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ORIGINAL ARTICLE

Changes in Lp-PLA$_2$ Are Associated With Elevated Alanine Aminotransferase Levels: A Nested Case-Control Study in a Three-Year Prospective Cohort

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Abstract

Background/Aim: Elevation in liver enzymes and hepatic fat may indicate a higher susceptibility to cardiovascular disease (CVD). This research sought to find anthropometric/biochemical variables significantly related to the alanine aminotransferase (ALT) increase in healthy populations.
Methods: Nine hundred healthy subjects were included in a 3-year prospective cohort study. The initial screening revealed that 538 were found to be nondiabetic (fasting glucose < 126 mg/dL) and had normal ALT levels. Among them, 79 individuals with slightly elevated ALT levels after three years were assigned to the elevated ALT group. Of the remaining 459 participants, 241 subjects matched to the increased ALT group were the control group.
Results: After three years of follow-up, individuals with elevated ALT showed notably higher aspartate aminotransferase (AST), ALT, gamma-glutamyltransferase (γ-GT), high sensitivity C-reactive protein (hs-CRP), lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$) activity, oxidised low-density lipoprotein (ox-LDL), urinary 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-PGF$_{2\alpha}$) levels and brachial-ankle pulse wave velocity (ba-PWV) in comparison to the control group. Changes (Δ) in ALT showed a positive correlation with Δ AST, Δ gamma-GT, Δ hs-CRP, Δ Lp-PLA$_2$ activity, Δ ox-LDL, Δ urinary 8-epi-PGF$_{2\alpha}$ and Δ ba-PWV. Furthermore, a direct positive link was observed between the Δ Lp-PLA$_2$ activity and Δ AST, Δ ox-LDL and Δ ba-PWV.
Conclusion: Increased Lp-PLA$_2$ activity and other CVD risk indicators were observed to have a pronounced association with elevated ALT levels. This mild ALT elevation could potentially contribute to chronic low-grade inflammation.

Key words: Alanine aminotransferase; Lp-PLA$_2$ activity; Inflammation; Arterial stiffness; ba-PW.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) typically induces an asymptomatic increase in the levels of the liver enzymes, including gamma-glutamyltransferase (γ-GT), aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Among these enzymes, ALT is frequently utilised as a surrogate biomarker for NAFLD because of a positive correlation with the increase of hepatic fat.[1, 2] Elevated γ-GT was commonly observed in patients with NAFLD. However, the

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correlation between γ-GT and hepatic fat, as measured by proton magnetic resonance spectroscopy, is markedly weaker than that of ALT with hepatic fat.[1] Besides, increased γ-GT appears less frequently than changes in ALT in NAFLD,[3, 4] as γ-GT is also produced in other tissues.[5] Therefore, increased ALT is commonly utilised as an indicator for NAFLD in epidemiological research.

Recent epidemiological research has shown that the ALT level is related to the future risk of various metabolic diseases.[2, 6, 7] However, the evidence has still been controversial. Additionally, data are scarce regarding the association between the changes in liver enzyme tests (a crude indicator of NAFLD) and the activity of lipoprotein-associated phospholipase A_2 (Lp-PLA_2) (a distinctive feature of vascular inflammation).[8]

The primary goal of this research was to explore alterations in Lp-PLA_2 activity that were closely linked to increased ALT levels. To achieve the goal, Lp-PLA_2 activity was evaluated in an elevated ALT group (n = 79) defined as nondiabetic individuals with elevated who had high ALT levels (fasting ALT ≥ 30 IU/L for both genders) after 3 years of follow-up. The control group for comparison consisted of subjects who maintained normal ALT levels, with fasting ALT levels below 30 IU/L for both genders. Other cardiovascular disease (CVD) risk factors, including oxidative stress biomarkers [eg urinary 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$) and oxidised low-density lipoprotein (ox-LDL)], high sensitivity C-reactive protein (hs-CRP) and brachial-ankle pulse wave velocity (ba-PWV), which is a representative indicator of atherosclerotic vascular damage and CVD were also analysed.

