Original Article

Serum Calcium Level is Associated with Brachial-ankle Pulse Wave Velocity in Middle-aged and Elderly Chinese*

DENG Xin Ru[1,2,‡], ZHANG Yin Fei[3,‡], WANG Tian Ge[1,2], XU Bai Hui[1,2], SUN Ji Chao[1,2,4], ZHAO Lie Bin[2], XU Min[1,2], CHEN Yu Hong[1,2], WANG Wei Qing[1,2], BI Yu Fang[1,2], and LU Jie Li[1,2,#]

1. Key Laboratory for Endocrine and Metabolic Diseases, Ministry of Health, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, E-Institute of Shanghai Universities, Shanghai 200025, China; 2. Shanghai Clinical Center for Endocrine and Metabolic Diseases, Shanghai Institute of Endocrine and Metabolic Diseases, Department of Endocrinology and Metabolism, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200025, China; 3. Department of Endocrinology and Metabolism, Central Hospital of Jiading District, Shanghai 201800, China; 4. Laboratory of Endocrine and Metabolic Diseases, Institute of Health Sciences, Shanghai Institutes for Biological Sciences, Shanghai 200025, China

Abstract

Objective To study the relation between serum calcium level and elevated BaPWV in Chinese subjects.

Methods The relation between serum calcium level and elevated BaPWV was studied in 9 615 subjects. The mean value of left and right BaPWV was analyzed. BaPWV was defined as high when it was ≥1 752.5 cm/s (the upper quartile) either side.

Results The BaPWV and its elevated percentage progressively increased across the quartiles of the serum calcium level (P<0.05). The prevalence of elevated BaPWV was significantly higher in subjects of the second, third and highest quartiles than in those of the lowest quartile (26.9%, 28.4%, and 33.2% *vs* 23.7%, P=0.0116, P=0.0004, and P<0.0001). Logistic regression analysis revealed that the risk of elevated BaPWV was 1.32- fold higher in subjects of the highest quartile than in those of the lowest quartile (OR=1.32, 95% CI: 1.08-1.60).

Conclusion The elevated serum calcium level is related to an elevated BaPWV and a higher risk of arterial stiffness, independent of conventional risk factors, in middle-aged and elderly Chinese subjects.

Key words: Calcium; Brachial-ankle pulse wave velocity; Vascular stiffness

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INTRODUCTION

Calcium (Ca) is one of the major mineral components in the skeletal system and an essential nutrient required for nerve conduction, muscle contraction, hormone and enzyme secretion, and blood clotting[1]. It has been reported that calcium supplementation or serum concentration are related to an increased risk of vascular diseases[2-4], such as cardiovascular problems, strokes and even death. Although there is a possibility of increased risk, there is no consensus

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†DENG Xin Ru and ZHANG Yin Fei contributed equally to the article.

#Correspondence should be addressed to LU Jie Li, MD, PhD, Tel: 86-21-64370045, Ext: 665340, E-mail: jielilu@hotmail.com

Biographical notes of the first authors: DENG Xin Ru, female, born in 1988, master of medicine, majoring in clinical epidemiology of diabetes and endocrinology; ZHANG Yin Fei, male, born in 1967, bachelor of medicine, majoring in clinical epidemiology of diabetes and endocrinology.

is available on such findings.

Arteriosclerosis, characterized as arterial wall thickening, stiffening and low flexibility, is not only one of the independent risk factors for cardio-cerebrovascular diseases, but is also closely related to hypertension, metabolic syndrome and vascular complications of diabetes[5-7]. Pulse wave velocity (PWV), widely used in clinical and epidemiological study, is a noninvasive and simple method of measuring arterial stiffness[8]. Brachial-ankle pulse wave velocity (BaPWV) was used as an indicator of arteriosclerosis in this study[9-11], which is one of the measurements of PWV and an independent predictor of cardiovascular complications in hypertension[12], and is well correlated with many atherosclerotic risk factors[13-14].

