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Relationship between plasma levels of 25-hydroxyvitamin D and arterial stiffness in elderly Chinese with non-dipper hypertension
An observational study

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Abstract

Elderly individuals with non-dipper hypertension are at high risk of cardiovascular disease because of increased stiffness of peripheral arteries. Since, vitamin D deficiency is prevalent in elderly Chinese. We examined whether reduced plasma levels of 25-hydroxyvitamin D [25(OH)D] may help promote this stiffness.

Hypertensive patients at least 60 years old without history of peripheral arterial disease at our hospital were retrospectively divided into dipper and non-dipper groups according to the results of 24-hour ambulatory blood pressure monitoring. Plasma levels of 25(OH)D were measured by enzyme immunoassay. Peripheral arterial stiffness was measured based on the cardio-ankle vascular index (CAVI).

Of the 155 patients enrolled, 95 (61.3%) were diagnosed with non-dipper hypertension and these patients had significantly lower plasma levels of 25(OH)D than the 60 patients with dipper hypertension (19.58 ± 5.97 vs 24.36 ± 6.95 nmol/L, $P < .01$) as well as significantly higher CAVI (8.46 ± 1.65 vs 7.56 ± 1.08 m/s, $P < .01$). Vitamin D deficiency was significantly more common among non-dipper patients (57.9% vs 31.7%, $P < .01$). Multivariate regression showed that age and 25(OH)D were independently related to CAVI, with each 1-ng/ml decrease in 25(OH)D associated with a CAVI increase of +0.04 m/s.

Non-dipper hypertension is associated with vitamin D deficiency and reduced plasma levels of 25(OH)D. The latter may contribute to stiffening of peripheral arteries, increasing the risk of cardiovascular disease.

Abbreviations: 25(OH)D = 25-hydroxyvitamin D, BMI = body mass index, CAVI = cardio-ankle vascular index, DBP = diastolic blood pressure, FBG = fasting blood glucose, HbA1c = glycosylated hemoglobin, MAPs = mean arterial pressures, RAAS = renin-angiotensin-aldosterone system, SBP = systolic blood pressure.

Keywords: 25-Hydroxyvitamin D, Elderly individuals, Non-dipper hypertension, Peripheral arterial stiffness

1. Introduction

Hypertension in elderly individuals is a major risk factor for adverse cardiovascular events, including stroke, acute myocardial infarction and heart failure.[1] This is particularly true in individuals with a "non-dipper" blood pressure pattern in which pressure falls by less than 10% at night. The non-dipper pattern has been associated with accelerated stiffening of peripheral arteries.[2–4] Studies suggest that abnormal activation of the renin-angiotensin-aldosterone system (RAAS) may cause the "non-dipper" phenomenon and that this may accelerate vascular endothelial damage[5,6]

Another potential contributor to the "non-dipper" phenomenon is deficiency in vitamin D, commonly assayed as its metabolite 25-hydroxyvitamin D [25(OH)D]. Patients with non-dipper hypertension show lower plasma levels of vitamin D than patients with dipper hypertension.[7,8] Vitamin D deficiency has been associated with increased arterial blood pressure and vascular endothelial damage.[9,10] This suggests that vitamin D deficiency may contribute to the arterial stiffening observed in patients with non-dipper hypertension.

To examine this possibility, we compared Chinese elderly with dipper or non-dipper hypertension in terms of plasma levels of 25 (OH)D and peripheral arterial stiffness. Since, vitamin D deficiency is prevalent in China: a study of more than 10,000 individuals aged 40 to 75 years indicated a prevalence of 75%,[11]

compared to 33% among people aged 18 years and older in the UK.[12]

2. Methods

2.1. Study population

This retrospective study involved individuals at least 60 years old who were diagnosed between January 2017 and June 2017 with essential hypertension at the Affiliated Hospital of North Sichuan Medical College (Nanchong, China). Hypertension was defined as resting systolic or diastolic blood pressure (DBP) ≥140/90 mmHg on two clinical visits or prescription of antihypertensive medication. Patients were excluded if they had arteritis and peripheral vascular stent implantation, cancer, severe hepatorenal or kidney insufficiency, or a disease affecting bone metabolism (hyper- or hypoparathyroidism, hyperthyroidism). Patients were also excluded if they had taken glucocorticoid or calcitonin in the previous 3 months, or if they were taking drugs that affect calcium or vitamin D status. The study was approved by the Ethics Committee of the Affiliated Hospital of North Sichuan Medical College and performed according to the Declaration of Helsinki. All participants gave written informed consent.

