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Serum alanine aminotransferase is correlated with hematocrit in healthy human subjects

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Abstract

Background—Serum alanine aminotransferase (ALT) activity is a widely-used surrogate marker for liver injury. However, mild elevation of serum ALT is frequently observed in apparently healthy individuals, making it sometimes challenging to interpret whether this laboratory abnormality is medically benign or serious. To obtain a better understanding of the factors influencing ALT levels, we examined the relation between ALT and a number of anthropometric and biochemistry measurements in humans.

Methods—We assessed the associations of ALT with hematocrit (HCT) in 1,200 apparently healthy adults from an Amish population. Multivariate analyses were carried out to determine whether observed associations were independent of other factors known to modulate ALT and HCT, including body mass index (BMI) and sex. The correlation detected in the Amish was then replicated in an independent population sample ($N = 9,842$) from the National Health and Nutrition Examination Survey (NHANES) III.

Results—ALT levels were positively correlated with HCT ($r = 0.33$, $p < 0.0001$) in both Amish and NHANES III. The magnitude of association was unchanged after adjustment for BMI, but was reduced by age/sex adjustment to $r = 0.18$ ($p < 0.0001$) and $r = 0.17$ ($p < 0.0001$) in the Amish and NHANES populations, respectively. HCT accounts for about 3% of the population variation in ALT, which is smaller than the contributions of gender and BMI, but larger than individual blood pressure and cholesterol components.

Conclusions—We observed a correlation between ALT and HCT, suggesting that HCT may be a newly identified modulator of ALT in humans.

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Keywords

Alanine transaminase; hematocrit; biological markers; association and humans

Introduction

Serum ALT level is traditionally a surrogate marker of liver injury [1–3]. However, ALT elevation is prevalent in the general population and is frequently observed in subjects without overt liver damage. For example, Clark et al. found that as many as 7.9% of the general population have elevated ALT and in the majority (69.0%) of the cases, the elevation cannot be explained by disease [4] and is considered asymptomatic [5]. At the population level, ALT levels have been associated with BMI, dyslipidemia, and hypertension [4], as well as other biomarkers, including GGT, uric acid, triglycerides, cholesterol and iron [4,6–8]. As a result, defining the upper limit of serum ALT levels is still a debatable issue in diagnosis [6].

Identifying additional ALT modulators may help to improve the diagnostic utility of ALT. In an exploratory analysis, we examined the relation between ALT and a number of anthropometric and blood chemistry variables in Old Order Amish of Lancaster PA [9], a population with a relatively homogenous genetic background and lifestyle with the rationale that less individual variation may increase the sensitivity to find new serum ALT modulators. The studied variables included hematocrit (HCT), a direct indicator of the volume of red blood cells and well-used marker for anemia and body fluid volume. However, its associations with parameters unrelated to red blood cells and body fluid have seldom been studied.

When we unexpectedly discovered the existence of a correlation between ALT and HCT in the Amish population, we attempted to replicate our result in a large population-based sample, the National Health and Nutrition Examination Survey (NHANES) III [10].

Methods

Amish study subjects

Subjects included in this study were relatively healthy adults of 20 years of age or older from the Amish population in Lancaster County, Pennsylvania who had participated in our previous studies of cardiovascular health [9,11]. Subjects were selected by design to be relatively healthy; study-wide exclusion criteria included: (1) age < 20 years, (2) currently pregnant or postpartum < 6 months, (3) blood pressure at the time of screening > 180/105 mm Hg, (4) coexisting malignancy, (5) ALT > 60 U/L ALT was measured by Quest Diagnostics (Lancaster, PA) in accordance with International Federation of Clinical Chemistry recommendations [12]. No subjects reported a history of heart failure or use of hematopoietic medication. All subjects provided informed consent to participate in the study according to the guidelines of the University of Maryland Institutional Review Board for Human Research.

Anthropometric and biochemical measurements in Amish subjects

Height and weight were measured using a stadiometer and calibrated scale with shoes removed and in light clothing, and body mass index (BMI) (kg/m^2) was computed. Blood pressure was measured in triplicate in the sitting position after the subject had been sitting quietly for 5 min by use of a standard sphygmomanometer, and the average of the measurements was calculated.

Venous blood was drawn at baseline after a 12- to 14-h overnight fast. Fasting low and high density lipoprotein cholesterol (LDL-C and HDL-C), ALT, aspartate aminotransferase (AST), hemoglobin, red and white blood cell counts, and HCT were assayed by Quest Diagnostics (Lancaster, PA).

