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Vitamin D status and functional performance in peripheral artery disease

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Abstract

The clinical implications of low vitamin D in peripheral artery disease (PAD) are unknown. We hypothesized that among individuals with PAD, lower levels of 25-hydroxyvitamin D would be associated with poorer functional performance, more adverse calf muscle characteristics, and poorer peripheral nerve function. Participants were 402 men and women with PAD who underwent measurement of 25-hydroxyvitamin D (DiaSorin radioimmunoassay) along with 6-minute walk testing, measurement of walking velocity at usual and fastest pace, computed tomography-measured calf muscle density, and peripheral nerve conduction velocity (NCV). Among PAD participants, 20.4% had 25-hydroxyvitamin D levels < 30 nmol/L, consistent with deficient vitamin D status. Adjusting for age, sex, and race, lower 25-hydroxyvitamin D levels were associated with poorer 6-minute walk performance (p trend = 0.002), slower usual-paced 4-meter walking velocity (p trend = 0.031), slower fast-paced 4-meter walking velocity (p trend = 0.043), and lower calf muscle density (p trend = 0.031). After additional adjustment for body mass index (BMI) and diabetes, none of these associations remained statistically significant. However, lower levels of 25-hydroxyvitamin D were associated with poorer peroneal NCV (p trend = 0.013) and poorer sural NCV (p trend = 0.039), even after adjusting for age, sex, race, BMI, comorbidities,

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smoking, physical activity, and other confounders. In conclusion, vitamin D deficiency is common among people with PAD encountered in clinical settings. After adjusting for BMI and diabetes mellitus, we found no significant associations of lower levels of 25-hydroxyvitamin D with poorer functional performance or calf muscle characteristics. Associations of low vitamin D levels with poorer peripheral nerve function require further study.

Keywords

intermittent claudication; peripheral artery; physical functioning; vitamin D

Introduction

Vitamin D levels are declining among adults in the United States,¹ and the clinical consequences of these declines are unclear. Although basic and animal research suggest that vitamin D is important for maintaining skeletal muscle health and physical function,²⁻⁴ a recent systematic review concluded that the association of low vitamin D levels with functional performance and functional decline among individuals without lower extremity peripheral artery disease (PAD) is unclear.⁵

A recent population-based study suggested that men and women with PAD have even lower circulating vitamin D levels than those without PAD.⁶ Low levels of vitamin D in individuals with PAD may contribute to the functional impairment, adverse lower extremity skeletal muscle characteristics, and impaired peripheral nerve function previously documented in PAD.⁷⁻¹¹

We studied associations of 25-hydroxyvitamin D levels with functional performance, calf skeletal muscle characteristics, and peripheral nerve function among participants with PAD. We hypothesized that lower levels of 25-hydroxyvitamin D would be associated with poorer functional performance, more adverse calf muscle characteristics, and poorer peripheral nerve function in people with PAD. To determine whether our results were unique to PAD patients, we also studied these associations in individuals without PAD.

Methods

Participant identification

The protocol was Institutional Review Board-approved by Northwestern University Feinberg School of Medicine and participating sites. Participants gave informed consent. Potential participants included 478 individuals with PAD who were part of the Walking and Leg Circulation Study (WALCS) II cohort and had stored blood samples from their baseline study visit.^{8,10} PAD participants were identified consecutively from among patients diagnosed with PAD in three Chicago-area non-invasive vascular laboratories. Approximately half of the non-PAD participants were identified from among consecutive patients who had normal lower extremity arterial testing in the Chicago-area vascular laboratories and the remainder was identified from among consecutive patients in a large general internal medicine practice. Participants were aged 59 years and older.

Inclusion and exclusion criteria

Inclusion and exclusion criteria for WALCS II have been reported previously^{8,10} and are summarized briefly here. PAD was defined as $ABI < 0.90$.^{8,10} The absence of PAD was defined as $ABI > 0.90$ and < 1.30 .^{8,10} Patients with dementia, nursing home residents, wheelchair-bound patients, patients with recent major surgery, and patients with foot or leg amputations were excluded. Non-English-speaking patients were excluded.

