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Original Article

Serum 25-Hydroxyvitamin D Levels: Related to Ambulatory Arterial Stiffness Index in Hypertensive Seniors

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SUMMARY

Background: This study aims to explore the relation between 25(OH)D level, ambulatory arterial stiffness index (AASI), and other parameters from ambulatory blood pressure monitoring (ABPM).
Methods: The study sample consisted of 102 older patients with essential hypertension. Clinical characteristics of population divided into three groups according to 25(OH)D tertile.
Results: The patients in the high tertile of 25(OH)D with low body mass index (BMI) ($P < 0.01$), low tertile group with high low-density lipoprotein (LDL) ($P < 0.05$). Significant differences were in terms of Office SBP, Office PP, 24 h SBP, 24 h PP, daytime SBP, daytime PP, night-time SBP, night-time PP ($P < 0.01$), nocturnal dipping ($P < 0.05$) and ASSI ($P < 0.01$) among three groups. AASI showed decrease as 25(OH)D increases. Differences are significant. Correlation test showed a significant relationship of AASI with BMI ($r = 0.368$, $P < 0.001$), 24 h average SBP ($r = 0.641$, $P < 0.001$), 24 h average PP (0.66, $P < 0.001$), nocturnal dipping ($r = -0.217$, $P < 0.05$), 25(OH)D ($r = -0.621$, $P < 0.001$). Multivariate liner regression analysis showed that 25(OH)D ($P < 0.01$) and 24 h average PP ($P < 0.01$) were independently related to AASI.
Conclusions: The relationship of AASI with BMI, 24 h average SBP, 24 h average PP, Nocturnal dipping, 25(OH)D are significant. 25(OH)D ($P < 0.01$) and 24 h average PP ($P < 0.01$) were independently related to AASI.

1. Introduction

Vitamin D is traditionally recognized for its important role in calcium and phosphorous homeostasis and in bone metabolism. Accumulated evidence from currenting studies suggests that vitamin D may be associated with cardiovascular disease, such as hypertension,[1] peripheral arterial disease,[2] myocardial infarction,[3,4] and related mortality.[5,6] Hypovitaminosis D may be an independent risk factor of cardiovascular disease, and there is a significant inverse association of baseline circulating levels of 25-hydroxyvitamin D [25(OH)D] with risk of incident hypertension in apparently. From the meta-analysis by Kunutsor et al.,[7] if the circulating 25(OH)D levels increase 10 ng/mL, the risk of future hypertension will be lowered by 12%, with 2432 articles reviewed for eligibility, eight unique prospective cohorts with aggregate data.

Other available data also indicate that a low 25(OH)D level may increase prevalence of CVD.[8–10] Vitamin D receptors (VDRs) are present in all cells which may play a role on modulation of endothelial functions,[11] including ECs, VSMCs, and immune cells. Vitamin D is also involved in this systemic inflammatory process directly.[12,13] Vitamin D regulate amounts of physiological and pathological processes such as vascular cell growth, migration, and differentiation; immune response modulation; cytokine expression; and inflammatory and fibrotic pathways, all of which effect on endothelial activation/dysfunction and the later stages of the plaque vulnerability and rupture.[12,13]

Ambulatory arterial stiffness index (AASI) which derived from ambulatory blood pressure (BP) monitoring (ABPM) was introduced as a marker of arterial stiffness suggested by Li et al.[14] AASI is a well-known predictor of cardiovascular mortality in hypertensive patients.[15]

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The aims of this study were to analyze AASI and 25(OH)D level in hypertensive seniors and to investigate determinants of AASI, thus to explore the relation between 25(OH)D level, other parameters from ambulatory blood pressure (BP) monitoring (ABPM), and AASI.

