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The Relationship between Serum Alkaline Phosphatase and Arterial Stiffness in Korean Adults

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Aim: Serum alkaline phosphatase (ALP), a useful marker of hepatobiliary or bone disorders, has recently been found to be associated with cardiovascular diseases. This study aimed to examine the association of serum ALP level with arterial stiffness, as measured by brachial-ankle pulse wave velocity.

Methods: This cross-sectional study included 2476 participants (1486 men and 990 women) aged ≥ 20 years who underwent a medical examination. Pearson correlation analyses were conducted to examine the bivariate correlations between baPWV and clinical variables. To examine the independent relationship between serum ALP and baPWV, a multiple linear regression analysis was conducted with baPWV as the dependent variable in a sex-specific manner.

Results: After adjusting for age, body mass index, current smoking, alcohol drinking, regular exercise, hypertension, type 2 diabetes, dyslipidemia, chronic kidney disease, log-transformed AST, log-transformed ALT, and log-transformed GGT levels, log-transformed serum ALP level was positively and independently associated with baPWV ($\beta = 78.6$ for men, $P = 0.001$; and $\beta = 85.3$ for women, $P < 0.001$).

Conclusions: Serum ALP level was positively and independently associated with baPWV in men and women, suggesting that an elevated ALP level may be a useful surrogate marker for arterial stiffness in adult men and women.

Key words: Alkaline phosphatase, Arterial stiffness, Pulse wave velocity

Introduction

Alkaline phosphatase (ALP), which is widely used in standard clinical practice, is a ubiquitous metalloenzyme that catalyzes the hydrolysis of monophosphate esters under alkaline pH conditions[1]. ALP is present in serum and on the external surface of most cells, mainly in the liver, bile duct, and bones, and it plays an integral role in metabolism within the hepatobiliary system and skeleton[2]. Thus, serum ALP has long been considered a useful marker of hepatobiliary or bone disorders[3]. However, several studies have indicated that an elevated ALP level, even within the normal range, is significantly associated with cardiovascular disease (CVD)[4-8].

Pulse wave velocity (PWV) is a non-invasive and useful measure of arterial stiffness[9-11] as well as being a reliable indicator of vascular damage and early atherosclerosis[12-15]. Increased arterial stiffness, as measured by PWV, has been reported to be a significant predictor of CVD events and mortality[16-19]. Although carotid-femoral PWV (cfPWV), a measure of arterial PWV throughout the entire aorta, is the most recognized and established index of central arterial stiffness[20], the cfPWV has some limitations, such as requiring more than 20 minutes for measurement and exhibiting examiner variability[21]. Recently, a simple, automated device has become available to measure brachial-ankle PWV (baPWV) using a volume-rendering method. Measuring baPWV is easier and more time-effective than conventional cfPWV measurements, and it has shown a good correlation with aortic

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PWV with high validity, reliability, and reproducibility in previous studies[22, 23].

Although precise mechanisms for the association between ALP and CVD incidence and mortality have been partially investigated, if the link between an elevate ALP level and CVD is indeed mediated by arterial stiffness, we would expect positive associations between serum ALP level and baPWV. However, few studies have examined the association between these two parameters. Thus, we investigated the association between serum ALP and baPWV in Korean adults.

Methods

Study Participants

We retrospectively reviewed the medical records of 3091 participants (1911 men and 1180 women) aged ≥ 20 years who underwent a medical examination at the Health Promotion Center of Gangnam Severance Hospital in Seoul, Korea, between November 2013 and July 2015. The participants voluntarily visited the health promotion center to regularly monitor their health conditions. Informed consent was obtained from each participant. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei University College of Medicine, Seoul, Korea. We excluded participants who met at least one of the following criteria (n =454): a history of osteoporosis, cancer, respiratory, renal, hepatobiliary, or rheumatologic disease; a positive test for hepatitis B antigens or hepatitis C antibodies; atrial fibrillation; ankle-brachial index <0.9; and missing data or not fasting for 12 hours prior to testing. We also excluded those with a history of CVD such as angina pectoris or myocardial infarction (n= 161). After these exclusions, 2476 participants (1486 men and 990 women) were included in the final analysis.