Methods

Study subjects

The current study was based on 900 healthy individuals aged 30 to 65 who underwent triennial health examinations from January 2008 to January 2014 at the National Health Insurance Corporation (NHIC) Ilsan Hospital, Goyang, the Republic of Korea. Among a total of 900 subjects, only those who were nondiabetic, with fasting glucose levels below 126 mg/dL and exhibited ALT levels within the standard limits (fasting ALT < 30 IU/L for both genders) were included (n = 538).

Subsequent to the 3-year follow-up point, individuals with marginally increased fasting ALT levels (≥ 30 IU/L for both genders) were assigned to the elevated ALT group (n = 79). Otherwise, 459 subjects maintained ALT levels within the normal range throughout the 3-year follow-up period. Of these 459 subjects, 241 were allocated to the control group after matching with the elevated ALT group using gender, body mass index (BMI), age and fasting blood glucose.

The research protocol was authorised by the Institutional Review Boards of the NHIC Ilsan Hospital and Yonsei University and it was undertaken adhering to the principles of the Helsinki Declaration. All participants received a thorough explanation of the study before providing written informed consent.

Anthropometrics and biochemical assessments

The physical parameters of body weight, height and waist circumference were taken in the morning and after a usual expiration to determine BMI. An automatic blood pressure monitor was utilised to measure blood pressure (BP) levels twice on the left and the average measurement was used. An automated waveform analyser (model VP-1000; Nippon Colin Ltd, Komaki, Japan) was utilised to collect Ba-PWV readings.

For biochemical assessments, venous blood was obtained after 12 hours of fasting. The detailed methods for assessing each indicator were delineated in the previous study.[9, 10] Serum lipid profile analysis was performed as follows. Fasting triglycerides [reference value, 0–2.26 mmol/L], total cholesterol [0–6.22 mmol/L] and high-density lipoprotein (HDL)-cholesterol [1.04–1.16 mmol/L] were assessed using commercial kits (Daiichi, Tokyo, Japan), while the values of low-density lipoprotein (LDL)-cholesterol [0–3.37 mmol/L] were calculated by use of the Friedewald formula. Using the Hitachi 7600 Autoanalyzer (Hitachi Ltd, Tokyo, Japan), enzyme tests for free fatty acids (FFA) [172–586 uEq/L] were carried out. Commercial kits were also used for analysing serum glycaemic parameters: insulin [1.8–12.8 μIU/mL] kits from DIAsource ImmunoAssays S.A. (Louvain-la-Neuve, Belgium) and fasting glucose [3.88–5.55 mmol/L] kits from Siemens

(Tarrytown, NY, USA). The colour reactions were observed using ADVIA 2400 (Siemens, Tarrytown, NY, USA) and SR-300 (Stratec, Birkenfeld, Germany) instruments. For the evaluation of insulin resistance (IR), the homeostasis-model assessment (HOMA) was utilised. Hitachi 7600 Autoanalyzer (Hitachi Ltd.) measured the enzymatical reaction of AST [0–40 IU/L], ALT [0–40 IU/L] and γ-GT [Male 10–17, Female 6–42 IU/L] for liver function testing. White blood cells (WBC) [4.00–10.00×10^3/μL] were counted using the HORIBA ABX diagnostic analyser (HORIBA ABXSAS, Parc Euromedicine, Montpellier, France). The hs-CRP level [0–5 mg/L] was assessed with CRPHS reagent kits (Roche, Mannheim, Germany) and a Cobas C502 (Roche, Mannheim, Germany). A urinary isoprostane ELISA kit was used (Oxford Biomedical Research Inc, Rochester Hills, MI) for analysing urinary 8-epi-$PGF_{2\alpha}$, thiobarbituric acid reactive substance assay kit (Zepto-Metrix Co, Buffalo, NY) for malondialdehyde (MDA) and ox-LDL enzyme immunoassay kit (Mercodia, Uppsala, Sweden) for ox-LDL. Lp-PLA_2 activity was measured by high-throughput radiometric activity assay.

