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Serum Levels of Alanine Aminotransferase Decrease with Age in Longitudinal Analysis

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Abstract

Background & Aims—An increased level of alanine aminotransferase (ALT) is a marker of liver injury. The mean ALT level has been reported to decrease with age; we performed a longitudinal analysis to determine whether serum levels of ALT changes with age among community-dwelling, older adults in the US.

Methods—We analyzed clinical data from 2 cohorts of individuals who participated in the Rancho Bernardo Study, in Southern CA. The first cohort comprised 1073 community-dwelling participants (59% women); clinical data was collected from 1984 to 1987 and 1992 to 1997. The second cohort comprised 416 participants (64% women); data was collected from 1984 to 1987, 1992 to 1997, and 1997 to 1999. Demographic, metabolic covariates, ALT, bilirubin, and albumin were measured. Changes in individual ALT over time were examined in unadjusted and multivariable-adjusted linear and logistic regression analyses.

Results—At the baseline visit, the patients' mean age was 65.7 years and body mass index was 24.9 kg/m². In cohort 1, the mean levels of ALT decreased with age by 10% (from 21 to 19 IU/L) between the time periods of 1984–1987 and 1992–1997 ($P<.0001$). In cohort 2, they decreased by 20% (from 20 to 16 IU/L) between the time periods of 1984–1987 and 1997–1999 ($P<.0001$). Categorically-defined increases in ALT also decreased with age ($P<.0001$). Results remained consistent in sex-specific analyses and after adjusting for metabolic syndrome components, alcohol use, bilirubin, and serum levels of albumin ($P<.0001$).

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Conclusions—In a longitudinal analysis, we observed that levels of ALT decrease with age, independent of sex, metabolic factors, alcohol use, and results from commonly used liver function tests (bilirubin and albumin). When interpreting serum levels of ALT, physicians should consider patients' age especially in elderly.

Keywords

alanine aminotransferase; age; aging; population study; epidemiology; serum transaminase; liver damage; diagnostic; elderly

INTRODUCTION

Serum alanine aminotransferase (ALT) level is an often used surrogate marker for hepatocyte injury. Normal ranges have historically been set at around 40 IU/L, but data suggest that the upper limits of normal should be lowered to <30 IU/L for men and <19 IU/L for women. (1) Many other factors have also been shown to influence ALT levels. Most of these are features related to the metabolic syndrome, including body mass index, waist-hip ratio, dyslipidemia, and glucose intolerance. (2–13) The relationship between ALT and age, however, remains somewhat ambiguous.

Traditionally, age has been considered to have no effect on serum ALT levels. (14) Studies done over the past decade have shown conflicting results. A study in healthy Iranian blood donors found no correlation between ALT and age (15), but others have reported that the prevalence of elevated ALT decreases with increasing age. (4,6–8,10,11,16) Most of these studies were performed using retrospective chart reviews of patients who had laboratory tests for medical reasons, in self-selected populations (such as blood donors), or in Asian populations, whose liver function may differ compared to Western populations.

Population based studies of ALT and age have been reported. In the United States National Health and Nutrition Examination Surveys (4,6,7), increased age was associated with a decreased prevalence of elevated ALT. A recent study of community dwelling older men from Australia showed that older participants had lower ALT levels. (17) In our previous cross-sectional analysis of the Rancho Bernardo Cohort (community dwelling participants residing in Southern California), we showed that older age was associated with decreased ALT, independent of sex, alcohol use, metabolic covariates, and surrogate markers of liver function. (18) All of the prior studies, however, were cross-sectional, with the potential for survivor bias. Thus, the question still remained whether a given individual's ALT decreases with age. To the best of our knowledge, this is the first longitudinal, population-based study to examine changes in ALT with age.

