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Correlation Between Serum Alanine Aminotransferase Activity and Age: An Inverted U Curve Pattern

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BACKGROUND: Alanine aminotransferase (ALT) activity is the most widely used laboratory test for the recognition of liver disease. Normality limits for values of serum ALT activity have been questioned lately. One reason for this recent uncertainty may be an unrecognized decline in aminotransferase levels in the aging population.

AIMS: Cross-sectional evaluation of the association between age and ALT activity.

METHODS: Laboratory data of residents in single home for the aged and of adult subjects in three general practice clinics in Jerusalem, Israel were reviewed, excluding subjects with known liver disease. A single laboratory performed all the tests. We examined the associations of serum aminotransferase levels with age, sex, body-mass-index (BMI), and estimated glomerular filtration rate (GFR). Polynomial regression and analysis of variance (ANOVA) with corrections for multiple comparisons were utilized for the statistical analyses.

RESULTS: One hundred and twenty-eight individuals from the home for the aged and 207 individuals from three family practices were included. ALT activity *linearly* regressed with age ($r = 0.22$, $p < 0.0001$). However, *polynomial* regression revealed a better fit ($r = 0.33$, $p < 0.0001$), creating an inverted U curve with a peak at 40–55 yr. According to age groups, serum ALT level was 19 ± 13 U/L in those under 40 yr, 25 ± 19 U/L in 40–55 yr olds, 22 ± 10 U/L in 56–72 yr olds, 17 ± 9 U/L in 73–83 yr olds, and 13 ± 5 U/L in 83–100 yr olds ($p < 0.0001$). GFR ($r = 0.1$, $p < 0.05$) and BMI ($r = 0.14$, $p < 0.01$) weakly correlated with ALT. Gender also associated with ALT; 22 ± 15 U/L in men, and 17 ± 11 U/L in women ($p < 0.005$). Multiple regression analysis including age, gender, GFR, and BMI revealed that age ($p = 0.01$) and gender ($p = 0.04$) retained association with ALT activity. No such associations were noted for aspartate aminotransferase (AST) activity.

CONCLUSIONS; Our data suggest a significant association between age and serum ALT activity. This association is not a simple linear correlation, but rather an inverted-U-like relation. Thus, when interpreting the laboratory results of a subject suspected of liver disease, age should probably be taken into account. Larger-scale studies are needed to better characterize this issue.

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INTRODUCTION

Alanine aminotransferase (ALT) activity is the most widely used laboratory parameter in evaluation of liver disease. Thus, determination of the true normal ranges of ALT activity is of utmost importance for screening of large populations and for recognition of occult liver abnormalities. Normality definitions of serum ALT activity have been re-examined lately (1–5). Wejstål and coworkers (2) as well as Piton and colleagues (3) suggested that ALT activity is independently related to body-mass-index (BMI) and gender. Prati and associates (4) confirmed this finding, and also indicated a relation of ALT with indicators of abnormal lipid and carbohydrate metabolism. The latter may be more abundant today than when Karmen and colleagues (1) set the normal range for ALT activity in the 1950s. Another possible reason for the recent uncertainty regarding normal ALT values may be an unrecognized change in aminotransferase levels in the aging population. The aim of the current study was to examine the association between age and ALT activity in this age group.

METHODS

Patients

Laboratory data of residents in single home for the aged and of adult (≥18 yr) subjects in three general practice

The first two authors contributed equally to this study.

clinics in Jerusalem were retrospectively reviewed. Individuals with known or suspected (according to their primary-care physician) to have liver disease and those taking hepatotoxic medications were excluded. Blood tests from the elderly subjects were collected as part of a mandatory routine, while the tests of the individuals in the general practice clinics were ordered for various indications, but none for suspected liver disease. Other data collected included age, gender, BMI, serum creatinine, and total cholesterol. Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) equation (6). We examined the associations of serum aminotransferase levels with age, gender, BMI, and estimated GFR. Age was treated as continuous variable, but also as an ordinal variable. The latter was achieved by splitting our subjects into five age groups.

Serum Liver Enzyme Levels

Serum for ALT and aspartate aminotransferase (AST) activity and cholesterol measurement was obtained in glass tubes, centrifuged and analyzed on the day of sampling using a Kone Progress Selective Chemistry Analyzer. All serum samples were processed in the same laboratory using the same methods and the same reference values. The "normal" upper thresholds for ALT activity in this laboratory was 42 U/L and 32 U/L for males and females, respectively, while normal AST activity was 40 U/L and 30 U/L for males and females, respectively.