Statistical analyses

For all statistical analyses, SPSS v.23.0 (IBM, Chicago, IL, USA) was utilised. A p-value < 0.05 (two-tailed) was used to identify the level of statistical significance. Skewed variables were transformed into logarithmic values. The Chi-squared test analysed categorical variables. An independent t-test examined differences in continuous parameters between the two groups at both the first assessment and follow-up point. When comparing changes in the variables, a general linear model was employed, which corrected for initial levels. Differences between values at the first assessment and the follow-up point within each group were evaluated using paired t-test. The associations between the variables were investigated using Pearson's correlation coefficients and a heat map was constructed to represent these associations visually.

Results

Clinical characteristics and liver enzymes

In all initial characteristics except AST and ALT there were no statistical difference between the elevated ALT group (n = 79) and the control group (normal ALT, n = 241) (Table 1). The elevated ALT group consisted of 59.5 % males and 40.5 % females, compared to 51.5 % males and 48.5 % females in the control group. The average age of the control group was 46.9 ± 0.55 years, while that of the elevated ALT group was 47.2 ± 1.06 years (data not shown).

After the 3-year period, considerable increases were observed in the control subject's diastolic BP, total- and LDL-cholesterol, AST, ALT and MDA levels. Besides, the subjects in the control group showed notable reductions in waist circumference, insulin, HOMA-IR, FFA, γ-GT and hs-CRP levels at the follow-up point. On the other hand, individuals with elevated ALT displayed substantial rises in waist circumference, diastolic BP, total- and LDL-cholesterol, AST, ALT, hs-CRP and MDA levels after 3 years compared with the initial values. Furthermore, the elevated ALT group had notably higher levels of FFA, AST, ALT, γ-GT and hs-CRP at the follow-up evaluation after 3 years than the control group. Changed values of waist circumference, FFA, AST, ALT, γ-GT and hs-CRP were more significant in the elevated ALT subjects than in the control subjects (Table 1).

Lp-PLA_2 activity, oxidative stress markers and ba-PWV

There were no remarkable differences in the initial traits, including Lp-PLA_2 activity, oxidative stress indicators (ox-LDL and 8-epi-$PGF_{2\alpha}$) and ba-PWV, between the control and elevated ALT subjects (Figure 1). Regarding changed values, the participants in the control group demonstrated a noteworthy decrease in Lp-PLA_2 activity, while ox-LDL levels substantially increased. Conversely, the elevated ALT group exhibited substantial increases in Lp-PLA_2 activity, ox-LDL, urinary 8-epi-$PGF_{2\alpha}$ and ba-PWV. Moreover, the observed changes were more prominent in the elevated ALT subjects, in contrast to the normal control subjects, after accounting for initial levels. Upon reaching the 3-year point of the follow-up, individuals with elevated levels of serum ALT displayed considerably higher levels of Lp-PLA_2

activity, ox-LDL, urinary levels of 8-epi-$PGF_{2\alpha}$ and ba-PWV when compared to individuals in the control group (Figure 1).

Relationship between the changes in ALT and waist circumference, biochemical parameters and ba-PWV

Figure 2 presents the correlation matrix between alterations in liver enzymes, waist circumference, biochemical parameters and ba-PWV within the entire study cohort (n = 320). The difference in ALT exhibited a positive correlation with variations in waist circumference (r = 0.194, p < 0.001), triacylglycerol (r = 0.206, p < 0.001), FFA (r = 0.178, p = 0.001), AST (r = 0.706, p < 0.001), γ-GT (r = 0.344, p < 0.001), hs-CRP (r = 0.123, p = 0.031), urinary 8-epi-$PGF_{2\alpha}$ (r = 0.141, p = 0.017), ba-PWV (r = 0.208, p < 0.001), ox-LDL (r = 0.133, p = 0.025) (Figure 3) and Lp-PLA_2 activity (r = 0.479, p < 0.001) (Figure 3). Furthermore, FFA (r = 0.221, p < 0.001), AST (r = 0.362, p < 0.001), ba-PWV (r = 0.170, p = 0.003) and ox-LDL (r = 0.198, p = 0.001) alterations had a positive association with changes in Lp-PLA_2 activity (Figure 3). Additionally, the difference in ba-PWV showed positive correlations with changes in waist circumference (r = 0.149, p = 0.008), AST (r = 0.210, p < 0.001), γ-GT (r = 0.141, p = 0.029) and hs-CRP (r = 0.142, p = 0.013).