However, the underlying mechanism for a higher serum calcium level contributing to the development of cardiovascular disease remains unclear. The hypothesis that elevated serum calcium level is related to higher BaPWV values in the general population was tested in the present study.

METHODS

Study Population

A population-based cross-sectional study was conducted by cluster sampling in a community of Jiading District, Shanghai, China, from March 2010 to August 2010. A total of 10 569 residents aged 40 years or older were invited to participate in interviews and undertake an extensive physical examination. Those with who did not have data on serum calcium and BaPWV were excluded from this study. Finally, 10 375 subjects (98.2%) were included in this study and 9 615 subjects were included in data analysis.

The study protocol was approved by the Institutional Review Board of Ruijin Hospital and conducted in accordance with the principle of Helsinki Declaration II. All participants gave their written informed consent.

Data Collection

Data, including socio-demographic characteristics, medical history and lifestyle factors were collected using a standard questionnaire. Individuals were divided into never-smoker group, former-smoker group and current-smoker group, while alcohol consumption individuals were divided into never-drinker group, former-drinker group and current-drinker group. Data on calcium intake were not collected.

Anthropometry

Body mass index (BMI) was calculated as body weight in kilograms divided by body height squared in meters, body height and weight were recorded to the nearest 0.1 cm and 0.1 kg, waist circumstance (WC) was measured to the nearest 0.1 cm at the umbilical level horizontally in a standing position. After a 5 min rest, blood pressure was measured 3 times (averaged for analysis) on the non-dominant arm in a sitting position at 1 min interval.

Blood Biochemical Assays

After the subjects were fasted for 10 h, blood samples were taken for laboratory assay. Serum levels of fasting blood glucose, insulin, calcium, TG, TC, LDL-C, HDL-C, albumin, and creatinine were measured. Glomerular filtration rate was estimated following the modified prediction equation[15]. Estimated glomerular filtration rate (eGFR)=186×[serum creatitine×0.011]$^{-1.154}$×[age]$^{-0.203}$×[0.742 if female]×1.233, while 1.233 was the adjusting coefficient for Chinese subjects[16]. Normal or decreased kidney function was defined as eGFR ≥90 mL/min/1.73 m^2 or <90 mL/min/1.73 m^2[15]. Insulin sensitivity was assessed according to the homeostasis model assessment insulin resistance (HOMA-IR). HOMA-IR=fasting insulin (μIU/mL)×fasting glucose (mmol/L)/22.5[17].

Measurement of BaPWV

After a 5 min rest, the BaPWV in each subject was measured. The mean BaPWV value of left BaPWV and right BaPWV was analyzed. BaPWV was defined as high when it was ≥1752.5 cm/s (the upper quartile) either side.

Statistical Analysis

The data were analyzed with SAS version 8.1 (SAS Institute, Cary, NC). Continuous variables with normal distribution were presented as mean±SD, while skewed variables were expressed as median (interquartile ranges) and logarithmically transformed before analysis. Categorical variables were presented as numbers (proportions). The serum calcium quartiles of the subjects were divided into quartile 1 (Q1) ≤2.24 mmol/L, quartile 2 (Q2) 2.25-2.31 mmol/L, quartile 3 (Q3) 2.32-2.37 mmol/L,

quartile 4 (Q4) ≥2.38 mmol/L. The trend was tested by Pearson and Spearman correlation analysis, and Cochran-Armitage trend analysis, respectively, according to the serum calcium quartiles. The categorical variables were compared by a χ^2 test. The correlation between BaPWV value and risk factors for arterial stiffness was tested by Pearson and Spearman correlation analysis, respectively. All potential risk factors for BaPWV were put into the multivariate stepwise linear regression models to identify the factors independently related with serum calcium. The risk of prevalent arterial stiffness was analyzed by logistic regression analysis based on the quartiles of serum calcium. Model 1 was unadjusted. Model 2 was adjusted for age, sex, BMI, smoking, drinking. Model 3 was adjusted for age, sex, BMI, smoking, drinking, TG, TC, HDL-C, SBP, albumin, and eGFR. Relation between arterial stiffness, and serum calcium level was analyzed within the strata of sex (men/women), age (<65/≥65 years), BMI (normal/overweight/obesity), eGFR (≥90/<90 mL/min/1.73 m^2), hypertension (yes/no), and diabetes (yes/no). Normal, overweight and obese were defined as <24 kg/m^2, 24-27.9 kg/m^2, and ≥28 kg/m^2, respectively. *P* value <0.05 was considered statistically significant.