2.2. Clinical and laboratory examinations

For all patients, clinical and demographic data were collected on the same day that blood was sampled and arterial stiffness was assessed. These data included age, height, weight, and duration of hypertension. Body mass index (BMI) was calculated as body weight/height^2 (kg/m^2). Serum levels of triglycerides, cholesterol, high-density lipoprotein, low-density lipoprotein, fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), and creatinine were measured after patients had fasted for at least 8 hours. Plasma levels of 25(OH)D, considered the best index of vitamin D status,[13] were measured using an enzyme immunoassay kit (Immunodiagnostic Systems, Fountain Hills, AZ). The results were used to classify patients as having vitamin D deficiency (<12 ng/mL), insufficient vitamin D (12–20 ng/mL), or sufficient vitamin D (>20 ng/mL).[14]

2.3. 24-hour ambulatory blood pressure

This measurement was made in all patients automatically every 30 min during the day (06:00–18:00) and every 60 min during the night (18:00–06:00) using a cuff (Welch Allyn, USA) attached to the patient's right upper arm. The effective 24-hour ambulatory blood pressure monitoring defined as more than 80% of the measurements obtained with this cuff were judged reliable based on the cuff manufacturer's internal quality control criteria. The average systolic blood pressure (SBP) and average DBP were calculated from the 24-hour ambulatory blood pressure measurements. The mean arterial pressures (MAPs) for day- and night-time were calculated as DBP + (SBP − DBP)/3. The percentage reduction in MAP at night-time was calculated as 100 × [1 − (night-time MAP/daytime MAP)]. If the night-time MAP declined by ≥10%, patients were classified as 'dippers'; otherwise, they were classified as 'non-dippers'.[1]

2.4. Arterial stiffness measurement

Peripheral arteriosclerosis was measured in terms of the cardio-ankle vascular index (CAVI)[2] using a blood pressure pulse measuring device (VS-1000 system, Beijing Futian Electronic Medical Equipment, China). The brachial and ankle arterial pulse waveforms were recorded and calculated as electro- and phonocardiograms. To achieve this, patients lay in a supine position on a pillow in a quiet environment for 5 to 10 minutes, after which blood pressure was measured using a cuff on the upper arm and another on the ankle; the cuffs were tightened so that only one finger could still fit under it. The heart monitor was then placed on the sternum at the level of the second ribs, and the electrocardiography electrodes were installed on both hands. The R-CAVI and L-CAVI were calculated automatically according to the formula:

$$CAVI = \frac{[\ln(P_s/P_d) \times 2p]}{(P \times PWV)},$$

where P_s represents systolic blood pressure; P_d, diastolic blood pressure; p, blood density; P, pulse pressure; and PWV, pulse wave velocity for the aortic valve to the ankle artery. Measurements were performed automatically twice at 10 min apart, then averaged to give the final result.

2.5. Statistical analysis

Data are expressed as the mean ± standard deviation for continuous variables, or as frequency (percentage) for categorical variables. Inter-group differences in continuous variables were assessed for significance using Student t test, while differences in categorical variables were assessed using the chi-squared test. Risk factors of poor CAVI were identified using multivariable regression involving variables associated with $P < .05$ in univariate regression. Statistical analyses were performed using SPSS for Windows 22.0 (IBM, Chicago, IL). All P values are two-sided, and differences associated with $P < .05$ were considered statistically significant.

3. Results

Of the 200 patients at least 60 years old who were diagnosed with essential hypertension at our hospital during the study period, 45 were excluded for the following reasons:

(1) they had arteritis and peripheral vascular stent implantation (n=7);
(2) they had cancer or severe hepatorenal or kidney insufficiency (n=5);
(3) they had hyperparathyroidism, hypoparathyroidism, hyperthyroidism, or other diseases affecting bone metabolism (n= 12);
(4) they had taken glucocorticoids or calcitonin in the previous three months; or
(5) they were taking drugs that affect calcium or vitamin D status (n=10).