Table 1: Clinical and biochemical characteristics of the control and elevated ALT groups

Parameter	Total subjects (n = 320)				P^a	P^b	P^c	P^d
	Control (n = 241)		Elevated ALT (n = 79)					
	Initial	Follow-up	Initial	Follow-up				
BMI (kg/m²)	23.3 ± 0.17	23.4 ± 0.17	23.4 ± 0.30	23.7 ± 0.34	0.903	0.441		
Waist (cm)	83 ± 0.44	83.6 ± 0.49	81.9 ± 0.77	84.6 ± 0.92**	0.226	0.306		
Change	**0.59 ± 0.38**		**2.7 ± 0.76**				0.008	0.017
Waist to hip ratio	0.89 ± 0.00	0.88 ± 0.00***	0.89 ± 0.01	0.88 ± 0.01	0.355	0.653		
Systolic BP (mmHg)	117.2 ± 0.85	118.5 ± 0.95	117.8 ± 1.42	119.6 ± 1.70	0.714	0.522		
Diastolic BP (mmHg)	72 ± 0.66	73.5 ± 0.69*	72 ± 1.18	74.8 ± 1.13 *	1	0.355		
Triglycerides (mmol/L)$^{\$}$	1.16 ± 0.05	1.24 ± 0.05	1.11 ± 0.06	1.41 ± 0.12	0.834	0.346		
Total-cholesterol (mmol/L)$^{\$}$	4.98 ± 0.05	5.17 ± 0.05***	4.76 ± 0.08	5.1 ± 0.10 **	0.052	0.48		
HDL-cholesterol (mmol/L)$^{\$}$	1.37 ± 0.02	1.35 ± 0.02	1.31 ± 0.04	1.29 ± 0.03	0.186	0.25		
LDL-cholesterol (mmol/L)$^{\$}$	3.08 ± 0.05	3.26 ± 0.05***	2.93 ± 0.08	3.19 ± 0.09 *	0.222	0.395		
Glucose (mmol/L)$^{\$}$	5.08 ± 0.03	5.11 ± 0.03	5.07 ± 0.06	5.14 ± 0.06	0.816	0.751		
Insulin (μIU/mL)$^{\$}$	8.32 ± 0.20	7.6 ± 0.21***	8.3 ± 0.38	7.91 ± 0.44	0.83	0.684		
HOMA-IR$^{\$}$	1.88 ± 0.05	1.73 ± 0.05**	1.87 ± 0.09	1.81 ± 0.11	0.845	0.606		
Free fatty acid (uEq/L)$^{\$}$	534.8 ± 15.3	474.4 ± 15.4***	506.3 ± 24.9	563.6 ± 29.7	0.349	0.002		
Change	**-60.4 ± 19.1**		**57.3 ± 32.5**				0.002	0.002
AST (IU/L)$^{\$}$	20.7 ± 0.23	21.3 ± 0.23**	22.5 ± 0.42	33.6 ± 1.13 ***	< 0.001	< 0.001		
Change	**0.6 ± 0.23**		**11.1 ± 1.17**				< 0.001	< 0.001
ALT (IU/L)$^{\$}$	17 ± 0.33	17.7 ± 0.31**	19.6 ± 0.55	37.1 ± 1.18 ***	< 0.001	< 0.001		
Change	**0.73 ± 0.31**		**17.5 ± 1.21**				< 0.001	< 0.001
Gamma-GT (U/L)$^{\$}$	23.2 ± 1.98	21.4 ± 1.77***	24.1 ± 1.63	26.5 ± 2.19	0.092	0.002		
Change	**-1.84 ± 0.68**		**2.47 ± 1.72**				0.023	0.002
hs-CRP (mg/L)$^{\$}$	1.41 ± 0.25	0.72 ± 0.05**	1.11 ± 0.22	1.88 ± 0.65 *	0.538	< 0.001		
Change	**0.72 ± 0.25**		**0.81 ± 0.72**				0.01	0.002
WBCs (x10³/μL)$^{\$}$	5.34 ± 0.12	5.16 ± 0.09	5.5 ± 0.19	5.38 ± 0.16	0.421	0.259		
Malondialdehyde (nmol/mL)$^{\$}$	9.49 ± 0.17	10.4 ± 0.20***	9.22 ± 0.27	10.6 ± 0.37**	0.539	0.761		

BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HOMA-IR: homeostatic model assessment for insulin resistance; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GT: glutamyl transferase; WBC: white blood cells;

*Mean ± SE. $^{\$}$The data were subjected to logarithmic transformation for testing. Pa-values were obtained from an independent t-test at the initial assessment. Pb-values were obtained from an independent t-test at follow-up assessment. Pc-values were obtained from an independent t-test of changed values. Pd-values adjust changed value with initial levels. *P < 0.05, **P < 0.01, ***P < 0.001 were assessed ased on the results of a paired t-test.*

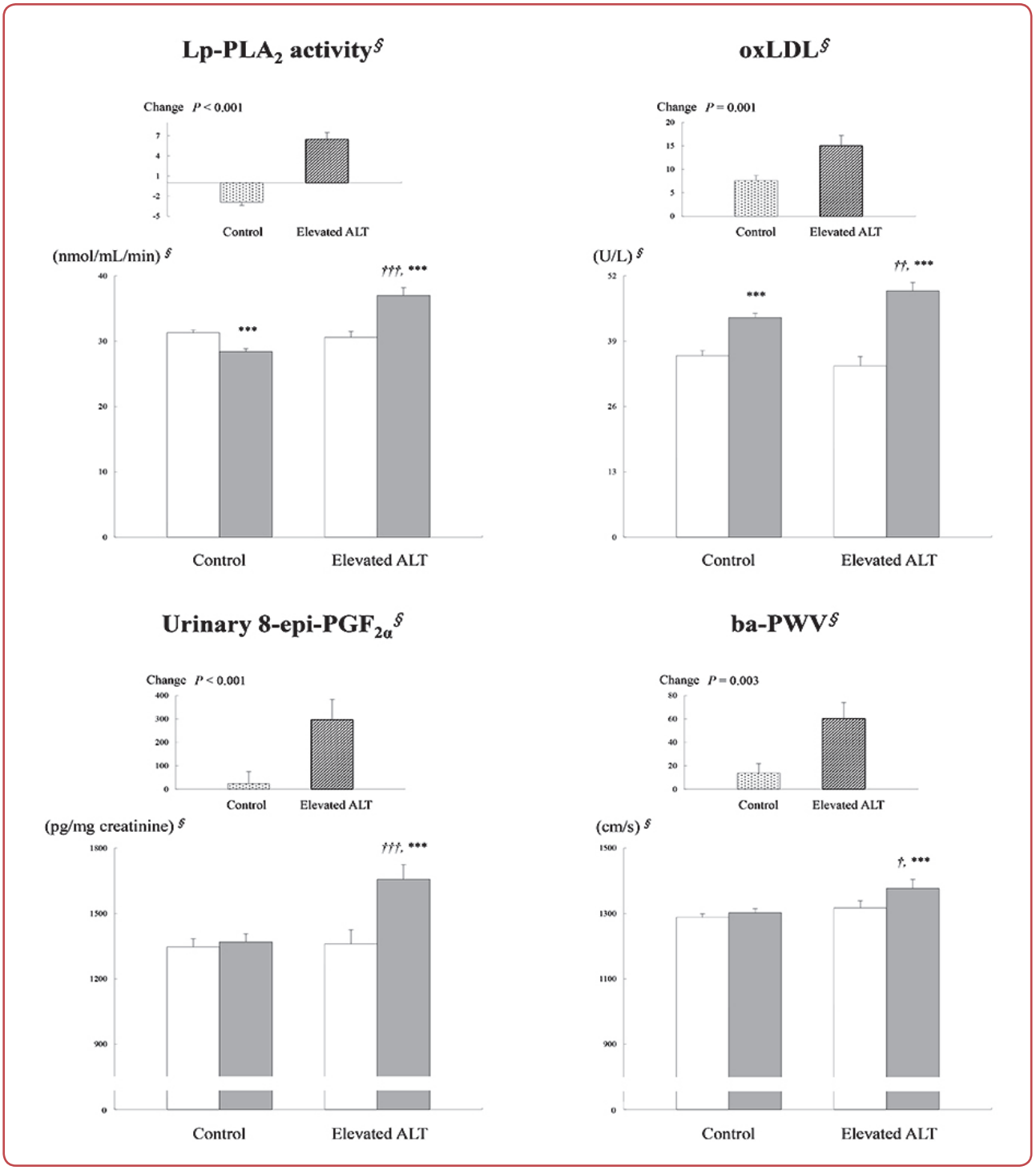

Figure 1: Lp-PLA$_2$ activity, ox-LDL, urinary 8-epi-PGF$_{2\alpha}$ and ba-PWV in control and elevated ALT subjects at initial (□) and follow-up (■).