RESULTS

Basic Characteristics of the Study Population

A total of 9 615 subjects (3 627 males and 5 988 females) aged 40 years and older (mean 58.5 years) were eligible for the analysis. The prevalence of arterial stiffness was 28.3%. Table 1 shows the characteristics

Table 1. Variables of Study Population Based on Quartiles of Serum Calcium Levels (*n*=9 615)

Variables	Quartile 1 ≤2.24 mmol/L (*n*=2 127)	Quartile 2 2.25-2.31 mmol/L (*n*=2 586)	Quartile 3 2.32-2.37 mmol/L (*n*=2 236)	Quartile 4 ≥2.38 mmol/L (*n*=2 666)	*P* for Trend
Ca (mmol/L)	2.19±0.05	2.28±0.02	2.34±0.02	2.44±0.06	<0.0001
Age (yr)	58.3±10.5	58.4±9.9	58.6±9.1	58.6±9.1	=0.1746
Male [*n* (%)]	879 (41.3%)	1 051 (40.6%)	804 (36.0%)	893 (33.5%)	<0.0001
Smoking status [*n* (%)]					<0.0001
Never-smoker	1 483 (72.2%)	1 855 (74.2%)	1 659 (77.1%)	2 045 (79.2%)	
Former-smoker	83 (4.0%)	97 (3.9%)	79 (3.7%)	82 (3.2%)	
Current-smoker	488 (23.8%)	547 (21.9%)	413 (19.2%)	454 (17.6%)	
Drinking status [*n* (%)]					=0.0244
Never-drinker	1 614 (86.2%)	1 975 (86.8%)	1 754 (87.9%)	2 123 (88.4%)	
Former-drinker	36 (1.9%)	44 (1.9%)	26 (1.3%)	33 (1.4%)	
Current-drinker	221 (11.8%)	256 (11.3%)	216 (10.8%)	246 (10.2)	
BMI (kg/m^2)	25.0±3.3	25.2±3.2	25.1±3.3	25.2±3.3	=0.0522
WC (cm)	82.1±9.1	82.8±9.0	82.7±9.0	83.1±9.0	=0.0004
SBP (mmHg)	139.0±19.9	140.2±20.3	141.6±19.5	143.3±20.2	<0.0001
DBP (mmHg)	81.2±10.4	82.3±9.0	83.1±10.1	84.5±10.2	<0.0001
TG (mmol/L)	1.18 (0.85-1.68)	1.33 (0.97-1.89)	1.43 (1.01-1.94)	1.58 (1.13-2.27)	<0.0001
TC (mmol/L)	5.00±0.95	5.23±0.94	5.41±0.98	5.6±1.05	<0.0001
LDL-C (mmol/L)	2.96±0.78	3.14±0.84	3.24±0.84	3.40±0.91	<0.0001
HDL-C (mmol/L)	1.29±0.32	1.31±0.30	1.34±0.32	1.35±0.33	<0.0001
Albumin (g/L)	47.1±2.4	48.3±2.1	49.1±2.1	50.0±2.1	<0.0001
eGFR (mL/min/1.73 m^2)	136.7±27.0	133.3±25.1	132.3±24.5	129.3±25.9	<0.0001
HOMA-IR	1.37 (0.88-2.11)	1.57 (1.06-2.38)	1.66 (1.12-2.47)	1.98 (1.30-3.03)	<0.0001
Central Obesity [*n* (%)]	262 (12.3%)	343 (13.3%)	252 (11.3%)	330 (12.4%)	=0.5460
Hypertension [*n* (%)]	1 149 (54.3%)	1488 (57.6%)	1402 (62.9%)	1 768 (66.5%)	<0.0001
Diabetes [*n* (%)]	163 (12.4%)	435 (16.9%)	413 (18.5%)	658 (24.7%)	<0.0001
BaPWV (cm/s)	1467.0 (1 288.0-1 698.0)	1 485.3 (1 308.0-1 734.0)	1 518.3 (1 338.8-1 750.3)	1 556.3 (1 360.5-1 820.5)	<0.0001