Data Collection

Each participant completed a questionnaire to self-report their lifestyle and medical history. Cigarette smokers were defined as those who currently smoked and the participants were classified into the following categories: non-smokers, ex-smokers, and current smokers. Alcohol drinking was defined as consumption of at least two drinks per week. Regular exercise was set as exercise ≥ three times per week. Menstrual history was also measured through a question "Did you ever experience a lack of menstruation for 1 year or more?" with three alternatives: "Yes", "No, but there was intermittent menstruation during the previous year" and "No, menstruation was normal". Menopause was defined as being present in an individual when there had been no menstrual periods for 12 consecutive months following a final menstrual period in the absence of a clear biological or physiological cause (n=202). Medical examinations were performed by trained medical staff members using a standardized procedure. Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, while the participants wore light indoor clothing without shoes. The body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using the patient's right arm with a standard mercury sphygmomanometer (Baumanometer, W.A. Baum Co Inc., Copiague, NY, US). Mean arterial pressure was calculated using the equation (SBP + 2 x DBP)/3. All blood samples were obtained from the antecubital vein after a 12-hour overnight fast. Serum fasting plasma glucose (FPG), total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), and ALP levels were measured via enzymatic methods using a Hitachi 7600-110 automated chemistry analyzer (Hitachi Co., Tokyo, Japan). High sensitivity C-reactive protein (hsCRP) concentrations were assessed using the Roche/Hitachi 912 System (Roche Diagnostics, Indianapolis, IN, US) via a latex-enhanced immunoturbidimetric method with a lower limit of detection of 0.02 mg/L. Hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or current use of anti-hypertensive medication. Type 2 diabetes was defined as FPG ≥ 7.0 mmol/L or current use of anti-diabetes medication. Dyslipidemia was defined as triglyceride ≥ 1.70 mmol/L, low HDL-cholesterol <1.04 mmol/L or current use of anti-dyslipidemic medications. An estimated GFR was calculated using the abbreviated equation from the Modification of Diet in Renal Disease study: estimated GFR (mL/min/1.73 m^2) = 186.3 × (serum creatinine$^{-1.154}$) × (age$^{-0.203}$) x 0.742 (if female). Chronic kidney disease (CKD) was defined based on the combination of renal tissue damage or reduced renal function. CKD was defined as estimated GFR <60 mL/min/1.73 m^2.

BaPWV Measurement

An automatic waveform analyzer (model BP-203RPE; Colin Co., Komaki, Japan) was used to measure PWV. This instrument simultaneously records the blood pressure at both the left and right brachial arteries and ankles, while also obtaining a phonocardiogram and an electrocardiogram. The participants were examined in the supine position after 10 minutes

of bed rest. Electrocardiogram electrodes were placed on both wrists, and a microphone for the phonogram was attached to the left edge of the sternum. Pneumonic cuffs were wrapped around both the upper arms and ankles and connected to a plethysmographic sensor to determine the volume pulse waveform. Waveforms for the upper arm (brachial artery) and ankle (tibial artery) were stored for 10-second sample times with an automatic gain analysis and quality adjustments. An oscillometric pressure sensor was attached to the cuffs to measure blood pressure in all four extremities. The baPWVs were recorded using a semiconductor pressure sensor (1200 Hz sample acquisition frequency) and calculated using the following equation: (La-Lb)/ΔTba. La and Lb were defined as the distances from the aortic valve to the elbow and to the ankle, respectively. The distances from the suprasternal notch to the elbow (La) and from the suprasternal notch to the ankle (Lb) were expressed by the following: La = 0.2195 x height of the participant (cm) − 2.0734 and Lb = 0.8129 × height of the participant (cm) + 12.328. The time interval between the arm and ankle distance (ΔTba) was defined as the pulse transit time between the brachial and tibial arterial pressure waveforms. La and Lb were automatically estimated based on the participants' height. The coefficients of variation for inter- and intra-observer reproducibility were 8.1% and 9.7%, respectively.