METHODS

Study Cohort and Setting

Utilizing a prospective cohort study design, we conducted a longitudinal analysis of participants from the Rancho Bernardo Study (RBS) cohort. The RBS cohort was established in 1972, when 82% of residents of a geographically defined suburban Southern California community were recruited to study risk factors for heart disease. The details of the cohort, selection criteria, and purpose of the RBS have been published. (19,20) The RBS cohort is almost entirely Caucasian of European ancestry, most with at least some college education, largely white-collar workers. From this population, we selected two cohorts, based upon available serum ALT data. The first (cohort 1) consisted of the 1073 participants who had available clinical and laboratory data from two research clinic visits in 1984–1987 and 1992–1997. The second (cohort 2) consisted of 416 participants who had available data

from three visits, 1984–1987, 1992–1997, and 1997–1999. All participants gave written informed consent; the study was approved by the institutional review board of the University of California, San Diego.

Clinical and Laboratory Assessment

During each research clinic visit, a trained interviewer obtained the medical history and recorded current medications, examining pills and prescriptions brought to the clinic for that purpose. Participants were asked if they had a history of chronic liver disease. Weight was acquired with participants wearing light clothing and no shoes. Height, waist and hip circumference, and systolic blood pressure were obtained in clinic by trained investigators. Blood pressure was averaged from two morning readings with the participant resting in a seated position. Blood pressure was measured using a regularly calibrated mercury sphygmomanometer, per Hypertension Detection and Follow-up Program protocol. (21) Alcohol use amount, type, and frequency, was self-reported and indirectly validated by showing a similar quantitative response to a nutritionist interviewer who obtained alcohol intake as part of a separate food-frequency questionnaire. One alcoholic drink was defined as 10g of alcohol.

Fasting venous blood was obtained during the research clinic visit. Serum ALT, bilirubin, and albumin were measured by spectrophotometry. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured using enzymatic methods in a Lipid Research Clinic-certified laboratory. Fasting glucose was analyzed using the glucose-oxidase method. Diabetes was defined as a fasting glucose $\geq 126\text{mg/dL}$ ($\geq 7\text{mmol/L}$), post challenge oral glucose tolerance test $\geq 200\text{mg/dL}$, or treatment with a diabetes medication.

History of chronic liver disease was based upon participant self-report by a standard question about the presence or absence of history of chronic liver disease.

Elevated ALT was defined a priori as an ALT $\geq 30\text{ IU/L}$ for men and $\geq 19\text{ IU/L}$ for women as proposed by Prati et al. (1)

Statistical Analysis

Serum ALT, bilirubin, and triglycerides were log transformed for statistical analyses to fulfill conditions of normality. Paired t tests were used to examine changes over time for each individual's body mass index (BMI), waist-hip ratio, systolic blood pressure, total cholesterol, HDL cholesterol, triglycerides, bilirubin, albumin, and log transformed ALT. The Wilcoxon signed rank sum test was used to compare actual (non log transformed) ALT values. McNemar test or Bowker's Test of Symmetry was used for categorical comparisons of elevated ALT, diabetes, and alcohol use. P values were obtained for the comparison between 1984–1987 and 1992–1997 visits in cohort 1 and between the 1984–1987 and 1997–1999 visits in cohort 2. Multivariate hierarchical models were used to examine the change of ALT over time that included: 1. Unadjusted, 2. Multiply adjusted for sex, BMI, systolic blood pressure, alcohol use, waist-hip ratio, diabetes, fasting glucose, total cholesterol-HDL cholesterol ratio, and triglycerides, and 3. Multiply adjusted for the above plus two commonly used liver function tests, bilirubin and albumin. P values for trend were analyzed. Similar analyses were performed after excluding participants who had a history of chronic liver disease. The prevalence of elevated ALT over time was examined using the generalized estimating equations approach. Statistical analyses were conducted using SAS version 9.2, SAS Institute, Cary, NC.