2. Materials and methods

2.1. Participants

Our study sample consisted of 102 older patients with essential hypertension who recruited from osteoporosis screening in Affiliated Hospital of Yangzhou University. The screen was including 766 older patients. The patients were aged ≥60 years, In these participants there are 261 hypertension patients. Hypertension was defined by clinic systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg or being treated with antihypertensive medication(s). Exclusion criteria included the presence of the following: life-threatening disease, secondary hypertension, known coronary artery disease (including acute coronary syndrome, myocardial infarction, angina pectoris or coronary revascularization procedure within the last 3 months), atrial fibrillation and other arrhythmias, chronic renal failure (creatinine level>133 μmol/L), chronic liver disorders, moderate or severe valvular disease, diabetes mellitus, the patients taking calcium, and the use of vitamin D. Stroke was not excluded unless with life-threatening. Written informed consent was obtained from all the patients. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Central South University. Written informed consent was obtained from all participants.

2.2. Laboratory tests

Venous blood was drawn in the morning after an overnight fasting plasma glucose (FPG), total cholesterol (TC), high-density protein cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), blood urea nitrogen (BUN), creatinine (Cr), serum calcium (Ca), serum phosphorus (P), other biochemical blood measurements were determined by a fully automatic biochemical analyser (Hitachi7170, Japan). Concentrations of 25(OH)D were measured using a high pressure liquid chromatography (HPLC) method by an auto high performance liquid chromatography analyser (Shimadzu LC-10AT, Japan), the intra-assay coefficients of variation were 5.6% respectively; the inter-assay coefficients of variation were 7.6% respectively.

2.3. Office BP measurement

Office BP was measured by a mercury sphygmomanometer from the right Arm, Participants were instructed to take the antihypertensive medication(s) as usual the morning of the examination. Three measurements were obtained at 2-min intervals after 10 min of rest in the sitting position in a quiet room, following European Society of Hypertension (ESH)/European society of Cardiology (ESC) guidelines.[16] The average of all the three measurements was recorded as the resting office BP. Office PP was defined by the difference between systolic and diastolic office BPs.

2.4. Ambulatory BP monitoring

ABPM was recorded during a routine day by an automatic BP recorder (MC-6800, Mindray, Shenzhen, China), which obtained blood pressure readings at 30-min intervals from 0600 h to 2200 h as daytime and at 60-min intervals from 2200 h to 0600 h as night-time, using manufacturer-provided software according to ESH/ESC guidelines.[16] On the non-dominant upper limb positioned the arm cuff. The subjects were asked to reduce movement and to keep their upper limb immobile during each measurement. Records containing less than 75% satisfactory readings out of total possible readings (40 readings) over the 24 h period measures were excluded from evaluation. From 24 h BP readings, we got the regression slope of DBP on SBP. AASI was calculated as 1 minus the regression slope. Nocturnal dipping (%) was defined as the percent nocturnal systolic BP reduction compared to daytime systolic BP.

2.5. Statistical analysis

Data analyses were performed using SPSS20.0 (SPSS Inc). Continuous variables were expressed as mean ± SD (standard deviation), and qualitative variables as frequency distributions. Continuous variables were analysed by ANOVA. Categorical variables were analysed using Chi-Square test. Correlations were tested using the Pearson coefficient correlation test. Afterwards multivariate regression analysis was performed to confirm the independent predictive power of arterial function. Multiple linear regression analysis was performed to study the association of ambulatory arterial stiffness index and other parameters. All statistical tests were 2 sided, $P < 0.05$ were considered statistically significant.

3. Results

3.1. General characteristics of study subjects

The 102 older patients included 59 (57.8%) male and the mean age was 70.5 (standard deviation, 6.3) years. Clinical characteristics of population divided according to 25-hydroxyvitamin D tertile are listed in Table 1. It showed the patients in the high tertile of 25-hydroxyvitamin D with low BMI ($P < 0.01$), low tertile group with high LDL ($P < 0.05$). There were no significant differences in terms of age, HDL, FBG, TCH, Ca, P, BUN and Cr.

Table 1
Clinical characteristics according to 25-hydroxyvitamin D tertile groups.