Note. Data are expressed as mean±SD or median (interquartile ranges) or number (percentage) of subjects. Data were missed for smoking status (*n*=326), drinking status (*n*=309), WC (*n*=6), SBP (*n*=14), DBP (*n*=14), HDL-C (*n*=1), diabetes (*n*=16), hypertension (*n*=15), central obesity (*n*=6). Ca: calcium; BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglycerides; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment of insulin resistance. *P* values for trend between groups are based on Person's and Spearman correlation analysis or the Cochran-armitage test.

of the subjects according to their quartiles of serum calcium level. The serum levels of calcium, TG, TC, LDL-C, HDL-C, albumin, HOMA-IR, and the WC, SBP, DBP were higher in females than in males. The prevalence of diabetes increased with the serum calcium quartiles. The BaPWV values showed the same tendency (P<0.001).

Prevalence of Elevated BaPWV in Different Serum Calcium Levels

The BaPWV value and prevalence of arterial stiffness were higher in subjects with a higher calcium level than in those with a lower calcium level. The prevalence of elevated BaPWV was 23.7%, 26.9%, 28.4%, and 33.2%, respectively, in the lowest quartile of serum calcium level (P<0.0001), and significantly higher in the second, third and the upper quartiles than in the lowest quartile (P=0.0116, P=0.0004, P<0.0001, Figure 1).

Relation between BaPWV and Serum Calcium Level

Pearson and Spearman correlation analysis showed that age, BMI, WC, SBP, DBP, Log-TG, TC, LDL-C, HDL-C, Log-HOMA-IR, albumin, eGFR, and quartiles of serum calcium level were correlated with BaPWV. Multivariate stepwise linear regression analysis suggested that age, BMI, SBP, Log-TG, HDL-C, Log-HOMA-IR, albumin, and eGFR were significantly correlated with BaPWV (Table 2). After adjustments for age, BMI, smoking, drinking, TG, TC, HDL-C, SBP, albumin, and eGFR, logistic regression analysis revealed that the risk of elevated BaPWV was 32% higher in the highest quartile of serum calcium level than the lowest quartile of serum calcium level (Table 3).

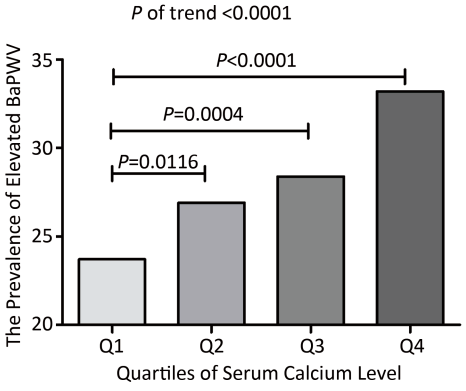

Figure 1. Prevalence of elevated BaPWV according to the quartiles of serum calcium levels.