*Mean ± SE. §The data were subjected to logarithmic transformation for testing. †P < 0.05, ††P < 0.01, †††P < 0.001 were obtained using an independent t-test comparing the groups at both initial and follow-up assessments. *P < 0.05, **P < 0.01, ***P < 0.001 were obtained from a paired t-test within each group.*

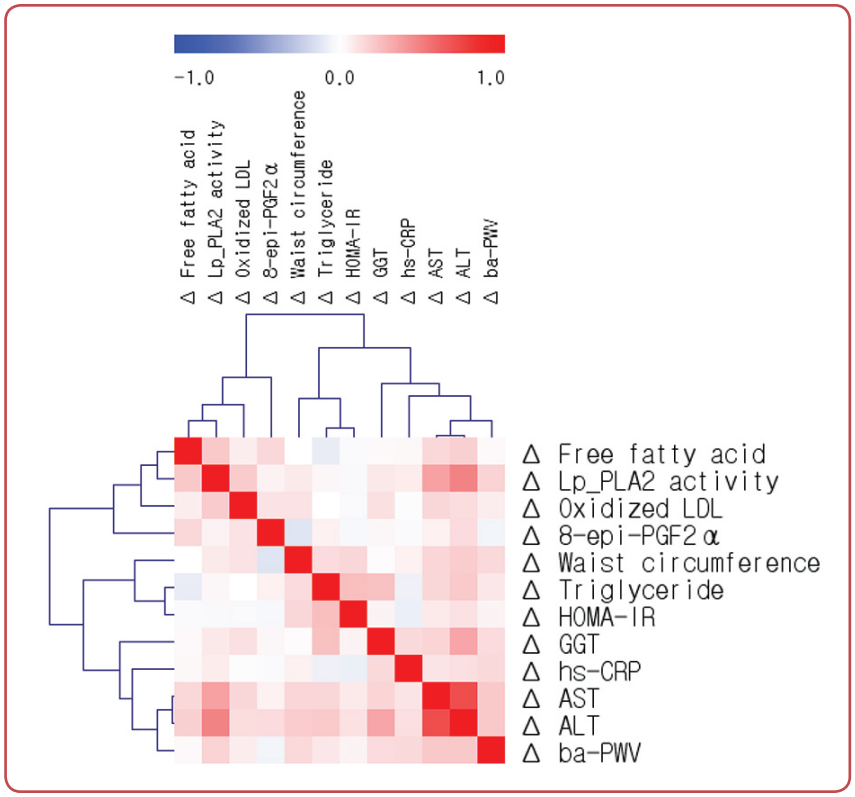

Figure 2: Correlation matrix of changes (Δ) in liver enzymes, waist circumference, biochemical parameters and ba-PWV across all study participants.0.001 were obtained from a paired t-test within each group.

Correlations between variables were determined using Pearson's correlation coefficient. Positive correlations are indicated by the colour Red, while negative correlations are denoted by the colour Blue in the correlation matrix.