25-hydroxyvitamin D tertile	Low ≤30.7 nmol/L	Middle >30.7/<54.7 nmol/L	High ≥54.7 nmol/L	*P* value
Numbers	34	34	34	
Sex, Male (%)	61.8	55.9	55.9	0.851
Age (year)	69.8 ± 6.7	70.3 ± 6.3	71.3 ± 5.8	0.609
BMI (kg/m^2)	26.4 ± 2.8	25.6 ± 1.4	24.6 ± 2.3	0.009
LDL (mmol/L)	3.1 ± 0.5	2.7 ± 0.4	2.9 ± 0.6	0.033
HDL (mmol/L)	1.3 ± 0.2	1.2 ± 0.2	1.3 ± 0.3	0.179
FBG (mmol/L)	5.9 ± 1.2	5.6 ± 1.4	5.5 ± 0.8	0.186
TCH (mmol/L)	5.4 ± 0.8	5.0 ± 0.5	5.1 ± 0.7	0.115
Ca (mmol/L)	2.24 ± 0.16	2.27 ± 0.15	2.27 ± 0.16	0.663
P (mmol/L)	1.20 ± 0.26	1.22 ± 0.24	1.26 ± 0.17	0.618
BUN (mmol/L)	5.8 ± 1.5	6.2 ± 1.5	6.2 ± 2.0	0.479
Cr (mmol/L)	75.6 ± 33.8	68.5 ± 27.5	77.8 ± 23.1	0.372

Clinical characteristics of population divided according to 25-hydroxyvitamin D tertile are listed. Data are reported as mean (±SD) or percentage unless otherwise noted. ANOVA and Chi-Square test were used. $P < 0.05$ were considered statistically significant.
Abbreviations: 25(OH)D: 25-hydroxyvitamin D; BMI: body mass index; BP: blood pressure; LDL: low-density lipoprotein; HDL: high-density lipoprotein; FPG: fasting plasma glucose; TCH: total cholesterol; Ca: serum calcium; P: serum phosphorus; BUN: blood urea nitrogen; Cr: creatinine.

3.2. The results of 24 h ambulatory blood pressure monitoring

Office blood pressure and 24 h ABPM parameters in three groups are shown in Table 2. Significant differences were in terms of Office SBP, Office PP, 24 h SBP, 24 h PP, daytime SBP, daytime PP, night-time SBP, night-time PP ($P < 0.01$), nocturnal dipping ($P < 0.05$) and ASSI ($P < 0.01$) among three groups.

3.3. Crude association between ambulatory arterial stiffness index and other parameters

AASI showed decrease as 25(OH)D increases (plotted by tertiles). Differences are significant (Fig. 1). Correlation test showed a significant relationship of AASI with BMI ($r = 0.368$, $P < 0.001$), 24-h average SBP ($r = 0.641$, $P < 0.001$), 24 h average PP (0.66, $P < 0.001$), Nocturnal dipping ($r = -0.217$, $P < 0.05$), 25(OH)D ($r = -0.621$, $P < 0.001$). Neither age nor 24 h average DBP showed any correlation (Table 3). Fig. 2 illustrates the significant correlation of ambulatory arterial stiffness index with 25(OH)D.

3.4. Independent correlation factors of ambulatory arterial stiffness index

Multivariate liner regression analysis showed that 25(OH)D ($P < 0.01$) and 24 h average PP ($P < 0.01$) were independently related to AASI (Table 4).

4. Discussion

In this study, the study population was divided into three groups according to 25-hydroxyvitamin D tertile for high, middle and low 25(OH)D levels. The general condition of the members of the three groups was compared, and the analysis of the results (Table 1) showed that there were no significant differences in the general condition among the three groups, besides the significant differences in LDL and BMI. There were also some similar findings in many other clinical and epidemiological studies,[17] where it was found that 25(OH)D level was lower in obese people, 25(OH)D level was relatively lower in patients with high BMI, and 25(OH)D deficiency might stimulate an increase in some factors such as LDL which can promote atherosclerosis.