Table 1. Stepwise Regression Analysis Showing Risk Factors for Log-BaPWV

Items	*r*	*P* value	Standardized β	*P* value
Age (years)	0.546	<0.0001	0.405	<0.0001
Sex (men=1, women=2)	-0.015	=0.1373	-	-
BMI (kg/m^2)	0.101	<0.0001	-0.105	<0.0001
WC (cm)	0.142	<0.0001	-	-
SBP (mmHg)	0.560	<0.0001	0.426	<0.0001
DBP (mmHg)	0.264	<0.0001	0.029	=0.0045
Log-TG (mmol/L)	0.183	<0.0001	0.070	<0.0001
TC (mmol/L)	0.130	<0.0001	-	-
LDL-C (mmol/L)	0.104	<0.0001	-	-
HDL-C (mmol/L)	-0.038	=0.0002	-0.022	=0.0098
Log-HOMA-IR	0.186	<0.0001	0.087	<0.0001
Albumin (g/L)	0.280	=0.006	0.036	<0.001
eGFR (mL/min/1.73 m^2)	-0.174	<0.0001	0.028	=0.0004
Ca (mmol/L)	0.105	<0.0001	0.020	=0.0158

Note. *r*: correlation coefficient; β: regression coefficient.

Table 3. Risk of Elevated BaPWV

Models	Q 1	Q 2	Q 3	Q 4	*P* for trend
Model 1	1.00	1.19 (1.04-1.35)	1.28 (1.12-1.46)	1.60 (1.41-1.82)	<0.0001
Model 2	1.00	1.19 (1.01-1.40)	1.34 (1.14-1.59)	1.79 (1.53-2.10)	<0.0001
Model 3	1.00	1.06 (0.88-1.27)	1.10 (0.91-1.33)	1.32 (1.08-1.60)	=0.0037

Note. See Table 1 for Ca quartiles definition. Model 1 was unadjusted. Model 2 was adjusted for age, sex, BMI, smoking, and drinking. Model 3 was adjusted for age, sex, BMI, smoking, drinking, TG, TC, HDL-C, SBP, albumin, and eGFR.

Relation between Risk of Elevated BaPWV and Serum Calcium Levels in Different Subgroups

The relation between Risk of Elevated BaPWV and Serum Calcium Levels in Different Subgroups is presented in Figure 2. In a fully adjusted model (adjusted for age, sex, BMI, smoking, drinking, TG, TC, LDL-C, HDL-C, SBP, DBP, albumin, and eGFR), the risk of elevated BaPWV was significantly related to serum calcium levels in women (OR 1.45, 95% CI 1.14-1.84, *P*=0.0028), relatively old subjects (OR 2.04, 95% CI 1.49-2.82, *P*<0.0001), subjects with normal BMI (OR 1.49, 95% CI 1.07-2.07, *P*=0.0178), subjects with normal kidney function (OR 1.24, 95% CI 1.02-1.52, *P*=0.0314), and subjects with hypertension (OR 1.36, 95% CI 1.10-1.68, *P*=0.0053).

DISCUSSION

In the present study, the serum calcium level was related with the BaPWV, an early marker of arteriosclerosis.

An elevated BaPWV suggests arterial stiffness, which is related with an increased risk of cardiovascular morbidity and mortality. It was reported that a BaPWV>1400 cm/s is a dependent variable for the risk stratification by Framinham score and for the discrimination of patients with atherosclerotic vascular disease and a potential marker of cardiovascular risk[18]. It has been shown that an increase in BaPWV by 1 cm/s corresponds with an increase of 12%, 13%, and 6% in total cardiovascular events, cardiovascular mortality, and all-cause mortality respectively[19].

The findings in the present study suggest that elevated serum calcium level is related with the risk of cardiovascular disease due to increased arterial stiffness. Serum calcium may be a potentially modifiable risk factor for coronary heart disease and strokes in community-dwelling adults (hazards ratio 1.01, 95% CI 0.96-1.06, and hazards ratio 1.16, 95% CI 1.07-1.26 respectively)[4,20], which is consistent with the findings in this study. It has been demonstrated that high intake of supplemental calcium is related with cardiovascular disease in men but not in women[21].

