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Body mass index is a good predictor of an elevated alanine transaminase level in the general population: hints from the Dionysos study

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Abstract

Aim. To establish the contribution of body mass index (BMI), sex, age, ethanol intake, hepatitis B (HBV) and hepatitis C (HCV) virus infection, coffee and drug consumption, and cigarette smoking to account for an elevated alanine transaminase (ALT) level in the general population.

Subjects. A total of 6315 adult subjects from the Dionysos study.

Methods. Logistic regression was used to quantify the contribution of the variables of interest to elevated ALT, defined as a value of ALT>60 U/l. Areas under ROC curves (AUCs) were calculated to assess accuracy.

Results. All the variables considered, with the exception of coffee and drug consumption, were significant predictors of elevated ALT at univariable analyses. When significant predictors were employed in a multivariable model, age and cigarette smoking were no longer significant. The AUC was 0.77 (95% CI=0.74–0.80) for the multivariable model and 0.64 (95% CI=0.60–0.68) for the univariable BMI model ($p<0.0001$ for the comparison).

Conclusion. BMI is a good predictor of elevated ALT serum activity in the general population. The ability to predict an elevated ALT is however increased substantially by considering sex, ethanol intake, HBV and HCV infection together with BMI.

Keywords: Alanine transaminase; Anti-HCV antibodies; Body mass index; Coffee; Ethanol; HbsAg; Smoking

1. Introduction

Our knowledge of the relationship between body mass index (BMI) and alanine transaminase (ALT) levels is based mainly on studies performed in selected populations such as blood donors, employees and workers [1–6]. The only available study performed on a representative sample of the general population [7,8] has not taken into account all known risk factors for elevated ALT. Taken together, these studies show that high BMI values are associated with elevated ALT levels [9]. This association is confirmed by observational studies showing a correlation between BMI changes and ALT changes [10,11]. Ethanol intake, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection and drug consumption are known risk factors for elevated ALT [9]. Cigarette smoking has also been proposed as risk factor for elevated ALT [12]. On the contrary, coffee may play a protective role for elevated ALT, especially in subjects drinking ethanol [13]. Through the population study, named Dionysos [14], we were previously able to demonstrate that steatosis is frequently encountered in healthy subjects (16%) and it is almost always present in obese subjects drinking more that 30 g/alcohol per day [15]. In our cohort, steatosis was also significantly more associated with obesity than heavy drinking, indicating a greater relative role of weight than alcohol consumption in inducing fat accumulation in the liver. In this paper, we took advantage of the ongoing Dionysos study to establish the contribution of BMI to elevated ALT in the general population, taking into

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account the possibly confounding effect of sex, age, ethanol intake, HBV and HCV infection, coffee and drug consumption, and cigarette smoking.

2. Materials and methods

2.1. Subjects

The Dionysos study was aimed at identifying the prevalence and etiology of liver disease in Northern Italy and was performed on 6917 out of 10150 inhabitants of two Italian communities (Campogalliano, MO, Italy and Cormons, GO, Italy) [14,15]. All subjects aged ≥18 years who took part in the Dionysos study were considered eligible for the present study. The analysis was performed on the 6315 adults (3352 females and 2963 males) for whom all the measurements of interest were available (99.1% of all subjects ≥18 years).

2.2. Methods

ALT was measured by common laboratory methods. BMI was calculated as weight (kg)/height $(m)^2$ [16]. Ethanol intake and coffee consumption were assessed using a food frequency questionnaire [14,15]. Smoking habits and drug consumption were determined by interview [14,15]. Hepatitis B surface antigen (HbsAg) and anti-HCV antibodies were detected using commercial kits {Abbott Laboratories, Chicago, IL, USA and second generation enzyme-linked immunosorbent assay (ELISA); Ortho Diagnostic Systems, Raritan, NJ, USA} [15].