In Table 2, the comparison of office blood pressure and 24 h ambulatory blood pressure among the three groups indicated that there were significant differences in office systolic blood pressure (OSBP) and pulse pressure (OPP), 24 h average systolic blood pressure (ASBP) and average pulse pressure (APP), 24 h daytime systolic blood pressure (dSBP) and daytime pulse pressure (dPP), 24 h nighttime systolic blood pressure (nSBP) and nighttime pulse pressure (nPP), the rate of nocturnal dipping of blood pressure and the ambulatory arterial stiffness index (ASSI). The systolic blood pressure and pulse pressure showed a downward tendency as the 25(OH)D level increased. The rate of nocturnal decrease of blood pressure was increased slightly in the group with high 25(OH)D level, and ASSI was relatively lower in groups with high 25(OH)D levels. Fig. 1 shows that: ASSI decreased somewhat as the 25(OH)D level increased, and the difference was significant ($P < 0.01$). In previous studies and reports, there have been many similar findings on the relationship between vitamin D and blood pressure. A survey on the health of men and women in Shanghai[18] showed that the serum 25(OH)D level is negatively correlated with blood pressure parameters (including systolic, diastolic and mean arterial pressures) in men. A study involving 80 patients with hypertension in Japan[19] showed that there exists an obvious correlation between vitamin D deficiency and non-dipper blood pressure. However,

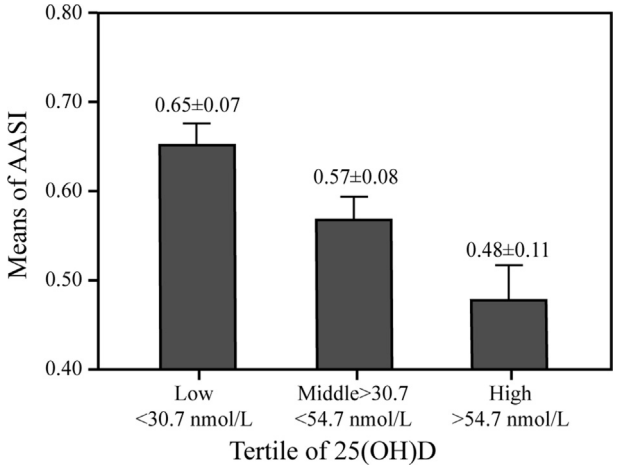

Fig. 1. AASI decreases as 25(OH)D increases (plotted by tertiles). Differences are significant (Table 2).

Table 3
Bivariate correlation of AASI with Clinical characteristics and 24-h ABPM parameters.

Variable	Pearson's correlation coefficient(r)	*P*
Age (year)	0.038	0.706
LDL (mmol/L)	0.107	0.282
FBG (mmol/L)	0.008	0.935
TCh (mmol/L)	0.046	0.647
BMI (kg/m^2)	0.368	<0.001
24-h average SBP (mmHg)	0.641	<0.001
24-h average DBP (mmHg)	−0.06	0.549
24-h average PP (mmHg)	0.66	<0.001
Nocturnal dipping (%)	−0.217	0.029
25(OH)D (nmol/L)	−0.621	<0.001

Pearson's correlation coefficient(r) were calculated, $P < 0.05$ were considered statistically significant.
Abbreviations: LDL: low-density lipoprotein; FPG: fasting plasma glucose; TCH: total cholesterol; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; 25(OH)D, 25-hydroxyvitamin D.

Table 2
Office blood pressure and 24-h ABPM parameters.