Statistical Analysis

The normal distribution was evaluated along with a determination of skewness using a Kolmogorov-Smirnov test; Serum triglycerides and AST, ALT, GGT, ALP, and hsCRP levels have a skewed distribution. Participants were divided into an upper and a lower stratum according to a cut-off value of the 75th percentile of serum ALP, which in the present study was 69 U/L for men and 71 U/L for women, respectively. The clinical characteristics of the study population by the upper and lower stratum of serum ALP levels were compared using an independent two-sample *t* test or a Wilcoxon-Rank sum test for continuous variables according to the normality of distributions and a chi-square test for categorical variables. Continuous data are presented as the mean (standard deviation, SD) or median (interquartile range, IQR), while categorical data are presented as frequency. Pearson correlation analyses were conducted to examine the bivariate correlations between baPWV and clinical variables. To examine the independent relationship between serum ALP levels and baPWV, a multiple linear regression analysis was conducted with baPWV as the dependent variable. All analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, US). All statistical tests were two-sided, and statistical significance was set at $P < 0.05$.

Results

Table 1 shows the demographic and clinical characteristics of the study population, which consisted of 2476 participants (1486 men and 990 women). The mean age was 53.0 (9.6) for all participants, 53.0 (9.7) years for men, and 52.9 (9.5) years for women. The mean or median values of BMI, blood pressure, FPG, triglyceride, AST, ALT, GGT, hsCRP, and baPWV were higher in the upper stratum than those in the lower stratum of ALP. In addition, total participants in the upper stratum of ALP had a higher percentage of smokers and hypertension. The mean HDL-cholesterol levels in the upper stratum were significantly lower than those in the lower stratum of ALP for both sexes. For men, the mean or median values of SBP, ALT, hsCRP, and baPWV and smoking rate in the upper stratum were higher than those in the lower stratum of ALP. For women, the mean or median values of BMI, blood pressure, FPG, triglyceride, AST, ALT, GGT, creatinine, hsCRP, and baPWV were higher and the prevalence of hypertension, and dyslipidemia were more prevalent in the upper stratum than those in the lower stratum of ALP.

Pearson correlation results between baPWV and clinical variables are presented in **Table 2**. For all participants, the baPWV was significantly correlated with age, BMI, blood pressure, FPG, log-transformed triglyceride, HDL-cholesterol, hepatic enzymes, creatinine, log-transformed hsCRP, and log-transformed ALP levels. For both sexes, the baPWV was also correlated with age, BMI, blood pressure, FPG, log-transformed hsCRP, and log-transformed ALP levels, whereas correlated with log-transformed triglyceride, HDL-cholesterol and hepatic enzymes only for women.

The multiple linear regression analysis, as shown in **Table 3**, indicated that the log-transformed serum ALP level was positively and independently related to baPWV after adjusting for age, BMI, cigarette smoking, alcohol drinking, regular exercise. ($\beta = 73.1$, standard error = 21.6 for men, $P < 0.001$; and $\beta = 89.7$, standard error = 23.7 for women, $P < 0.001$). This tendency remained even after adjusting for additional potential cardiovascular and hepatobiliary confounding variables including hypertension, type 2 diabetes, dyslipidemia, CKD, log-transformed AST, log-transformed ALT, and log-transformed GGT levels ($\beta = 78.6$, standard error = 23.9 for men, $P = 0.001$; and $\beta = 85.3$, standard error = 23.6 for women, $P < 0.001$).