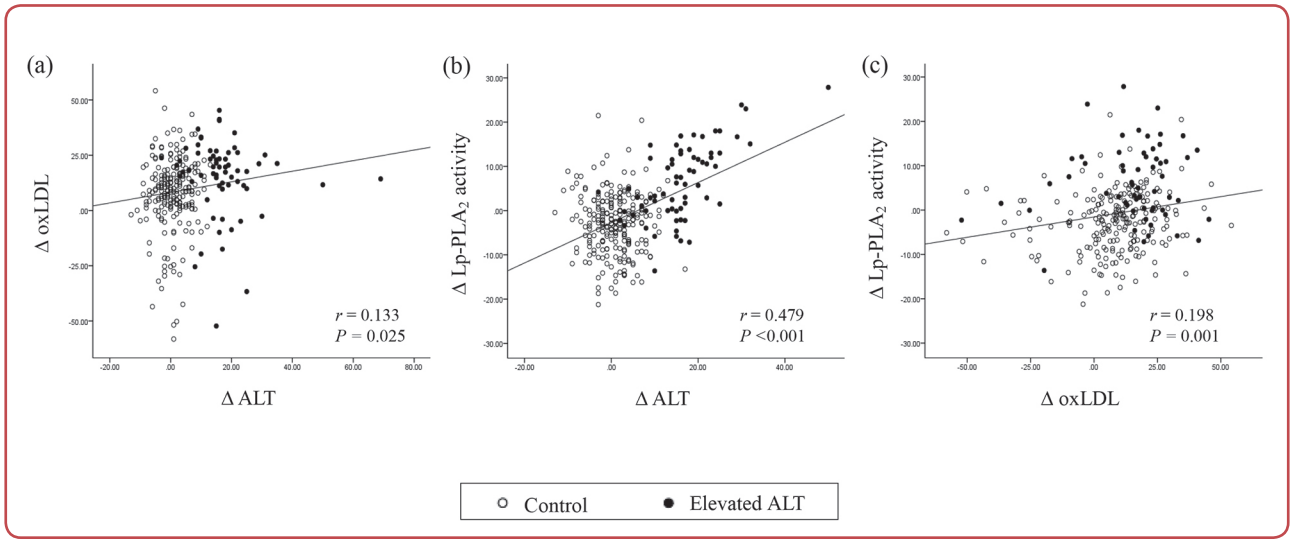

Figure 3: Correlations between changes (Δ) in ALT and ox-LDL, ALT and Lp-PLA$_2$ activity and ox-LDL and Lp-PLA$_2$ activity across all study participants.

(a) Correlation between Δ ALT and Δ ox-LDL. (b) Correlation between Δ ALT and Δ Lp-PLA$_2$ activity. (c) Correlation between Δ ox-LDL and Δ Lp-PLA$_2$ activity.

Discussion

In this prospective study, aim was to find anthropometric/ biochemical indicators significantly associated with the increase in ALT for three years in healthy populations. As a result, the link between ALT rise and changes in Lp-PLA_2 activity was verified.

Over the course of the 3-year study, the group with increased ALT levels displayed a noteworthy 1.9-fold rise in serum ALT levels. Generally, ALT concentrations decrease with aging.[11] Therefore, the increase in ALT over three years in presented study could result from abnormal metabolism, including liver damage.[11] Mild increases of ALT and AST (less than five times the upper limit of normal) are typical in primary care in the USA, it is estimated that subjects with elevated transaminase levels account for about 10 % of the population.[12] Indeed, confirmed changes in ALT were directly and strongly linked to changes in circulating Lp-PLA_2 activity and other liver enzyme activities such as AST and γ-GT. Additionally, alteration of ALT levels was positively linked to inflammation, oxidative stress and arterial stiffness indicators. Presented results suggest a significant association between elevation in Lp-PLA_2 activity, along with other CVD risk factors and elevated ALT levels.