RESULTS

Population Characteristics

Characteristics of the 1073 participants in cohort 1 (59% women) and 416 participants in cohort 2 (64% women) are shown in tables 1 and 2, respectively. For cohort 1, the mean (range) age was 65.7 years (30–89) during the 1984–1987 visit and 74.1 years (37–96) during the 1992–1997 visit. For cohort 2, the mean (range) age was 69.2 years (53–85) during the 1984–1987 visit, 77.6 years (60–92) during the 1992–1997 visit, and 82.1 years (65–96) during the 1997–1999 visit. For both of the cohorts, as age increased, so did waist-hip ratio, systolic blood pressure, triglycerides, bilirubin, and prevalence of diabetes. Serum albumin decreased with increasing age. The proportion of participants who drank moderate to heavy amounts of alcohol (≥ 1 drink per day) also decreased with age. For cohort 1, BMI and total cholesterol to HDL cholesterol ratio increased with age. For cohort 2, BMI and total cholesterol to HDL cholesterol ratio increased from the 1984–1987 visit to the 1992–1997 visit, but subsequently declined from the 1992–1997 visit to the 1997–1999 visit. Sixty participants (5.6%) in cohort 1 and 27 participants (6.5%) in cohort 2 self reported a history of chronic liver disease.

ALT Decreases With Age

In cohort 1 (comparing 1984–1987 and 1992–1997 visits), the mean ALT decreased from 21 IU/L to 19 IU/L (10% decline, $p < 0.0001$). This represented a decrease from 23 IU/L to 19 IU/L in men (17% decline, $p < 0.0001$), and from 19 IU/L to 18 IU/L in women (5% decline, $p < 0.0001$). In cohort 2 (comparing 1984–1987 and 1997–1999 visits), the mean ALT decreased from 20 IU/L to 16 IU/L (20% decline, $p < 0.0001$), with a decrease from 20 IU/L to 18 IU/L in men (10% decline, $p < 0.0001$) and a decrease from 19 IU/L to 15 IU/L in women (21% decline, $p < 0.0001$). (See figure 1) After excluding participants with a history of chronic liver disease (5.6% of participants in cohort 1 and 6.5% of participants in cohort 2), the trend of decreasing ALT with age remained significant, with a decline from 18 IU/L to 16 IU/L in cohort 1 and from 18 IU/L to 15 IU/L in cohort 2 (both $p < 0.0001$).

Prevalence of Elevated ALT Decreases With Age

Elevated ALT was defined as ALT ≥ 30 IU/L for men and ≥ 19 IU/L for women. Using these criteria, the prevalence of elevated ALT decreased from 31% during the 1984–1987 visit to 19% during the 1992–1997 visit ($p < 0.0001$) for cohort 1. For cohort 2, the prevalence of elevated ALT dropped from 30% in 1984–1987 to 17% in 1992–1997 and 14% in 1997–1999 ($p < 0.0001$). (See figure 2) After exclusion of participants with self reported chronic liver disease, this trend remained highly significant, with a decline from 31% to 19% in cohort 1 and a decline from 30% to 19%, then to 15% in cohort 2 (both $p < 0.0001$).

Multivariate Analyses

The trend of decreasing ALT with age persisted after multivariable adjustment for sex, BMI, systolic blood pressure, alcohol use, waist-hip ratio, diabetes, fasting glucose, total cholesterol to HDL ratio, triglycerides ($p < 0.0001$), and after multivariable adjustment for the above plus two commonly used surrogates of liver function (bilirubin and albumin) ($p < 0.0001$) (See Table 3). Further, after excluding participants with a history of chronic liver disease, the trend of decreasing ALT with age remained significant both in unadjusted and in multivariable adjusted analyses ($p < 0.0001$) (See Table 4). The decline in prevalence of elevated ALT also remained significant after the above multivariable adjustments ($p < 0.0001$) both including and excluding those with self-reported chronic liver disease (supplementary online Table A).

DISCUSSION

In this longitudinal, population-based, community-dwelling cohort of older men and women residing in Southern California, both absolute ALT levels and prevalence of categorically-defined elevated ALT decreased with age, independent of factors found in other studies to influence ALT levels (sex, alcohol use, BMI, waist-hip ratio, diabetes, fasting glucose, total cholesterol to HDL ratio, triglycerides) (1,4–11) and markers of liver function (bilirubin and albumin). In our previous cross-sectional study of this cohort¹⁸, we showed that ALT was lower in older age groups. This is the first prospective study to show that each given individual's ALT actually declines over time with age independent of sex, BMI, alcohol use, hypertension, diabetes and dyslipidemia as well as liver function tests (including bilirubin and albumin).