Table 1. Characteristics of the study population

Variables	Total			Men		
	ALP ≤ 69	ALP ≥ 70	*P* value	ALP ≤ 69	ALP ≥ 70	*P* value
N	1898	578		1156	330	
Age (year)	52.4 (9.5)	55.0 (9.7)	<0.001	52.9 (9.4)	53.4 (11.0)	0.462
BMI (kg/m^2)	23.7 (3.1)	24.0 (2.9)	0.043	24.6 (2.8)	24.4 (2.7)	0.277
SBP (mmHg)	123.6 (17.0)	127.6 (17.6)	<0.001	126.3 (15.9)	128.8 (15.9)	0.012
DBP (mmHg)	76.8 (12.1)	78.4 (10.1)	0.001	79.0 (9.6)	79.8 (9.5)	0.211
MAP (mmHg)	92.4 (12.1)	94.8 (12.1)	<0.001	94.8 (11.1)	96.1 (11.1)	0.055
FPG (mmol/L)	5.32 (1.00)	5.50 (1.26)	0.002	5.47 (1.04)	5.60 (1.25)	0.078
Triglyceride (mmol/L)	1.09 (0.79–1.59)	1.17 (0.84–1.66)	0.033	1.26 (0.92–1.83)	1.25 (0.92–1.72)	0.942
HDL-cholesterol (mmol/L)	1.32 (0.33)	1.26 (0.30)	<0.001	1.22 (0.28)	1.17 (0.25)	<0.001
AST (U/L)	20 (17–24)	21 (18–26)	<0.001	21 (18–25)	21 (18–26)	0.314
ALT (U/L)	20 (15–26)	22 (17–30)	<0.001	22 (17–29)	23 (18–32)	0.003
GGT (U/L)	23 (15–35)	26 (18–39)	<0.001	29 (21–41)	31 (22–44)	0.078
Creatinine (μmol/L)	85.76 (17.13)	85.02 (17.03)	0.361	95.26 (13.71)	94.62 (14.52)	0.462
hsCRP (mg/L)	0.70 (0.35–1.40)	1.00 (0.50–2.10)	<0.001	0.72 (0.40–1.48)	1.07 (0.60–2.20)	<0.001
Pulse wave velocity, cm/s	1378 (223)	1461 (283)	<0.001	1400 (213)	1444 (272)	0.007
Current smoking (%)	20.9	26.5	<0.001	30.5	40.9	<0.001
Alcohol drinking (%)[a]	37.2	36.3	0.685	50.3	52.9	0.436
Regular exercise (%)[b]	41.4	38.4	0.202	42.9	40.0	0.354
Hypertension (%)[c]	34.8	41.0	0.007	39.7	42.4	0.374
Type 2 diabetes (%)[d]	8.1	9.9	0.173	10.2	12.7	0.192
Dyslipidemia (%)[e]	31.0	34.9	0.077	29.4	26.4	0.280
Chronic kidney disease[f] (%)	4.1	4.3	0.820	4.9	5.5	0.701

Variables	Women		
	ALP ≤ 71	ALP ≥ 72	*P* value
N	769	221	
Age (year)	51.8 (9.8)	56.8 (7.2)	<0.001
BMI (kg/m^2)	22.3 (2.9)	23.4 (3.2)	<0.001
SBP (mmHg)	119.9 (17.9)	122.5 (19.7)	<0.001
DBP (mmHg)	73.6 (10.6)	76.3 (10.8)	0.001
MAP (mmHg)	89.1 (12.7)	92.7 (13.2)	<0.001
FPG (mmol/L)	5.10 (0.91)	5.35 (1.23)	0.005
Triglyceride (mmol/L)	0.89 (0.68–1.25)	1.02 (0.78–1.45)	0.001
HDL-cholesterol (mmol/L)	1.47 (0.33)	1.39 (0.33)	<0.001
AST (U/L)	19 (16–23)	21 (18–27)	<0.001
ALT (U/L)	16 (12–21)	20 (16–27)	<0.001
GGT (U/L)	15 (12–21)	20 (14–31)	<0.001
Creatinine (μmol/L)	70.92 (9.87)	72.53 (10.69)	0.037
hsCRP (mg/L)	0.50 (0.30–1.20)	1.00 (0.50–2.10)	<0.001
Pulse wave velocity, cm/s	1352 (242)	1472 (290)	<0.001
Current smoking (%)	5.2	7.4	0.141
Alcohol drinking (%)[a]	16.3	13.8	0.382
Regular exercise (%)[b]	38.9	33.2	0.081
Hypertension (%)[c]	28.6	36.2	0.030
Type 2 diabetes (%)[d]	4.8	5.9	0.527
Dyslipidemia (%)[e]	34.3	45.3	0.030
Chronic kidney disease[f] (%)	3.0	2.3	0.564