This research discovered alteration in circulating Lp-PLA_2 activity and other liver enzyme activities (AST and γ-GT) were directly correlated with ALT changes, which positively correlated with indicators of oxidative stress, inflammation and vascular stiffness. The findings suggested that the inflammatory response in NAFLD contributes to systemic inflammation prompted by the interaction between elevated liver enzymes[6] and increased Lp-PLA_2 activity. Several studies are lined with presented research. A recent study demonstrated positive relationships between serum Lp-PLA_2 activity and ALT levels.[13] Another study carried out by Colak et al[14] revealed that serum Lp-PLA_2 levels were considerably elevated in NAFLD patients compared to normal subjects. Besides, the changed value of ALT and AST levels were substantially more extensive in individuals with increased ALT compared to those with normal ALT in the present study. This finding implies that liver enzymes, including ALT, could be rapidly abnormal in individuals with ALT levels at the upper portion of the reference range. Therefore, both serum ALT levels and Lp-PLA_2 activity could serve as valuable non-invasive markers for detecting the advanced status of NAFLD.

Lp-PLA_2 is produced primarily by various cell types, including mast cells, monocytes, liver cells, macrophages and T lymphocytes.[15, 16] Hepatic macrophages, which generate various inflammatory mediators, including Lp-PLA_2, regulate the phenotype of neighbouring cells.[17] Just as lipoprotein particles infiltrate the vascular wall, the buildup of fat in the liver triggers the release of hepatic cytokine, aggravating increased CRP levels. Indeed, Lp-PLA_2 activity and hs-CRP concentration were positively correlated with alteration in ALT in the present study. Similarly, Kerner et al[18] observed a correlation between elevated liver enzymes and CRP concentration.

The interplay between ox-LDL and Lp-PLA_2 within the vascular wall generates oxidised fatty acids and lysophosphatidylcholines, the strongest inflammatory and atherogenic factors.[19] At first, it was considered that circulating Lp-PLA_2 strongly preferred phospholipids with short fatty acid chains at the sn-2 position; no significant activity was detected in chains longer than nine carbons.[20, 21] However, oxidatively modified phospholipids such as 8-epi-$PGF_{2\alpha}$[22] and phospholipid hydroperoxides[23] have been newly identified as plasma Lp-PLA_2 substrates. Urinary 8-epi-$PGF_{2\alpha}$ is considered the most reliable biomarker for assessing non-enzymatic lipid peroxidation and oxidative stress.[24] Throughout the study, substantial increases in Lp-PLA_2 activity, ox-LDL, as well as urinary levels of 8-epi-$PGF_{2\alpha}$ were observed in the subjects with elevated ALT. Additionally, meaningful correlations were found among these variables, with the highest degree of association found between Lp-PLA_2 activity and ALT. This result points to a potential hepatic role of systemic inflammation in modest ALT elevation status.

Furthermore, elevated Lp-PLA_2 levels are linked with higher PWV values.[8] Lp-PLA_2 activity has been considered a primary trigger of the pro-inflammatory process that causes elastin loss and increased collagen deposition, resulting in faster arterial stiffness.[8] The ba-PWV is a straightforward index used to assess the severity of arterial atherosclerosis and stiffness, reflecting the stiffness of both peripheral and central muscular arteries.[25-27] Changes in ba-PWV were closely linked to variations in liver enzymes, Lp-

PLA_2 and hs-CRP in this study. Individuals with elevated ALT levels had a markedly greater increase in ba-PWV than controls. Consequently, the current study proposed that a mild increase in ALT levels could contribute to arterial stiffening with an impact on inflammatory markers.

It should be mentioned that the number of subjects who participated in this study was small. In addition, correlation analysis was performed only between the change value of indicators. Despite these limitations, an increase in Lp-PLA_2 activity and other CVD risk factors linked to elevation of ALT levels was confirmed. However, further analysis is needed to verify presented results.

Conclusion

It was revealed that elevated ALT levels were linked to rises in Lp-PLA_2 activity and additional risk factors for CVD in healthy populations. Therefore, the modest ALT increase could be associated with chronic low-grade inflammation. If this correlation is substantiated through further research, the combination of ALT and Lp-PLA_2 may be utilised as an integrated tool for the management of chronic disease risk.

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Conflict of interest

None.

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