NHANES III participants

The original NHANES III sample data was collected from 1988 to 1994 [10]. The same exclusion criteria as used for the Amish population were applied to the NHANES III population. After exclusions, a total of 9,842 subjects were available for statistical analysis.

Statistical analysis

All parameters are reported as mean $\pm$ standard error (SE) unless otherwise stated. To evaluate trends, we estimated the mean $\pm$ SE of the anthropometric and blood chemistry variables by quartile of ALT and HCT for men and women separately. We then tested in the Amish whether each variable was associated with ALT (or HCT) levels adjusting for BMI or age/sex, using a regression-based approach that incorporated relatedness among study participants as a random effect (polygenic component) as implemented in the SOLAR software program (version 4.07 Southwest Foundation for Biomedical Research, San Antonio, Texas). We further partitioned the total variation in ALT into variation attributable to the independent variables by evaluating the reduction in residual ALT variance following introduction of the independent variables. This analysis was also carried out using SOLAR. The NHANES analysis was completed using SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina). ALT was natural logarithm transformed prior to analysis, and the transformed values were approximately normally distributed. Similarly, we logarithm-transformed other non-normally distributed variables (e.g. AST, red blood cell (RBC) counts) prior to analysis. We considered a p -value of < 0.05 statistically significant and created plots using Prism (GraphPad Software; La Jolla, CA).

Results

Association of ALT with anthropometric and biochemistry parameters in Amish subjects

All analyses were conducted on 1,200 apparently healthy subjects (age = 44.1 ± 14.0 years, BMI = 26.8 ± 4.7 kg/m^2 ; mean $\pm$ SD).

Since there was a significant difference in ALT levels between men and women ($20.8 \text{ U/L} \pm 7.6$ [$n = 607$] vs. $16.9 \text{ U/L} \pm 7.0$ [$n = 593$], $p < 0.0001$), we examined the ALT association with other parameters separately in men and women. Table Ia shows mean values of metabolic traits and anthropometric parameters by quartiles of ALT levels in men. As age is

a common factor influencing ALT and HCT, we adjusted for age to examine the association of ALT and HCT with other clinical measurements. Following age adjustment, increased ALT levels were associated with higher levels of BMI, LDL-C, triglyceride and blood pressure, and lower HDL-C. ALT levels were not associated with smoking status in the Amish, although only 20% of Amish men reported smoking, and among those that do, few use cigarettes and the intensity of smoking is low. Amish women do not use tobacco. Interestingly, ALT levels were correlated with red blood cell (RBC) parameters including RBC counts, hemoglobin and HCT levels. Similar associations of ALT were observed in women except that ALT appeared less associated with cholesterol in women than they did in men (Table IB). As expected, ALT was strongly correlated with another liver injury marker, AST ($r = 0.68$, $p < 0.0001$, Table I).

Association of HCT with anthropometric and biochemistry parameters

Since mean HCT levels were significantly higher in men than women ($42.8\% \pm 2.6$ vs. $38.3\% \pm 2.4$ [$p < 0.0001$]), associations between HCT and other parameters were therefore assessed within men and women separately. Clinical characteristics of study participants by HCT quartiles in men and women are shown in Tables IIA and IIB. After adjustment for age, HCT in both sexes was significantly correlated with BMI and diastolic blood pressure (DBP), and inversely correlated with HDL-C. Notably, HCT was significantly associated with ALT, but much less so with AST, another liver injury marker. As expected, HCT was closely correlated with other measurement of red blood cell abundance, i.e. RBC and hemoglobin levels, but not with white blood cell (WBC) counts (Table IIAB).

Correlation of ALT with HCT is independent of BMI, and partially dependent of age and sex

A formal test for interaction was carried out to determine if the association of ALT (or HCT) with the measured parameters differed between men and women but provided no strong evidence that the strength of association differed by sex. Thus, we conducted sex-pooled analyses to estimate the extent of correlations between ALT and HCT with or without adjustments for BMI or age and sex. Without adjustment, ALT was significantly correlated with HCT ($r = 0.33$, $p < 0.0001$, Figure 1A). The correlation increased slightly after adjustment for BMI ($r = 0.35$, $p < 0.0001$, Figure 1B) but was reduced to $r = 0.18$ after adjustment for age/sex, although still significant ($p < 0.0001$, Figure 1C).

Replication of the ALT-HCT correlation in the general population (NHANES III)

To exclude the possibility that the observed correlation of ALT with HCT found in the Amish was unique to this population, we examined the relationship among participants in NHANES III. A dataset of 9,842 subjects (4,668 men, 5,174 women; age: $47.5 \text{ yrs} \pm 17.9$) was derived after using the same exclusion criteria applied for the Amish population. Impressively, the same correlation value of $r = 0.33$ was observed in NHANES III (Figure 2A) as in the Amish population. The correlation value was unchanged after adjustment for BMI (Figure 2B), but after adjustment for age/sex was reduced to $r = 0.17$ (Figure 2C), although it remained statistically significant ($p < 0.0001$).