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; FPG, fasting plasma glucose; HDL, high density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-gutamyl transferase; hsCRP, high sensitivity C-reactive protein. Data are expressed as mean (SD), median (IQR), or percentage (%). *P*-values were calculated using independent two sample *t*-test, Wilcoxon-Rank sum test, or chi-square test.
[a]Alcohol drinking ≥ twice/week. [b]Regular exercise ≥ three times/week. [c]Hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or current use of anti-hypertensive medication. [d]Type 2 diabetes was defined as FPG ≥ 7.0 mmol/L or current use of anti-diabetes medication. [e]Dyslipidemia was defined as triglyceride ≥ 1.70 mmol/L, low HDL cholesterol <1.04 mmol/L or current use of dyslipidemia meidcations. [f]Chronic kidney disease was as defined as estimated glomerular filtration rate by MDRD equation <60 mL/min/1.73 m^2.

Table 2. Pearson's correlation among brachial-ankle pulse wave velocity and clinical variables

	Total		Men		Women	
	r	*P* value	*r*	*P* value	*r*	*P* value
Age (year)	0.537	<0.001	0.511	<0.001	0.579	<0.001
BMI (kg/m^2)	0.057	0.004	0.145	<0.001	0.180	<0.001
SBP (mmHg)	0.465	<0.001	0.353	<0.001	0.567	<0.001
DBP (mmHg)	0.413	<0.001	0.300	<0.001	0.541	<0.001
MAP (mmHg)	0.451	<0.001	0.341	<0.001	0.572	<0.001
FPG (mmol/L)	0.287	<0.001	0.227	<0.001	0.363	<0.001
Triglyceride[a] (mmol/L)	0.132	<0.001	0.015	0.563	0.262	<0.001
HDL-cholesterol (mmol/L)	-0.110	<0.001	-0.111	0.668	-0.184	<0.001
AST[a] (U/L)	0.078	<0.001	0.048	0.084	0.103	0.001
ALT[a] (U/L)	0.083	<0.001	-0.017	0.502	0.171	<0.001
GGT[a] (U/L)	0.118	<0.001	-0.111	0.846	0.224	<0.001
Creatinine (μmol/L)	0.083	<0.001	0.061	0.018	0.045	0.157
hsCRP[a] (mg/L)	0.168	<0.001	0.083	0.274	0.274	<0.001
ALP[a] (U/L)	0.206	<0.001	0.274	<0.001	0.328	<0.001

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; FPG, fasting plasma glucose; HDL, high density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-gutamyl transferase; hsCRP, high sensitivity C-reactive protein. Data are expressed as correlation coefficient (*r*) and *P* values were calculated using Pearson's correlation analysis for clinical variables. [a]Indicates log-transformed values.

Table 3. Multiple linear regression analysis showing the independent relationship between log-transformed ALP level and brachial-ankle pulse wave velocity

	β coefficient	95% CI	SE	*P* value
Men				
Model 1	73.1	30.6–115.5	21.6	<0.001
Model 2	72.8	26.6–119.1	23.5	0.002
Model 3	78.6	31.6–125.5	23.9	0.001
Women				
Model 1	89.7	42.9–130.3	23.7	<0.001
Model 2	81.5	36.1–126.9	23.2	<0.001
Model 3	85.3	38.9–131.6	23.6	<0.001
Model 4	90.6	37.1–144.2	27.3	<0.001

Abbreviations: CI, confidence interval; SE, standard error.
Model 1: adjusted for age, body mass index, cigarette smoking, alcohol drinking, and regular exercise.
Model 2: adjusted for variables included in Model 1 and hypertension, type 2 diabetes, dyslipidemia, and chronic kidney disease.
Model 3: adjusted for variables included in Model 2 and log-transformed AST, log-transformed ALT, and log-transformed GGT levels.
Model 4: adjusted for variables included in Model 3 and menopause status.

