show rather high baseline ALT levels even in the absence of any other apparent risk factors. The correlations between the lipid status and liver enzymes were also strong among young men, possibly indicating accumulation of adverse health effects due to a lifestyle involving overconsumption of the Western diet[39-41]. Previously, a high risk of liver injury in combination of obesity and alcohol use has been observed in studies among older age groups[42]. In experimental animals aging also promotes the development of diet-induced steatohepatitis and induction of serum amino transferase levels[39]. It is likely that alcohol intake by subjects with overweight stimulates oxidative stress in an additive and more striking manner, as also supported here by the findings in GGT activities[43,44]. Alcohol has a high energy content and in experimental animals the adverse effects of ethanol are aggravated by high-fat-diets[45]. Moreover, genotypic differences in alcohol-metabolizing enzymes could also contribute to the risk of gaining body weight in some alcohol consumers[46].

In accordance with previous data[10,17] the present observations also point to a significant synergistic effect of smoking and alcohol use in increasing GGT levels. However, while previous work reported such effects in male construction workers[10] our data suggests even stronger interactions among women. This could, however, be explained by the relatively lower quantities of smoking in the present material. In addition, coffee consumption was found to interact with GGT levels such that a high intake of coffee (⩾ 5 cups/d) in those with the most abundant amounts of ethanol intake was more likely to be associated with atypically low GGT levels indicating a possible protective effect of coffee towards alcohol-induced liver damage and oxidative stress[47-49].

Increased ALT and GGT levels commonly co-occur with accumulation of triglycerides and liver steatosis and compelling evidence from the past decade have also linked such phenomena with extrahepatic health risks, such as type 2 diabetes, metabolic syndrome, insulin resistance and cardiovascular morbidity[12,15,21,50-54]. Serum liver enzyme activities may even predict mortality from cardiovascular or cerebrovascular events[11,15,41,51]. While the specific mechanisms underlying such observations have remained unclear, it should be noted that recent studies have indicated a role for GGT as a link between fatty liver and development of early atherosclerosis due to the ability of GGT to trigger iron-dependent oxidation of LDL also in coronary plaques[51]. Therefore, it is notable that the present data also indicates a strong correlation between LDL cholesterol and GGT levels, especially in men.

The cross sectional setting of the survey can be kept as a limitation of this study as some of the biomarkers used may have day to day variation. Lack of follow-up data also prevents analyses on the specific relationships between enzyme elevations and duration of drinking or obesity status, which clearly warrant future prospective studies. Also disease status was self-reported and thus the exclusions might not be fully accurate causing conserva-

tive estimate of healthy population. It is also possible that the alcohol recall techniques overestimate the proportion of those not drinking alcohol at all[55]. However, all these issues most likely have diluting effects to the observed results and the real associations and interactions might be even stronger. It should also be noted that due to both financial and ethical considerations, analyses of hepatitis serology were not carried out in the present material. However, due to the low prevalence of viral hepatitis in Finland (observed rates of 1-2 cases/10000 blood donors per year) this should not create a significant confounding factor here.

Taken together, the present data provides novel information on the individual contributions of various factors of life style on the early-phase activation of liver enzymes and shows that even moderate drinking may lead to significant enzyme elevations in an age-, gender-, and BMI-dependent manner. Current data should be considered in the definition of more accurate safe limits of ethanol intake in different demographic categories and in the definition of normal values for liver enzymes. The possible mechanistic roles of liver enzymes as pathophysiological links between hepatic and extrahepatic disease manifestations warrant further studies.

COMMENTS

Background

The global burden of liver diseases due to excessive alcohol intake and obesity has shown a dramatic increase during the past decades. Measurements of liver enzymes, gamma-glutamyltransferase (GGT) and alanine aminotransferase (ALT), are widely used tools for detecting liver problems. However, the interpretation of the enzyme data in clinical work has been problematic due to the lack of knowledge on their early-phase responses towards the various factors of life style and the cut-offs defining normality in the assays.

Research frontiers

Serum ALT and GGT activities are known to increase as a result of alcohol use and increasing body weight. In this study among 6269 healthy volunteers, the authors demonstrate distinct age- and gender-dependent effects of alcohol use, overweight, coffee consumption and smoking on the activities of these enzymes.

Innovations and breakthroughs

The present studies demonstrate both individual and joint effects of the various factors of life style in creating increased activities of serum liver enzymes. The data also describes the lower and upper normal limits for ALT and GGT based on the present population of normal-weight non-drinkers.

Applications

By further understanding of the influences created by the various factors of life style and by more detailed definitions of liver enzyme normal limits, the clinical value of serum liver enzyme determinations can be markedly improved.

Terminology

Serum ALT and GGT are both commonly used in the diagnosis of liver diseases and have recently received increasing attention also as biomarkers of prognostic significance in extrahepatic conditions.

Peer review

This study investigated the relationships of liver enzymes and anthropometric and lifestyle factors in a general population of apparently healthy individuals. The results are interesting and may provide new insights into the clinical use of serum GGT and ALT as biomarkers of liver status.

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P- Reviewer: Grattagliano I, Weiss R **S- Editor**: Qi Y
L- Editor: A **E- Editor**: Ma S

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ISSN 1007-9327