In considering potential explanations for a decreasing ALT with age, the possibility of changing prevalence of liver disease was explored. Analysis of our cohort showed that waist-hip ratio, systolic blood pressure, triglycerides, and prevalence of diabetes all increased with age, suggesting that the prevalence of the metabolic syndrome and non-alcoholic fatty liver disease (NAFLD) may increase as well. Although ALT is an imperfect surrogate for histology in NAFLD (22,23), a rising ALT would be consistent with this hypothesis. Information regarding viral hepatitis was not available in our study cohort, therefore these participants could not be excluded, however, analyses conducted excluding the approximately 5–7% of participants who reported a history of chronic liver disease did not materially change the results. Moderate to heavy alcohol consumption (≥ 1 drink/day) decreased with age, which could lead to lower ALT. Multivariable analyses controlling for metabolic syndrome components and alcohol use did not change the significant trend of decreasing ALT with age, indicating that the decline in ALT was not explained by these factors.

Decreasing ALT may reflect a decrease in the mass or function of the aging liver, supported by the observation that albumin levels decrease and bilirubin levels somewhat increase with age. By animal studies, older livers have slower and weaker regenerative capacity, reduced organ weight, a lower inflammatory response rate, and increased fibrosis when compared to younger livers. (24–26) In humans, older livers progressively decrease in size and blood flow, and show changes presumably related to accumulation of oxidative stress. (27–29) However, bilirubin and albumin are also complex biomarkers and do not solely reflect hepatic function. Furthermore, in our study, decreasing ALT with age remained after adjusting for bilirubin and albumin.

Elinav et al. (30) and Le Couteur et al. (17) have reported that an ALT value below the median is a strong and independent predictor of mortality in community-dwelling elderly men. Our study finding of decreasing ALT with age independent of metabolic syndrome components, alcohol use, and other surrogates of liver function (bilirubin and albumin) also suggests that ALT may perhaps be a new biomarker of aging, and perhaps, independent of liver function.

We acknowledge following limitations of this study. The true prevalence of chronic liver disease in the Rancho Bernardo Study cohort is unknown. It is possible that this could potentially have an effect on the true gradient of decline with aging. Furthermore, the potential effect of survivor bias on ALT trends is uncertain. We also acknowledge that ALT decline with aging are small and exact clinical significance remains to be explored.

CONCLUSIONS

In conclusion, ALT levels decrease with age for both men and women, independent of metabolic traits, alcohol use, and other markers of hepatic function. As a result, the prevalence of elevated ALT also declines with age. Whether this decline correlates with a loss of hepatocyte mass or function remains to be determined, but our findings may suggest that ALT is an independent biomarker of aging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ALT	alanine aminotransferase
RBS	Rancho Bernardo Study
HDL	high-density lipoprotein
BMI	body mass index
NAFLD	non-alcoholic fatty liver disease
CI	confidence interval

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Figure 1a

ALT Decreases With Aging: Cohort 1

Figure 1b

ALT Decreases With Aging: Cohort 2 **Figure 1. ALT Decreases With Age**

ALT decreases with age for both men and women in cohort 1 (1073 participants between 1984–1987 and 1992–1997) (figure 1a) and cohort 2 (416 participants between 1984–1987, 1992–1997, and 1997–1999) (figure 1b). P value in figure 1b represents comparisons between the 1984–1987 and 1997–1999 visits.

Figure 2. Prevalence of Elevated ALT Decreases With Age

The prevalence of elevated ALT decreases with age for cohort 1 (N=1073) as well as cohort 2 (N=416). P values are for trend.