2.3. Statistical analysis

Continuous variables are given as medians and interquartile ranges on account of skewed distributions. Between-sex comparisons of continuous variables were performed with the Mann–Whitney *U*-test and those of ordinal variables with Fisher's Exact test. Simple and multiple logistic regression models were used to establish the contribution of the variables of interest to elevated ALT. The latter was defined as a value of ALT>60 U/l detected at least twice in 30 days, a cut-point corresponding to twice the upper normal value (30 U/l) and to the 96.5th internal percentile. Even if the choice of a cut-point for elevated ALT is to some extent arbitrary [17], we chose a value of ALT>60 U/l because it is the threshold over which clinical action is usually considered [9,17]. On the basis of BMI, subjects were classified as under- and normal-weight (≤24.9 kg/m^2), pre-obese (25.0≤BMI≤29.9 kg/m^2) and obese (≥30.0 kg/m^2) [17]. (Since the prevalence of elevated ALT was the same in under- and normal-weight subjects, the two classes were pooled). Age was initially analyzed as quartiles but because the odds ratios (ORs) of the second, third and fourth quartiles were similar, further analyses were performed comparing the subjects in the first quartile (18–29 years) vs. the remaining ones (≥30 years). Based on the results of the Dionysos study [14,15], ethanol intake was dichotomised in ≤30 g day^{-1} vs. >30 g day^{-1}. Coffee intake was initially analysed as quartiles but, due to the lack of a trend, it was dichotomised (yes/no) for further analysis. Drug consumption was coded as the consumption of any drug (yes/no), pill included. Smoking was initially analysed as quartiles of smoked cigarettes but, due to the lack of a trend, it was dichotomised (yes/no) for further analyses. ORs and 95% confidence intervals (CIs) were computed and goodness of fit was assessed using the Hosmer–Lemeshow statistic [18]. The sensitivity (SN) and specificity (SP) of each model were calculated and ROC curves were drawn by plotting SN vs. (1−SP) [19]. Paired comparisons of ROC curves were performed with the Venkatraman–Begg procedure [20]. Statistical significance was set to a value of $p<0.05$ for all tests. Statistical analysis was performed using SPSS 11.0 (SPSS, Chicago, IL, USA).

3. Results

The characteristics of the study subjects are given in Table 1.

The median age of the subjects was 42 years, with males slightly older than females ($p=0.032$). ALT, BMI and ethanol intake were higher in males than females ($p<0.0001$). Males smoked in greater number than females ($p<0.0001$) but there was no difference in coffee consumption ($p=0.565$). Mainly on account of the use of the pill, females took drugs more frequently than males ($p<0.0001$). Males tested positive for HbsAg more frequently than females ($p=0.002$) but the frequency of anti-HCV positivity was the same ($p=0.148$).

The univariable contributions of the variables of interest to elevated ALT are given in Table 2.

Male sex was a significant predictor of elevated ALT (OR=3.0, 95% CI=2.2–4.0). Subjects aged ≥30 years had an OR of 1.7 (95% CI=1.2–2.4) for elevated ALT. Pre-obese subjects had an OR of 2.6 (95% CI=1.9–3.5) for elevated ALT, a value that increased to 3.9 (95% CI=2.6–5.8) in obese subjects. Individuals consuming more than 30 g day^{-1} of ethanol had an OR of 3.3 (95% CI=2.5–4.3) for elevated ALT. Furthermore, HbsAg positivity (OR=2.9, 95% CI=1.4–6.2) and anti-HCV positivity (OR=9.0, 95% CI=6.3–12.9) were significant predictors of elevated ALT. Neither coffee consumption (OR=1.0, 95% CI=0.7–1.4) nor drug consumption (OR=1.0, 95% CI=0.7 to 1.3) were associated with elevated ALT. Smoking was however a predictor of elevated ALT (OR=1.5, 95% CI=1.1–1.9).

The accuracy of significant predictors, as determined by ROC curves, ranged between 0.54 (95% CI=0.51–0.58)

Table 1
Characteristics of the study subjects

	All (6315)	F (3352)	M (2963)	p* F vs. M
Age (years)	42 (24)	42 (23)	43 (24)	0.032
ALT (U/l)	19 (14)	16 (10)	24 (15)	<0.0001
BMI (kg/m^2)	24.5 (5.2)	23.3 (5.3)	25.4 (4.3)	<0.0001
Ethanol intake (g day^{-1})	8 (24)	1 (16)	21 (42)	<0.0001
Smokers (%)	43.8	33.5	55.5	<0.0001
Coffee drinkers (%)	77.6	77.9	77.3	0.565
Drug users (%)	47.0	57.8	34.9	<0.0001
HbsAg positivity (%)	1.3	0.9	1.8	0.002
Anti-HCV positivity (%)	3.5	3.8	3.1	0.148