Impact of HCT on the variance of ALT

To assess the contribution of HCT to ALT variation relative to other known ALT modulators, we estimated the variance attributable to each factor, adjusting for the others. As shown in Figure 3, in the Amish and general population, gender explained 7.5–10% and BMI explained 6.8–11.3% of ALT variability. Age accounted for 5.9% of ALT population variation in Amish women and 8.2% in NHANES men. Notably, there was a constant ~3% contribution of HCT to ALT variability across population and gender. The HCT impact on ALT is modest; it is less influential than BMI and gender but more influential than individual blood pressure or cholesterol components.

Discussion

We have shown a positive correlation between serum ALT levels and HCT in 1,200 relatively healthy Amish subjects and then replicated this result in an independent sample of 9,842 participants from NHANES III. Elevated serum ALT activity is regarded as evidence of liver damage. However, elevated ALT levels are frequently associated with other clinical conditions such as obesity [13,14], muscle diseases [15–17] and are observed in many asymptomatic or ‘healthy’ patients [1,4,18,19]. For example, ALT levels are not only influenced by demographic and body size characteristics, including gender, age and BMI, but are also associated with many clinical blood chemistry markers, such as GGT, uric acid, triglycerides, cholesterol and iron [4,20]. Identification of additional ALT modulators will contribute to understanding the source of population variation in this measure, as well as its potential utility as a diagnostic marker.

HCT is a direct indicator of the volume of red blood cell counts and hemoglobin relative to that of total body fluid. Increased HCT is usually observed in conditions of dehydration and abnormal erythropoiesis, whereas a decrease is seen in anemia. Higher HCT levels are positively correlated with blood viscosity. Viscosity increases the peripheral resistance to blood flow and therefore is more correlated with diastolic blood pressure than systolic blood pressure [21], which is consistent with our finding that HCT was significantly associated with diastolic blood pressure (Table IIAB).

The mechanism underlying the positive association of ALT with HCT is not clear at present. After adjustment for BMI, sex and age, the correlation remains significant and hence, appears intrinsic. One possible mechanism for this association is through hypoxia, which is a major physiological stimulator of erythropoiesis and is also considered an independent risk factor for non-alcoholic fatty liver disease (NAFLD) [22,23], a prevalent but underdiagnosed disease. Thus, an elevated HCT level may reflect a certain degree of sub-hypoxia in NAFLD patients. Moreover, ALT has two isoenzymes, ALT1 and ALT2, each with distinct tissue distributions [24–26]. How each individual ALT isoenzyme is related to HCT deserves further study.

In conclusion, we have demonstrated that ALT and HCT are closely correlated in two independent populations. In healthy subjects, HCT contributes about 3% to ALT variance, which is less than gender and BMI, but more than the individual components of blood pressure and plasma lipids. Thus we have identified HCT as a new modulator for serum

ALT levels, which will help our understanding of the regulation of ALT in apparent healthy conditions.

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Figure 1. Correlation between ALT and HCT in Amish subjects. Pearson correlations were conducted between HCT and log-transformed ALT (tALT) or log-transformed ALT residue (tALTr) without (A) or with adjustment for age/sex (B), BMI (C). $N = 1,191$.

Figure 2.

Correlation between ALT and HCT in NHANES III participants. Pearson correlations were conducted between HCT and log-transformed ALT (tALT) or log-transformed ALT residue (tALTTr) without (A) or with adjustment for age/sex (B), BMI (C). $N = 9,842$.

Figure 3.

Comparison of HCT with other factors in percent contribution to ALT variability in the Amish and NHANES populations. SBP, systolic blood pressure; DBP, diastolic blood pressure; CHL, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol.

Table 1

Association of ALT quartiles with selective clinical characteristics in (a) men and (b) women.