Table 1

Characteristics of Cohort 1

	1992–1997 Visit	1984–1987 Visit	p ¹
Age (years) (mean [range])	65.7 (30–89)	74.1 (37–96)	
Women (%)	59	59	
BMI (kg/m ²)	24.9 (24.7–25.2)	25.2 (25.0–25.5)	<.0001
Waist-hip ratio	0.84 (0.83–0.84)	0.85 (0.84–0.85)	<.0001
Systolic blood pressure (mmHg)	133.4 (132.2–134.6)	139.0 (137.7–140.3)	<.0001
Total cholesterol (mg/dl)	221.6 (219.2–224.0)	206.9 (204.6–209.1)	<.0001
HDL cholesterol (mg/dl)	63.1 (62.0–64.2)	57.4 (56.4–58.4)	<.0001
Total/HDL cholesterol ratio	3.8 (3.7–3.9)	4.0 (3.9–4.0)	<.0001
†Triglycerides (mg/dl)	99.5 (96.3–102.8)	103.8 (100.6–107.1)	.0009
†Bilirubin (mg/dl)	0.48 (0.47–0.49)	0.68 (0.67–0.70)	<.0001
Albumin (g/dl)	4.4 (4.3–4.4)	4.1 (4.1–4.1)	<.0001
†ALT (IU/L)	18.1 (17.6–18.6)	16.2 (15.7–16.6)	<.0001
Men	20.0 (19.1–20.9)	17.7 (17.1–18.4)	<.0001
Women	16.9 (16.3–17.5)	15.2 (14.6–15.7)	<.0001
			p ²
ALT (IU/L)	20.6 (19.8–21.3)	18.5 (17.3–19.8)	<.0001
Men	22.6 (21.4–23.8)	19.3 (18.5–20.2)	<.0001
Women	19.1 (18.2–20.1)	18.0 (15.9–20.0)	<.0001
			p ³
Elevated ALT (%)	30.9	18.7	<.0001
Diabetes (%)	12.0	20.1	<.0001
Alcohol Use (%)			<.0001
None	34.5	33.2	
< 1 drink/day	21.3	35.9	
1–2 drinks/day	28.2	20.6	
> 2 drinks/day	16.1	10.4	

N = 1073

All values are presented as mean (95% confidence interval) unless otherwise stated

† Geometric means

p¹ - paired t-testp² - Wilcoxon signed rank sum testp³ - McNemar test (2×2) or Bowker's Test of SymmetryElevated ALT defined as ≥ 30 IU/L for men and ≥ 19 IU/L for women

Abbreviations in tables: BMI: body-mass-index, HDL: high-density-lipoprotein, ALT: alanine aminotransferase

Table 2

Characteristics of Cohort 2

	1984–1987 Visit	1992–1997 Visit	1997–1999 Visit	p ¹
Age (years) (mean [range])	69.2 (53–85)	77.6 (60–92)	82.1 (65–96)	
Women (%)	63.5	63.5	63.5	
BMI (kg/m ²)	24.8 (24.5–25.1)	25.0 (24.7–25.4)	24.8 (24.4–25.2)	.8355
Waist-hip ratio	0.83 (0.83–0.84)	0.84 (0.83–0.85)	0.86 (0.84–0.87)	<.0001
Systolic blood pressure (mmHg)	136.3 (134.6–138.0)	142.3 (140.3–144.3)	143.4 (141.3–145.5)	<.0001
Total cholesterol (mg/dl)	225.5 (221.5–229.4)	207.7 (204.1–211.2)	206.6 (202.9–210.3)	<.0001
HDL cholesterol (mg/dl)	64.1 (62.2–65.9)	58.7 (57.0–60.4)	58.7 (57.0–60.4)	.0208
Total/HDL cholesterol ratio	3.8 (3.7–3.9)	3.9 (3.8–4.0)	3.6 (3.5–3.7)	.0001
[†] Triglycerides (mg/dl)	99.9 (95.0–105.1)	102.2 (97.6–107.1)	107.2 (102.3–112.3)	.0013
[†] Bilirubin (mg/dl)	0.50 (0.48–0.52)	0.68 (0.66–0.70)	0.72 (0.70–0.74)	<.0001
Albumin (g/dl)	4.3 (4.3–4.4)	4.0 (4.0–4.1)	4.0 (4.0–4.1)	<.0001
[†] ALT (IU/L)	17.7 (16.9–18.4)	15.8 (15.2–16.4)	14.6 (14.0–15.2)	<.0001
Men	19.0 (17.9–20.2)	17.7 (16.6–18.7)	16.2 (15.2–17.3)	<.0001
Women	16.9 (16.0–17.9)	14.9 (14.2–15.6)	13.7 (13.0–14.4)	<.0001
				p ²
ALT (IU/L)	19.5 (18.5–20.4)	17.2 (16.4–17.9)	16.2 (15.0–17.3)	<.0001
Men	20.4 (19.1–21.7)	18.9 (17.7–20.2)	17.6 (16.4–18.9)	<.0001
Women	18.9 (17.7–20.2)	16.1 (15.2–17.1)	15.4 (13.7–17.0)	<.0001
				p ³
Elevated ALT (%)	30.3	17.4	14.4	<.0001
Diabetes (%)	13.2	22.4	23.8	<.0001
Alcohol Use (%)				<.0001
None	31.8	31.7	31.8	
< 1 drink/day	19.5	33.4	34.2	
1–2 drinks/day	33.0	24.7	27.0	
> 2 drinks/day	15.7	10.2	7.0	