Statistical Analysis

Linear, polynomial, and multiple regressions, as well as *t*-tests, χ^2, and analysis of variance (ANOVA) with corrections for multiple comparisons (Bonferroni) were utilized for the statistical analyses, as appropriate. Two-sided $p < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the Two Patient Subgroups

Included in the study were 128 subjects from the home for the aged ("older subgroup"), and 207 subjects from three general practice clinics ("younger subgroup"). The basic anthropometrical and laboratory characteristics of the study population are displayed in the Table 1. Mean ALT and AST activity levels were significantly lower in the older subgroup as compared to the younger subgroup, $p < 0.0001$ and $p < 0.01$, respectively. While among the younger subgroup neither ALT ($r = 0.03$, $p = 0.7$) nor AST ($r = 0$, 1, $p = 1$) activities were linearly correlated with age (although a weak second-order polynomial regression was significant for ALT, not shown), in the older subgroup ALT activity had a significant negative correlation with age ($r = 0.39$, CI $= -0.53$ to -0.24). No significant correlation was found between BMI or total serum cholesterol and ALT activity in either subgroup. Gender significantly associated with ALT activity only in the older subgroup, in which men's ALT activity was 18 ± 11 U/L and women's ALT activity was 14 ± 7 U/L ($p < 0.05$, data not shown).

Characteristics of the Combined Patient Group

We next analyzed the variables affecting ALT activity in the combined study population. ALT had a right-tailed, normal-appearing distribution (Fig. 1). ALT activity *linearly* regressed with age ($r = 0.22$, $p < 0.0001$). However, *polynomial* regression revealed a better-appearing fit ($r = 0.33$, $p < 0.0001$), creating an inverted U curve with a peak at 40–55 yr (Fig. 2). According to age groups, serum ALT level was 19 ± 13 U/L in those under 40 yr, 25 ± 19 U/L in 40–55 yr olds, 22 ± 10 U/L in 56–72 yr olds, 17 ± 9 U/L in 73–83 yr olds, and 13 ± 5 U/L in 83–100 yr olds (ANOVA, $p < 0.0001$) . GFR ($r = 0.1$, $p < 0.05$) and BMI ($r = 0.14$, $p < 0.01$) weakly correlated with ALT activity. Gender also influenced ALT; 22 ± 15 U/L in men, and 17 ± 11 U/L in women ($p < 0.005$). Multiple regression analysis including age-squared, gender, GFR, and BMI revealed that age-squared ($p = 0.003$) and gender ($p = 0.03$) retained association with ALT activity. No such associations were noted for AST activity.

DISCUSSION

In this study comprising two different groups of Jerusalem residents, serum ALT activity was significantly correlated with age. However, whereas in the younger members of general practice clinics, ALT activity had no linear correlation with age, it negatively correlated with age in the elderly inhabitants of a home for the aged. Overall, the best fitting

Table 1. Basic Anthropometrical and Laboratory Characteristics of the Study Population

	All Subjects (n = 335)	Home-for-the-Aged Subgroup (n = 128)	Community Subgroup (n = 207)
Age (yr)	65 ± 22	84 ± 8	$52 \pm 19^{**}$
Sex, % female	65	73	58^{*}
BMI (kg/m^2)	26.3 ± 4.4	24.6 ± 4.6	$27.2 \pm 4.1^{**}$
GFR (mL/min/1.73 m^2)	74 ± 19	67 ± 17	$78 \pm 19^{**}$
Cholesterol	206 ± 45	212 ± 41	203 ± 47
AST (U/L)	20 ± 11	18 ± 6	$22 \pm 13^{*}$
ALT (U/L)	19 ± 13	15 ± 9	$21 \pm 14^{**}$