Continuous variables are given as medians and interquartile ranges (between parentheses). Abbreviations: F=females; M=males; ALT=alanine aminotransferase, BMI=body mass index; HbsAg=hepatitis B surface antigen; anti-HCV=antibodies against hepatitis C virus.
* Mann–Whitney *U*-test for continuous variables and Fisher's Exact test for ordinal variables.

for age and 0.64 for BMI (95% CI=0.60–0.68) (Table 2). Thus, as determined by ROC curves, BMI was the best univariable predictor of increased ALT, although its accuracy was not very high in absolute terms. Even if HbsAg positivity was a significant predictor of elevated ALT, its low prevalence (1.3%) was responsible for a low accuracy (AUC=0.51, 95% CI=0.47–0.55).

When the significant predictors were entered in a multivariable model, both age (OR=0.8, 95% CI=0.6–1.2) and smoking (OR=1.1, 95% CI=0.6–1.2) were no longer significant. The final model, based on sex, BMI, ethanol intake, HbsAg status and anti-HCV status, is given in Table 3.

The model fitted well (p=0.697, Hosmer–Lemeshow test) and its accuracy was good [area under the ROC curve (AUC)=0.77; 95% CI=0.74–0.80, p<0.0001] and greater than that of the univariable BMI model (ΔAUC=+0.13, p<0.0001) (Fig. 1).

Table 2
Univariable prediction of alanine transaminase ≥60 U/l

Predictor	%	OR (95% CI)	p OR	AUC (95% CI)	p AUC
Sex					
Female	53.1	1			
Male	46.9	3.0 (2.2–4.0)	<0.0001	0.63 (0.59–0.66)	<0.0001
Age (years)					
18–29	26.1	1			
≥30.0	73.9	1.7 (1.2–2.4)	0.005	0.54 (0.51–0.58)	0.029
BMI (kg/m^2)					
<24.9	55.2	1			
25.0–29.9	35.3	2.6 (1.9–3.5)	<0.0001		
≥30.0	9.5	3.9 (2.6–5.8)	<0.0001	0.64 (0.60–0.68)	<0.0001
Ethanol (g day^{-1})					
0–30	77.6	1			
>30	22.4	3.3 (2.5–4.3)	<0.0001	0.63 (0.59–0.67)	<0.0001
HbsAg					
Negative	98.7	1			
Positive	1.3	2.9 (1.4–6.2)	0.004	0.51 (0.47–0.55)	0.549
Anti-HCV					
Negative	96.5	1			
Positive	3.5	9.0 (6.3–12.9)	<0.0001	0.59 (0.55–0.63)	<0.0001
Coffee					
No	22.4	1			
Yes	77.6	1.0 (0.7–1.4)	0.912	0.50 (0.46–0.50)	0.937
Drugs					
No	53.0	1			
Yes	47.0	1.0 (0.7–1.3)	0.844	0.50 (0.47–0.54)	0.865
Smoking					
No	56.2	1			
Yes	43.8	1.5 (1.1–1.9)	0.004	0.55 (0.51–0.59)	0.014

Abbreviations: OR=odds ratio; AUC=area under ROC curve; BMI=body mass index; HbsAg=hepatitis B surface antigen; anti-HCV=antibodies against hepatitis C virus.

Table 3
Multivariable prediction of alanine transaminase ≥60 U/l

Variable	β	S.E.(β)	p	OR (95% CI)
Sex (M)	0.726	0.178	<0.0001	2.1 (1.5–2.9)
25.0≤BMI≤29.9 kg/m^2	0.680	0.164	<0.0001	2.0 (1.4–2.7)
BMI≥30.0 kg/m^2	1.145	0.210	<0.0001	3.1 (2.1–4.7)
Ethanol (≥30 g day^{-1})	0.704	0.162	<0.0001	2.0 (1.5–2.8)
HbsAg (positive)	1.130	0.391	0.004	3.1 (1.4–6.7)
Anti-HCV (positive)	2.332	0.194	<0.0001	10.3 (7.0–15.1)

Abbreviations: β=regression coefficient; S.E.(β)=standard error of regression coefficient; OR=odds ratio; 95% CI=95% confidence interval.