	Quartile 1 ALT: 7–15 (n = 141)	Quartile 2 ALT: 16–19 (n = 162)	Quartile 3 ALT: 20–23 (n = 146)	Quartile 4 ALT: 24–71 (n = 158)	p value for trend Adjusted for age
(a)					
ALT * (U/L)	13.0 ± 0.2	17.6 ± 0.1	21.4 ± 0.1	30.6 ± 0.6	NA
Age (years)	43.0 ± 1.3	44.2 ± 1.1	40.6 ± 1.0	42.9 ± 1.0	NA
BMI (kg/m ²)	24.1 ± 0.2	25.5 ± 0.3	25.7 ± 0.2	27.5 ± 0.3	<0.0001
Cholesterol (mmol/L)	5.04 ± 0.09	5.30 ± 0.09	5.33 ± 0.09	5.37 ± 0.09	0.0003
HDL-C (mmol/L)	1.41 ± 0.03	1.38 ± 0.03	1.36 ± 0.03	1.32 ± 0.03	0.002
LDL-C (mmol/L)	3.35 ± 0.08	3.58 ± 0.08	3.64 ± 0.09	3.65 ± 0.09	0.0001
AST * (U/L)	16.3 ± 0.2	18.1 ± 0.3	20.5 ± 0.3	24.0 ± 0.5	<0.0001
SBP (mm Hg)	118.7 ± 1.0	121.6 ± 1.1	120.7 ± 0.9	122.1 ± 1.1	0.0007
DBP (mm Hg)	73.7 ± 0.6	77.3 ± 0.7	76.0 ± 0.7	77.7 ± 0.7	<0.0001
WBC (10 ⁹ /L)	5.6 ± 0.1	5.6 ± 0.1	5.5 ± 0.1	5.7 ± 0.1	0.96
RBC(10 ¹² /L) *	4.66 ± 0.03	4.71 ± 0.02	4.74 ± 0.03	4.80 ± 0.02	<0.0001
Hemoglobin (g/L)	144.4 ± 0.8	146.5 ± 0.7	146.3 ± 0.7	148.4 ± 0.6	<0.0001
Hematocrit (%)	42.2 ± 0.2	42.8 ± 0.2	42.7 ± 0.2	43.4 ± 0.2	0.0001
(b)					
	Quartile 1 ALT: 6–12 (n = 144)	Quartile 2 ALT: 13–14 (n = 113)	Quartile 3 ALT: 15–19 (n = 187)	Quartile 4 ALT: 20–70 (n = 149)	p value for trend Adjusted for age
ALT * (U/L)	10.5 ± 0.1	13.5 ± 0.1	16.7 ± 0.1	25.7 ± 0.7	NA
Age (years)	38.4 ± 1.1	43.8 ± 1.4	49.5 ± 1.0	48.8 ± 1.0	NA
BMI (kg/m ²)	26.0 ± 0.3	26.9 ± 0.5	27.9 ± 0.4	30.3 ± 0.5	<0.0001
Cholesterol (mmol/L)	5.24 ± 0.09	5.60 ± 0.14	5.55 ± 0.09	5.64 ± 0.11	0.24
HDL-C (mmol/L)	1.55 ± 0.03	1.61 ± 0.04	1.57 ± 0.03	1.51 ± 0.04	0.004
LDL-C (mmol/L)	3.37 ± 0.08	3.67 ± 0.13	3.57 ± 0.08	3.67 ± 0.10	0.27
AST * (U/L)	13.8 ± 0.2	16.0 ± 0.2	18.1 ± 0.3	22.6 ± 0.6	<0.0001
SBP (mm Hg)	114.7 ± 1.0	118.8 ± 1.5	121.8 ± 1.3	123.3 ± 1.4	0.04
DBP (mm Hg)	71.4 ± 0.6	73.6 ± 0.8	74.3 ± 0.6	75.9 ± 0.7	0.008
WBC (10 ⁹ /L)	5.4 ± 0.1	5.6 ± 0.1	5.4 ± 0.1	5.7 ± 0.1	0.008

	Quartile 1 ALT: 6–12 (n = 144)	Quartile 2 ALT: 13–14 (n = 113)	Quartile 3 ALT: 15–19 (n = 187)	Quartile 4 ALT: 20–70 (n = 149)	p value for trend Adjusted for age
RBC * (10 ¹² /L)	4.22 ± 0.03	4.21 ± 0.03	4.24 ± 0.02	4.31 ± 0.03	< 0.0001
Hemoglobin (g/L)	128.5 ± 0.7	129.7 ± 0.7	130.3 ± 0.6	132.6 ± 0.7	< 0.0001
Hematocrit (%)	37.8 ± 0.2	38.1 ± 0.2	38.2 ± 0.2	38.9 ± 0.2	< 0.0001

* p-values obtained with log-transformed variables; same for all tables

Table II

Association of HCT quartiles with clinical characteristics in (a) men and (b) women.