Eleven patients refused to participate in the study. In the end, 155 patients (63 women, 40.6%) were included in the study, with an average age of 66.8 ± 4.47 years (Table 1).

Based on 24-hour ambulatory blood pressure, 60 patients (38.7%), of whom 22 (36.7%) were women, were diagnosed with dipper hypertension. Average SBP was significantly higher among those with non-dipper hypertension (135.72 ± 14.23 vs 130.42 ± 13.17 mmHg, $P = .02$). The two groups were similar in age, BMI, duration of hypertension, triglycerides, cholesterol,

Clinico-demographic characteristics and plasma levels of 25(OH)D in elderly Chinese with dipper or non-dipper hypertension.

Variable	Total (n = 155)	Dipper (n = 60)	Non-dipper (n = 95)	P
Age, yr	66.8 ± 4.47	66.25 ± 4.28	67.10 ± 4.58	.25
Female	63(40.6)	22(36.7)	41(43.2)	.42
BMI, kg/m^2	26.22 ± 4.62	26.11 ± 4.39	26.28 ± 4.79	.83
Average SBP	133.66 ± 14.03	130.42 ± 13.17	135.72 ± 14.23	.02
Average DBP	84.22 ± 11.81	83.40 ± 11.14	84.74 ± 12.24	.49
Duration of hypertension, yr	14.46 ± 4.92	14.33 ± 5.51	14.54 ± 4.55	.80
TC, mmol/L	4.76 ± 0.97	4.69 ± 0.96	4.81 ± 0.98	.46
TG, mmol/L	1.78 ± 0.99	1.76 ± 1.08	1.80 ± 0.99	.82
HDL, mmol/L	1.16 ± 0.33	1.17 ± 0.37	1.16 ± 0.30	.78
LDL, mmol/L	3.08 ± 0.86	3.04 ± 0.88	3.10 ± 0.88	.67
Cr, mmol/L	74.84 ± 20.39	74.83 ± 20.10	74.84 ± 20.70	1.00
FBG, mmol/L	5.48 ± 1.52	5.30 ± 1.12	5.60 ± 1.72	.24
HbA1c, %	5.77 ± 1.14	5.66 ± 1.04	5.85 ± 1.20	.33
25(OH)D, ng/ml	21.43 ± 6.67	24.36 ± 6.95	19.58 ± 5.97	<.01

Values shown are n (%) or mean ± SD.
25(OH)D = 25-hydroxyvitamin D, BMI = body mass index, Cr = creatinine, DBP = diastolic blood pressure, FBG = fasting blood glucose, HbA1c = hemoglobin A1c, HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, SBP = systolic blood pressure, TC = total cholesterol, TG = total triglyceride.

high-density lipoprotein, low-density lipoprotein, creatinine, FBG, and HbA1c.

Plasma levels of 25(OH)D were significantly lower among those with non-dipper hypertension than among those with dipper hypertension (19.58 ± 5.97 vs 24.36 ± 6.95 ng/mL, P < .01; Table 1). Conversely, incidence of vitamin D deficiency was significantly higher among those with the non-dipper pattern (57.9% vs 31.7%, P < .01). The percentage of patients with a 25(OH)D level below 12 ng/mL was 10.5% in the non-dipper group but 0 in the dipper group (Fig. 1).

Patients with non-dipper hypertension showed significantly higher CAVI (8.46 ± 1.65 vs 7.56 ± 1.08 m/s, P < 0.01; Fig. 2). We first performed univariate analysis to identify factors potentially associated with higher CAVI: in this analysis, the dependent variable was CAVI, while age, average DBP, duration of hypertension, FBG, HbA1c, 25(OH)D, BMI, average SBP, triglycerides, cholesterol, high-density lipoprotein, low-density lipoprotein, and creatinine were independent variables (Table 2). The first six factors emerged as significant in this analysis, and entering them in multivariable regression identified only age and

25(OH)D as related to CAVI. Each 1-ng/mL decrease in 25(OH)D level was associated with a CAVI increase of 0.04 m/s.