4. Discussion

The present study aimed to establish the relative contribution of BMI, sex, age, ethanol intake, HBV and HCV infection, coffee and drug consumption, and cigarette smoking to elevated ALT in the general population.

Owing to the high prevalence of overweight (44.8%) in the Dionysos population, BMI was the best single predictor of elevated ALT. Sex, ethanol intake >30 g day^{-1}, anti-HCV and HbsAg positivity, smoking and age were also significant predictors at univariable analyses but coffee and drug consumption were not. At multivariable analysis, however, only BMI, sex, ethanol consumption, HbsAg and anti-HCV were associated with increased ALT levels. Not surprisingly [9], ethanol consumption, HbsAg status and anti-HCV status were predictors of increased ALT in the Dionysos population. However, drug consumption was not and we were not able to confirm that cigarette smoking is a risk factor [12] and coffee consumption a protective factor [13] for increased ALT.

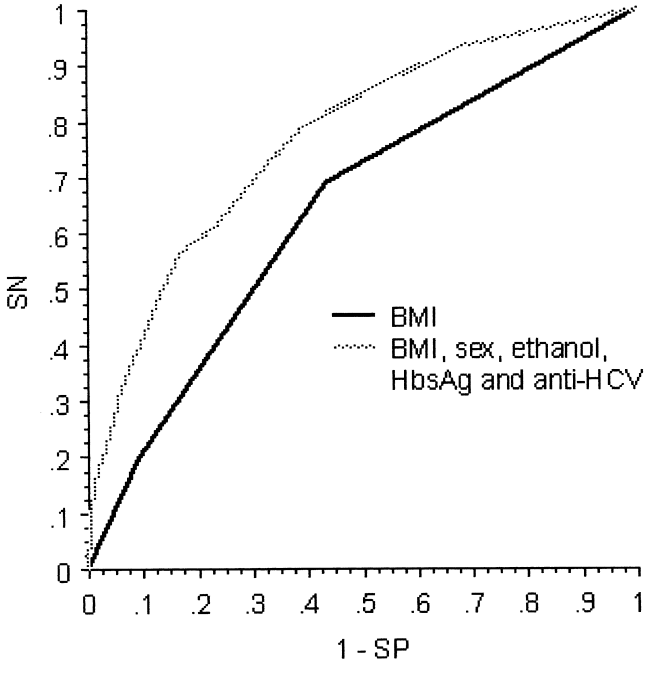

Fig. 1. Accuracy in detecting alanine transaminase >60 U/l achieved by body mass index alone and in combination with sex, ethanol consumption, hepatitis B surface antigen and antibodies against hepatitis C virus. Abbreviations: SN=sensitivity; SP=specificity; BMI=body mass index; HbsAg=hepatitis B surface antigen; anti-HCV=antibodies against hepatitis C virus.

It is noteworthy that the contribution of ethanol to increased ALT was lower than that of BMI both in univariable and multivariable models. This is in agreement with the longitudinal findings of others [10] and supports, albeit indirectly, our previous observation that being overweight is more important than alcohol intake in increasing liver enzymes and promoting fat accumulation in the liver [15].

The main strength of the present study is that it was performed on the general population. Even if the studied population was not intended to be representative of the entire Italian population, it is expected to offer more generalizable findings than those obtained in blood donors, employees and workers [1–6]. As compared to the only available study performed on a representative sample of the general population [7,8], the present study took into account also the effects of HBV and HCV infection. In the Dionysos population, both these factors contributed significantly to elevated ALT.

In conclusion, BMI is a significant predictor of elevated ALT in the general population of Northern Italy and it is a stronger predictor than alcohol intake. However, consideration of sex, ethanol intake, HbsAg status and anti-HCV status together with BMI increases substantially the ability of detecting elevated ALT in this population.

Conflict of interest statement

None declared.

List of abbreviations

ALT, alanine transaminase; Anti-HCV, antibodies against hepatitis C virus; AUC, area under the curve; BMI, body mass index; ELISA, enzyme-linked immunosorbent assay; HbsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio.

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