Discussion

In this cross-sectional study, serum ALP level was positively and independently associated with baPWV for both men and women after adjusting for potential confounding variables. Our findings are in agreement with previous results that high serum ALP level, even still within the normal range, is positively associated with cardiovascular disease and metabolic syndrome. Tonelli *et al.* reported an independent relationship between higher serum ALP level and all-cause and CVD mortality among 4115 survivors of myocardial infarction from the Cholesterol and Recurrent Events cohort with a median follow-up duration of 58.9 months. Compared with the lowest serum ALP tertile, the adjusted mortality risk in the highest tertile was 1.43 (95% CI, 1.08–1.89), and the incidence risk of heart failure was 1.38 (95% CI, 1.01–1.88)[4]. In addition, among 5995 men and non-pregnant women aged ≥ 40 years who participated in the National

Health and Nutrition Examination Survey (NHANES) from 1999–2004, the highest quartile of serum ALP level was associated significantly with peripheral arterial disease. Compared with the lowest quartile, the OR (95% CI) for peripheral arterial disease was 1.65 (1.10–2.46) after adjusting for confounding factors[24]. More recently, Krishnamurthy et al. showed that the prevalence of metabolic syndrome gradually increased from the lowest serum ALP quartile (14%) to the highest quartile (41%) in the general United States population from the NHANES III[25].

The exact mechanism by which serum ALP level is positively associated with arterial stiffness is not known, but some possible explanations for the relationship between increased serum ALP level and increased baPWV deserve consideration. First, ALP catalyzes the hydrolysis of inorganic pyrophosphate, inhibiting hydroxyapatite formation and thereby decreasing the inorganic pyrophosphate level and promoting vascular calcification[2, 26-28]. Second, elevated serum ALP level and arterial stiffness may be linked by low-grade inflammation in the vessel walls. Chronic low-grade inflammation plays a crucial role in initiating and propagating the atherosclerotic process. Serum ALP level was significantly correlated with elevated serum hsCRP level in the present study and may contribute to systemic inflammation and other important effects on arterial stiffness[29, 30]. In the chronic low-grade inflammatory state, tumor necrosis factor (TNF)-α and interleukin (IL)-1β levels are elevated, which can stimulate ALP expression and activity in vascular smooth muscle cells and lead to increased risk of arterial stiffness[31]. Moreover, these stimulated inflammatory cells contain a variety of cytokines that have an increased tendency to adhere to the vascular endothelium and easily penetrate the intima, which can induce further vascular damage and increase vascular resistance.

Some limitations should be considered when interpreting this study. First, because of its cross-sectional design, caution should be used in causal and temporal interpretations of our findings. Although a significant positive relationship between serum ALP level and baPWV existed in this study, it cannot be definitively concluded whether ALP is a risk factor that is actively involved in the development of arterial stiffness, a bystander, or an epiphenomenon of arterial stiffness. Thus, further prospective research is warranted to identify the positive association between serum ALP level and arterial stiffness. Second, because the study population was limited to participants who visited a single hospital for health promotion screenings and appeared to be slightly healthier than most community-based cohorts, it may not be representative of the general population. This makes the generalization of our results difficult. Third, although several studies have shown that menstrual cycle may affect vascular function and arterial stiffness[32, 33], we could not measure the serum ALP level and baPWV at the same menstrual cycle. To compensate for this limitation, we conducted multiple linear regression analysis, additionally adjusting for menopause status in model 4. Fourth, we could not determine whether hepatic ALP or bone ALP was associated with baPWV because we did not measure ALP isoenzymes. To minimize this limitation, we performed analysis adjusting for the hepatobiliary markers such as AST, ALT, and GGT as confounding factors. Lastly, arterial stiffness was assessed using baPWV instead of cfPWV in the present study. Conventionally, cfPWV has been considered the gold standard measure of arterial stiffness. However, as previously described, it is easier and more time-effective to assess baPWV than other conventional measurements of aortic or carotid-femoral PWV, and baPWV has a good correlation with aortic PWV. Despite these potential limitations, we believe this is the first study to report a positive association between serum ALP level and arterial stiffness.

In conclusion, serum ALP level, a simple laboratory marker, was positively associated with baPWV. Our results suggest that an elevated ALP level may be a useful surrogate marker for arterial stiffness in adult men and women.

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Competing Interests

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