4. Discussion

The present study suggests that among elderly Chinese, vitamin D deficiency is more common in individuals with non-dipper hypertension than in those with dipper hypertension. We further show evidence that non-dipper hypertension is associated with lower plasma levels of 25(OH)D and greater peripheral arterial stiffness. This is consistent with the idea that 25(OH)D deficiency promotes arterial stiffening in non-dipper hypertension.

The large, long-term US-based National Health and Nutrition Examination Survey provides strong evidence that plasma levels of 25(OH)D were negatively associated with blood pressure.[15,16] The present study further found that vitamin D deficiency is more common in elderly Chinese with non-dipper hypertension compared with those with dipper hypertension. This could be partly explained by the cross talk between vitamin D and RAAS. Vitamin D deficiency causes the non-dipper
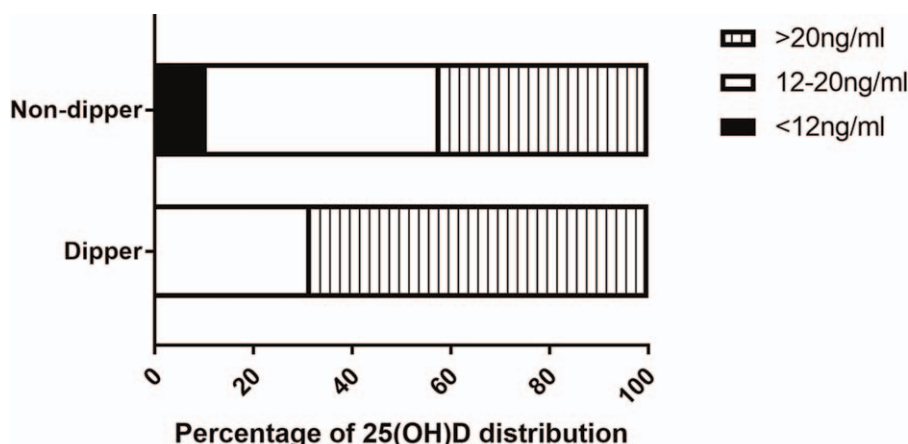
Figure 1. Distribution of plasma levels of 25(OH)D in elderly Chinese with dipper or non-dipper hypertension. 25(OH)D = 25-hydroxyvitamin D.
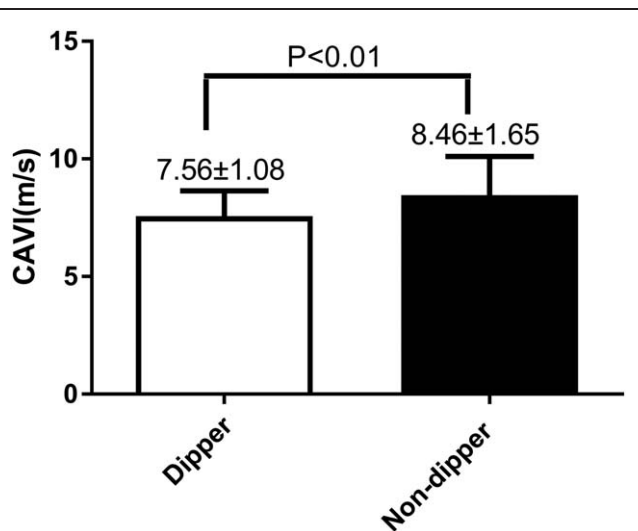
Figure 2. Comparison of the CAVI between elderly Chinese with dipper or non-dipper hypertension. CAVI = cardio-ankle vascular index.

hypertensive pattern by boosting secretion of parathyroid hormone, especially at middle night, which consequently stimulates adrenal glands to secrete aldosterone and renders the target tissues more sensitive to the hormone, resulting in an increase in blood pressure.[17,18] Lower levels of 25(OH)D have been linked to substantial up-regulation of renin and angiotensin II, leading to stimulation of the RAAS,[19] angiotensin II in turns reduces renal klotho expression resulting in modulations of 1-α hydroxylase activity, which directly influenced plasma levels of 25(OH)D.[20] Future work should explore the cross talk in detail, especially as it relates to potential therapies.