N = 416

All values are presented as mean (95% confidence interval) unless otherwise stated

[†]Geometric means

P values are comparisons between 1984–1987 and 1995–1997 visits

p¹ - paired t-testp² - Wilcoxon signed rank sum testp³ - McNemar test (2×2) or Bowker's Test of SymmetryElevated ALT defined as ≥ 30 IU/L for men and ≥ 19 IU/L for women

Abbreviations in tables: BMI: body-mass-index, HDL: high-density-lipoprotein, ALT: alanine aminotransferase

Table 3

Unadjusted and Multivariate Adjusted Trends in ALT

Cohort 1 (N=1073)	1992–1997	1984–1987	1997–1999	P
Unadjusted ALT (IU/L)	18.1	16.2	NA	<.0001
[†] Multivariate adjusted (IU/L)	18.7	16.7	NA	<.0001
[†] Multivariate adjusted with addition of bilirubin and albumin (IU/L)	18.7	16.7	NA	<.0001
Cohort 2 (N=416)				
Unadjusted ALT (IU/L)	17.7	15.9	14.6	<.0001
[†] Multivariate adjusted (IU/L)	17.8	16.0	14.7	<.0001
[†] Multivariate adjusted with addition of bilirubin and albumin (IU/L)	17.7	15.9	14.6	<.0001

[†] Multivariate adjustment for sex, BMI, systolic blood pressure, alcohol use, waist-hip ratio, diabetes, fasting glucose, total-HDL ratio, triglycerides

Geometric means used for ALT, fasting glucose, triglycerides, and bilirubin

Table 4

Unadjusted and Multivariate Adjusted Trends in ALT After Exclusion of Participants With Self Reported Chronic Liver Disease

Cohort 1 (N=1013)	1992–1997	1984–1987	1997–1999	P
Unadjusted ALT (IU/L)	18.0	16.1	NA	<.0001
[†] Multivariate adjusted (IU/L)	18.7	16.8	NA	<.0001
[†] Multivariate adjusted with addition of bilirubin and albumin (IU/L)	18.7	16.8	NA	<.0001
Cohort 2 (N=389)				
Unadjusted ALT (IU/L)	17.5	16.0	14.7	<.0001
[†] Multivariate adjusted (IU/L)	17.7	16.1	14.9	<.0001
[†] Multivariate adjusted with addition of bilirubin and albumin (IU/L)	17.7	16.1	14.9	<.0001

[†] Multivariate adjustment for sex, BMI, systolic blood pressure, alcohol use, waist-hip ratio, diabetes, fasting glucose, total-HDL ratio, triglycerides

Geometric means used for ALT, fasting glucose, triglycerides, and bilirubin