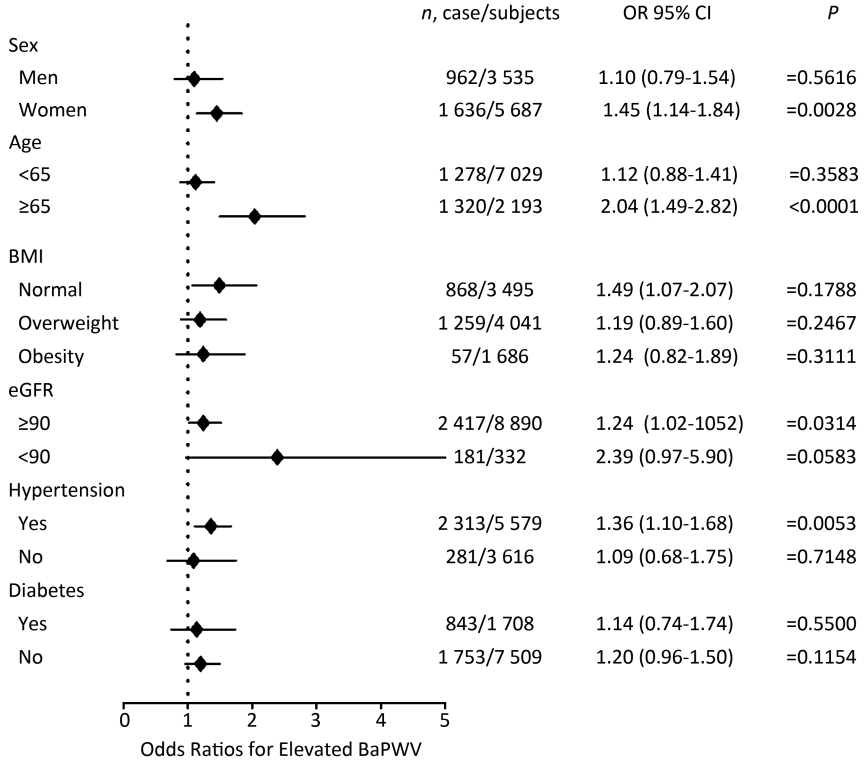

Figure 2. Relation between risk of elevated BaPWV and highest quartile of Ca. The OR value was adjusted for age, sex, BMI, smoking, drinking, TG, TC, HDL-C, SBP, albumin, and eGFR except for the strata variables.

Due to hormone change-related calcium loss potentially resulting in osteoporosis, especially in women, calcium supplements are considered as one of the main treatment modalities of osteoporosis[22]. The American Dietetic Association recommended that the dietary allowance intake of calcium is 1 000 mg/d for adults and 1 200 mg/d for people aged 51 years and over[23]. However, a perspective from the American Association of Clinical Endocrinologists based on a review of all relevant articles during the year of 1992 and 2011 revealed that calcium supple- mentation of more than 500 mg daily is related to an increasing risk of cardiovascular disease[24]. Thus, increasing calcium intake for osteoporosis management may induce health problems.

One possible explanation for our findings may be the calcium deposit in vascular structures[25]. The vascular calcification that contributes to arterial stiffness is intertwined with bone mineralization[21]. The majority of vascular calcifications are related to vascular smooth muscle cells de-differentiating into osteoblast/chondrocyte-like cells which may lead to calcium deposition within or around vascular smooth muscle cells[26].

Several limitations in our study should be addressed. First, because it was an observational study, a conclusion about causality could not be drawn. Second, any possible effect of serum vitamin D and serum parathyroid hormone levels was not assessed, since such variables were not detected. Third, elevated BaPWV was defined as >1 752.5 cm/s, which may be a surrogate for increased arterial stiffness, because BaPWV >1 400 cm/s can predict cardiovascular disease[18]. The prevalence of arterial stiffness was thus underestimated in the general population aged 40 years or older. Forth, no accurate information about the use of anti-hypertension drugs was taken into analysis, which would influence our observations.

In conclusion, elevated serum calcium level is independently related with a higher BaPWV. Further studies are needed to determine the relationship between serum calcium level and BaPWV.

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