Previous studies have demonstrated that non-dipper hypertension was associated with accelerated peripheral arterial stiffness, such that affected individuals show thicker carotid intima-media and faster brachial-ankle pulse wave velocity.[21,22] The present study also confirmed this point and further found that 25(OH)D deficiency promotes arterial stiffening in non-dipper hypertension. The underline mechanisms could be explained as follows: lower plasma levels of 25(OH)D resulted hyperactive RAAS, that can

damage vasculature and stiffen arteries.[23] Vitamin D deficiency may also lead to vessel stiffening through other mechanisms, since vitamin D suppresses proliferation of vascular smooth muscle cells[24] and activation of macrophages.[25] Vitamin D also suppresses T-cell proliferation and inflammatory cytokine production, mitigating inflammation.[26] Any or all of these pathways may help explain why non-dipper hypertension with vitamin D deficiency is associated with faster progression of peripheral arteriosclerosis. As a result, these individuals are at higher risk of cardiovascular disease than those with dipper hypertension.

4.1. Clinical implications

The present study of elderly Chinese provides evidence that vitamin D deficiency is more prevalent among those with a non-dipper hypertensive pattern than those with a dipper pattern, and that the non-dipper pattern is associated with greater stiffness of peripheral arteries. Consistent with these findings, vitamin D supplementation can inhibit atherosclerosis in animal studies[27,28] and can slow arterial stiffening in patients who are overweight or diabetic or have chronic kidney disease.[29–31] However, further study is needed to optimize the dose, frequency, and duration of vitamin D supplementation,[32] and the present study highlights the need for such work on patients with non-dipper hypertension.

4.2. Limitations

There are limitations in our study. Although we did not compare the two groups in propensity score matching style, we actually minimized potential confounding through multivariable analysis, which may reduce the impact of data comparison. Furthermore, this was a cross-sectional analysis, and thus, the relationship between changes in vitamin D status and progression of arterial stiffness in elderly individuals with non-dipper hypertension cannot be established in the present study. Future work is also needed to further examine whether vitamin D status is linked to arterial stiffness in normotensive individuals.

5. Conclusions

Vitamin D deficiency is more prevalent among elderly Chinese with non-dipper hypertension than among those with dipper

Table 2

Screening of potential risk factors of elevated cardio-ankle vascular index.

Variable	Univariate analysis		Multivariable analysis	
	B (95%CI)	P	B (95%CI)	P
Age, yr	0.19 (0.15 to 0.24)	<.01	0.17 (0.13 to 0.21)	<.01
BMI, kg/m^2	−0.02 (−0.07 to 0.04)	.54		
Duration of hypertension, yr	0.08 (0.03 to 0.13)	<.01	0.04 (−0.01 to 0.08)	.09
Average SBP	0.01 (−001 to 0.03)	.26		
Average DBP	−003 (−0.05 to −0.01)	.01	−0.02 (−0.03 to 0.00)	.11
TC, mmol/L	−0.05 (−0.31 to 0.21)	.67		
TG, mmol/L	0.01 (−0.25 to 0.26)	.96		
HDL, mmol/L	0.03 (−0.76 to 0.82)	.93		
LDL, mmol/L	0.06 (−0.22 to 0.35)	.66		
FBG, mmol/L	0.17 (0.01 to 0.34)	.03	−0.05 (−0.30 to 0.20)	.70
HbA1c, %	0.36 (0.15 to 0.58)	<.01	0.21 (−0.14 to 0.56)	.24
Cr, mmol/L	0.01 (−0.01 to −0.02)	.50		
25(OH)D, ng/mL	−0.05 (−0.08 to −001)	.01	−0.04 (−0.07 to −0.01)	.02

25(OH)D = 25-hydroxyvitamin D, BMI = body mass index, Cr = creatinine, DBP = diastolic blood pressure, FBG = fasting blood glucose, HbA1c = hemoglobin A1c, HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, SBP = systolic blood pressure, TC = total cholesterol, TG = total triglyceride.

hypertension. The non-dipper pattern is associated with lower plasma levels of 25(OH)D and greater peripheral arterial stiffness.

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