$^{*}p < 0.01$ for the comparison between the older and younger subgroups.
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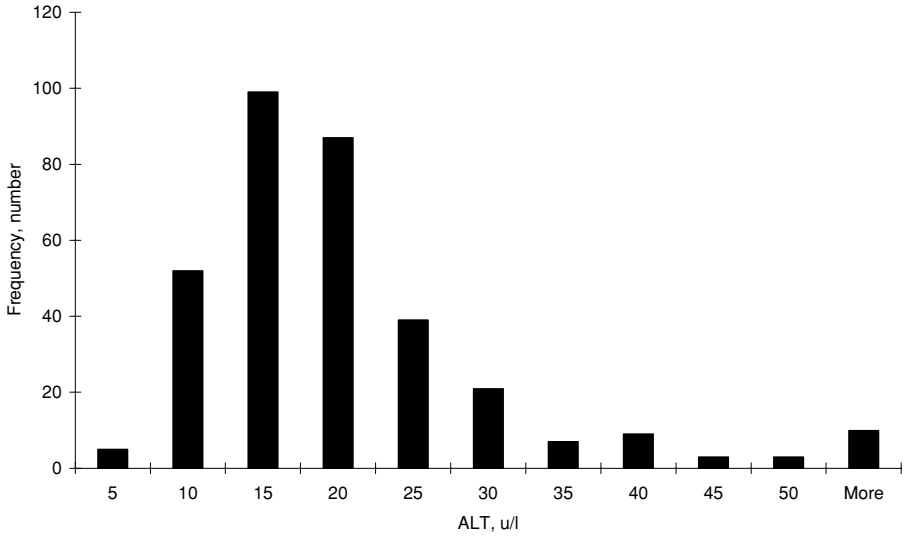

**P<0.0001 for the comparison between the older and younger subgroups

Figure 1. Distribution of ALT activity according to the different age groups of the study population.

curve for the association of ALT with age was shaped as an inverted-U, peaking before 50 yr.

Several studies demonstrated significant associations of ALT with several anthropometrical variables. Wejstål and coworkers evaluated Swedish blood donors (2). They observed a higher weight and a higher percentage of males in donors with elevated ALT activity. BMI and male gender were independently correlated with ALT activity in French donors, as well (3). The authors recommended four different limits of upper normal ALT value based on gender and BMI. In a retrospective cohort study, Prati and colleagues evaluated Milanese blood donors for the presence of HCV infection (4). In multivariate analysis, BMI and triglyceride levels were related to ALT activity in both the sexes. Age association with ALT activity was found in males, but not in females.

The results of our study differ from the above reports in that we found age to be more consistently associated with ALT activity than BMI. In multivariate analysis BMI did not significantly relate to ALT, whereas the relation of gender with ALT activity ($p = 0.04$) appeared weaker than that of age and ALT activity ($p = 0.01$). Possible explanations for our unique finding include: (1) the unselected nature of our population, as opposed to blood donors, (2) the older age of our subjects, as compared to those studied above, (3) the low incidence of alcohol consumption in our population(7), which may weaken the association of ALT activity with BMI and gender. Additionally, previous studies may have not considered the nonlinear relation of ALT with age, thereby overlooking a significant correlation. The major limitations of our study are its relatively small subject population, and the

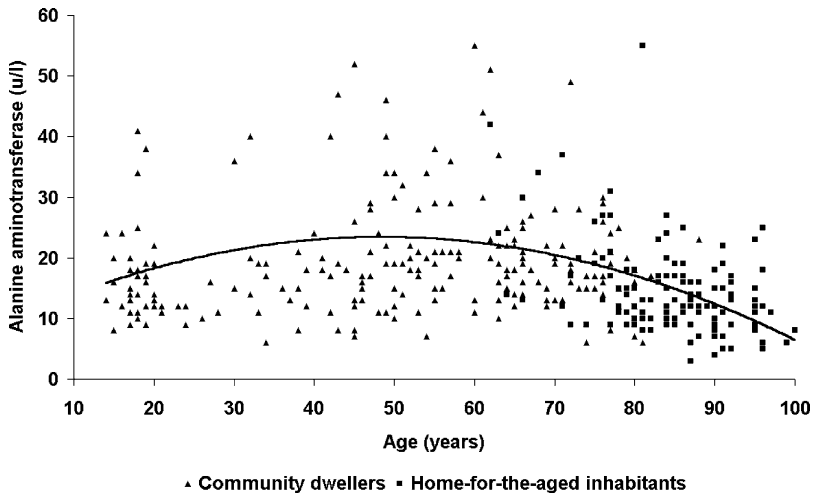

Figure 2. Correlation between ALT activity and age confers to an inverted U curve pattern, with peak at 40–55 of age.

method of subject inclusion. However, significant findings (which do not qualitatively contradict those of previous studies) were noticed despite these limitations, thus dictating the need for a larger scale evaluation of this issue.

In conclusion, the redefinition of upper limit of serum ALT activity has implications for the screening of blood donors, for evaluating subjects with suspected liver disease, and for the assessment of the response to treatment in patients with established liver disease. Our study suggests a nonlinear association of ALT level with age, with a peak value between 40 and 55 yr. Further studies are needed to evaluate the clinical significance of this finding.

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