	Quartile 1 HCT 31–41 (n = 147)	Quartile 2 HCT 41.1–42.7 (n = 144)	Quartile 3 HCT 42.8–44.3 (n = 157)	Quartile 4 HCT: 44.4–50.9 (n = 159)	p value for trend Adjusted for age
(a)					
Hematocrit (%)	39.5 ± 0.1	41.9 ± 0.03	43.5 ± 0.04	45.9 ± 0.1	NA
Age (years)	46.5 ± 1.2	43.9 ± 1.0	40.3 ± 1.1	40.5 ± 1.1	NA
BMI (kg/m ²)	25.0 ± 0.3	25.4 ± 0.3	25.7 ± 0.3	26.8 ± 0.3	<0.0001
Cholesterol (mmol/L)	5.35 ± 0.10	5.34 ± 0.09	5.23 ± 0.09	5.15 ± 0.08	0.84
HDL-C (mmol/L)	1.44 ± 0.03	1.39 ± 0.03	1.36 ± 0.02	1.29 ± 0.03	<0.0001
LDL-C (mmol/L)	3.59 ± 0.09	3.63 ± 0.09	3.54 ± 0.09	3.47 ± 0.08	0.60
AST * (U/L)	20.1 ± 0.4	19.5 ± 0.4	19.8 ± 0.4	19.8 ± 0.5	0.89
ALT * (U/L)	19.3 ± 0.5	20.8 ± 0.6	20.9 ± 0.6	22.3 ± 0.7	<0.0001
SBP (mm Hg)	120.7 ± 1.1	118.6 ± 0.9	120.6 ± 0.9	123.2 ± 1.1	0.004
DBP (mm Hg)	74.3 ± 0.7	76.1 ± 0.7	76.4 ± 0.6	78.2 ± 0.8	<0.0001
WBC (10 ⁹ /L)	5.5 ± 0.1	5.6 ± 0.1	5.5 ± 0.1	5.8 ± 0.1	0.006
RBC * (10 ¹² /L)	4.38 ± 0.02	4.64 ± 0.02	4.83 ± 0.01	5.05 ± 0.02	<0.0001
Hemoglobin (g/L)	135.8 ± 0.5	143.6 ± 0.3	149.1 ± 0.2	156.3 ± 0.4	<0.0001
(b)					
	Quartile 1 HCT 30.2–36.5 (n = 145)	Quartile 2 HCT 36.6–38.2 (n = 141)	Quartile 3 HCT 38.3–39.7 (n = 139)	Quartile 4 HCT 39.8–45.5 (n = 160)	p for trend Adjusted for age
Hematocrit (%)	35.1 ± 0.1	37.5 ± 0.04	38.9 ± 0.03	41.2 ± 0.1	NA
Age (years)	47.0 ± 1.1	44.6 ± 1.2	44.4 ± 0.5	46.2 ± 1.1	NA
BMI (kg/m ²)	26.9 ± 0.4	27.4 ± 0.5	27.9 ± 0.5	28.8 ± 0.5	0.002
Cholesterol (mmol/L)	5.28 ± 0.10	5.62 ± 0.11	5.55 ± 0.11	5.56 ± 0.09	0.006
HDL-C (mmol/L)	1.59 ± 0.03	1.62 ± 0.03	1.55 ± 0.04	1.48 ± 0.03	0.08
LDL-C (mmol/L)	3.37 ± 0.09	3.66 ± 0.11	3.58 ± 0.10	3.64 ± 0.08	0.02
AST * (U/L)	17.3 ± 0.5	17.6 ± 0.4	17.8 ± 0.4	18.5 ± 0.5	0.02
ALT * (U/L)	15.1 ± 0.4	17.1 ± 0.7	17.1 ± 0.6	18.1 ± 0.6	<0.0001
SBP (mm Hg)	118.9 ± 1.4	120.5 ± 1.5	117.7 ± 1.3	122.1 ± 1.2	0.08
DBP (mm Hg)	72.6 ± 0.7	74.5 ± 0.9	72.2 ± 0.6	75.8 ± 0.6	0.002
WBC (10 ⁹ /L)	5.3 ± 0.1	5.5 ± 0.1	5.6 ± 0.1	5.6 ± 0.1	0.07

	Quartile 1 HCT 30.2–36.5 (n = 145)	Quartile 2 HCT 36.6–38.2 (n = 141)	Quartile 3 HCT 38.3–39.7 (n = 139)	Quartile 4 HCT 39.8–45.5 (n = 160)	p for trend Adjusted for age
RBC * (10 ¹² /L)	3.94 ± 0.02	4.14 ± 0.01	4.31 ± 0.01	4.56 ± 0.02	< 0.0001
Hemoglobin (g/L)	119.8 ± 0.4	128.2 ± 0.3	132.5 ± 0.2	139.7 ± 0.4	< 0.0001