25-hydroxyvitamin D tertile	Low <30.7	Middle >30.7/<54.7	High >54.7	*P*
Number	34	34	34	
Office blood pressure				
SBP (mmHg)	153.7 ± 6.9	146.5 ± 3.6	143.7 ± 3.0	<0.001
DBP (mmHg)	85.9 ± 5.5	84.9 ± 4.2	86.2 ± 4.4	0.495
PP (mmHg)	67.8 ± 7.0	61.6 ± 4.6	57.4 ± 4.7	<0.001
24-h ambulatory blood pressure measurements				
SBP (mmHg)	150.3 ± 6.7	143.1 ± 3.8	137.9 ± 4.3	<0.001
DBP (mmHg)	83.3 ± 5.5	82.8 ± 4.3	82.1 ± 5.9	0.665
PP (mmHg)	67.0 ± 6.8	60.3 ± 5.3	55.8 ± 5.5	<0.001
24-h ambulatory blood pressure measurements, daytime				
SBP (mmHg)	152.1 ± 6.5	145.2 ± 3.8	140.6 ± 4.6	<0.001
DBP (mmHg)	84.2 ± 5.6	83.9 ± 4.4	83.7 ± 6.3	0.931
PP (mmHg)	67.7 ± 7.1	61.1 ± 5.8	56.7 ± 5.9	<0.001
24-h ambulatory blood pressure measurements, night-time				
SBP (mmHg)	142.7 ± 11.3	133.3 ± 7.5	125.8 ± 6.8	<0.001
DBP (mmHg)	80.7 ± 6.3	79.4 ± 5.0	78.7 ± 6.6	0.408
PP (mmHg)	62.2 ± 8.6	53.8 ± 4.9	47.0 ± 5.8	<0.001
Nocturnal dipping (%)	6.1 ± 7.3	8.1 ± 5.1	10.4 ± 5.9	0.017
AASI	0.65 ± 0.07	0.57 ± 0.08	0.48 ± 0.11	<0.001

Data are reported as mean (±SD) unless otherwise noted. ANOVA were used. $P < 0.05$ were considered statistically significant.
Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; AASI: ambulatory arterial stiffness index.

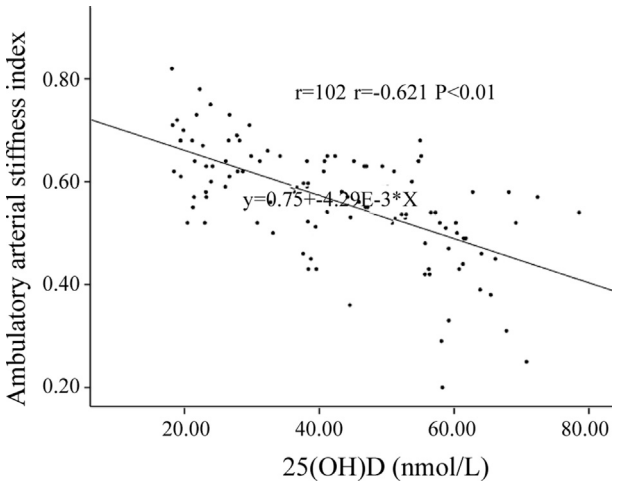

Fig. 2. Correlation of ambulatory arterial stiffness index with 25-hydroxyvitamin D.

Table 4
Independent predictors of AASI in multiple linear regression analysis models.

Variable	Nonstandard coefficient B	95%CI		*P*
		lower bound	upper bound	
LDL (mmol/L)	−0.003	−0.030	0.024	0.852
BMI (kg/m^2)	0.006	−0.001	0.014	0.082
25(OH)D (nmol/L)	−0.002	−0.003	−0.001	0.006
Nocturnal dipping (%)	−0.001	−0.004	−0.001	0.373
24-h average PP (mmHg)	0.007	0.004	0.009	0.000

Abbreviations: LDL: low density lipoprotein; BMI: body mass index; 25(OH)D: 25-hydroxyvitamin D; PP: pulse pressure.
The multiple linear regression model included LDL, BMI, 25(OH)D, Nocturnal dipping, 24-average PP. $P < 0.05$ were considered statistically significant.

there have been no previous studies on the relationship between 25(OH)D level and ASSI.

Further analysis showed that: ASSI was correlated with BMI ($r = 0.368$, $P < 0.001$), 24 h average SBP ($r = 0.641$, $P < 0.001$), 24 h average PP (0.66, $P < 0.001$), rate of nocturnal dipping of blood pressure ($r = -0.217$, $P < 0.05$) and 25(OH)D ($r = -0.621$, $P < 0.001$), but it was not correlated with age, LDL, FBG, TCH and diastolic blood pressure. Fig. 2 shows that ASSI is obviously correlated with 25(OH)D. Multiple linear regression analyses revealed: 25(OH)D and 24 h average PP were independently associated with ASSI.

ASSI was firstly proposed by Li et al., in 2006.[14] It is proposed that the ambulatory arterial stiffness index (AASI) = 1 - the linear regression coefficient for diastolic and systolic blood pressures the slope of the linear regression line between DBP and SBP values, (Fitting equation: the diastolic blood pressure = a + b × the systolic pressure, wherein, the diastolic blood pressure is the dependent variable, the systolic blood pressure is the independent variable, b is the linear regression coefficient). In some recent studies, AASI was taken as an index of arterial stiffness and was confirmed in some of the studies to be related with arterial function, and thus can predict the future risk of cardiovascular disease and stroke.[20] The correlations of ASSI with the parameters of ambulatory blood pressure parameters such as 24 h PP, 24 h SBP and the rate of nocturnal dipping of blood pressure have been mentioned in several other studies and observations.[21] A study has also indicated that: ASSI is correlated with BMI, PP, age, HbA1c and LDL.[22,23] The correlation between 25(OH)D and ASSI in the elderly hypertension which was discovered in this study has not yet been explained in other existing studies.

The cardiovascular benefits of vitamin D have recently received extensive attention. Vitamin D can protect blood vessels to prevent the onset of atherosclerosis. It can directly influence the development of atherosclerosis mainly through the following aspects: 1. The endothelial cells express the vitamin D receptors (VDR) and synthesize $1,25(OH)_2D$; thus the endothelial function is affected at the molecular level.[24] 2. Vitamin D can promote the synthesis of nitric oxide and thus protect endothelial function.[25] 3. Vitamin D can stimulate the expression of IκB-α to increase the activity of superoxide dismutase (SOD) in vascular smooth muscle cells and reduce the oxidation of LDL regulated by vascular cells.[26] 4. Vitamin D can inhibit the immune responses associated with atherosclerosis.[27] Vitamin D can also play an indirect role in regulation of atherosclerosis through modulating insulin secretion, regulating lipid metabolism and acting on the renin-angiotensin-aldosterone system.[28] Since Vitamin D is now known as one of the protective factors of cardiovascular disease, it may play an important role in preventing the vessels from developing atherosclerosis. AASI is a new measure readily available and noninvasive from ABPM, provides additional novel information of arterial function, cardiovascular outcome and other target organ damage.[21] It predicts cardiovascular morbidity and mortality, especially stroke, independently of other known risk factors. ASSI was used to reflect the extent of arteriosclerosis, and now thought as an index of arteriosclerosis and was confirmed in some of the studies to be related with arterial function.[15,22,23] AASI was also considered as a predicting factor of stroke which was superior to pulse wave velocity. Moreover, a number of studies had demonstrated that there was an independent association of AASI with cardiovascular mortality and morbidity. As the other measures of arterial stiffness, such as pulse wave velocity, require dedicated equipment and trained personnel and the results are also rely on the ambient pressure. AASI as an additional piece of information derived from routine ABPM is widely available in routine clinical practice. Thus, the evaluation of AASI as additional information from routine ABPM seems to be feasible in the clinical practice. So, it was valuable to pay further attention on this index. As long as Vitamin D is now known as one of the protective factors of cardiovascular disease, it may play an important role in preventing the vessels from developing atherosclerosis. To find the association between Vitamin D and AASI was available and worthwhile. The regulating effect of Vitamin D on cardiovascular may be the basis for the correlation between vitamin D level and ASSI which was discovered in this study. The study may also provide clinical evidence for the relationship between vitamin D and cardiovascular disease. But whether ASSI is related to other factors is not covered in this article. Although the correlation between vitamin D and atherosclerosis has been shown in some studies, there is a lack of large-scale clinical validation, and Why ASSI may represent atherosclerosis remains arguable. In addition, the selection of study population in this study may also have some limitations, and related aspects are worthy of further study and discussion.

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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