Ankle-brachial index (ABI) measurement

After participants rested supine for 5 minutes, a hand-held Doppler probe (Nicolet Vascular Pocket Dop II, Golden, CO, USA) was used to measure systolic pressures in the right brachial, dorsalis pedis, and posterior tibial arteries and the left dorsalis pedis, posterior tibial, and brachial arteries. Each pressure was measured twice.⁷ The ABI was calculated by dividing the average pressures in each leg by the average of the four brachial pressures.¹² The average brachial pressure in the arm with the highest pressure was used when one brachial pressure was higher than the opposite brachial pressure in both measurement sets, and the two brachial pressures differed by 10 or more mmHg in at least one measurement set, since in such cases subclavian stenosis was possible.¹³ The lowest leg ABI was used in analyses.

Six-minute walk

Following a standardized protocol,^{7,8,11} participants walked up and down a 100-foot (30.5 meters) hallway for 6 minutes after instructions to cover as much distance as possible.

Repeated chair rises

Participants sat in a straight-backed chair with arms folded across their chest and stood five times consecutively as quickly as possible. Time to complete five chair rises was measured.¹⁴

Standing balance

Participants were asked to hold three increasingly difficult standing positions for 10 seconds each: standing with feet together side-by-side and parallel (side-by-side stand), standing with feet parallel with the toes of one foot adjacent to and touching the heel of the opposite foot (semi-tandem stand), and standing with one foot directly in front of the other (tandem stand).¹⁴

Four-meter walking velocity

Walking velocity was measured with a 4-meter walk performed at 'usual' and 'fastest' pace. For the usual-paced walk, participants were instructed to walk at their usual pace, 'as if going down the street to the store'. Each walk was performed twice. The faster walk in each pair was used in analyses.¹⁴

Short Physical Performance Battery (SPPB)

The SPPB combines data from the usual-paced 4-meter walking velocity, time to rise from a seated position five times, and standing balance. Individuals receive a zero score for each

task they are unable to complete. Scores of 1–4 are assigned for remaining tasks, based upon quartiles of performance for participants in the Established Populations for the Epidemiologic Study of the Elderly.¹⁴ Scores are summed to obtain the SPPB, ranging from 0 to 12.

Calf skeletal muscle cross-sectional area

Using a computed tomography (CT) scanner (LightSpeed; General Electric Medical Systems, Waukesha, WI, USA), 2.5-mm cross-sectional images of the calves were obtained at 66.7% of the distance from the distal to the proximal tibia.⁸ Images were analyzed using BonAlyse (BonAlyse Oy, Jyväskylä, Finland), a software for processing CT images that identifies muscle tissue, fat, and bone.^{8,15} The muscle outline was traced manually, excluding subcutaneous fat and bone. As previously described, BonAlyse software quantifies voxels to define calf muscle area, intra-muscular fat area, and muscle density.^{8,15,16} These methods provide estimates of calf muscle area that correlate highly with anatomic measures.¹⁶

Peripheral nerve function

Nerve function was measured in both legs and in a randomly selected ulnar motor nerve by the electrodiagnostic supervisor at Northwestern Memorial Hospital. The methods have been described previously.¹⁰ Results for the leg with the lowest ABI were used in analyses.

Isometric strength measures

Maximum upper and lower extremity isometric strength was measured in Newtons using a computer-linked strength chair (Good Strength Chair; Metitur Oy, Jyväskylä, Finland).^{9,17} Transducers were placed for measurement of hand grip, knee extension, and plantarflexion. Strength measurements using the Good Strength Chair have excellent test–re-test reliability (Pearson product moment correlations = 0.88–0.96).¹⁷

Leg power

Knee extension power was measured using a flywheel that is accelerated by pushing a footplate until the leg is extended.^{9,18} Power is derived from the final velocity of the flywheel measured with an optoswitch attached to a microcomputer.

Comorbidities

Validated algorithms that combine data from patient report, physical examination, medical record review, medications, laboratory values, and a primary care physician questionnaire were used to verify and document comorbidities.¹⁹ Comorbidities assessed were diabetes mellitus, pulmonary disease, cancer, and number of cardiovascular diseases (angina, myocardial infarction, stroke, heart failure) and number of arthritic diseases (spinal stenosis, disk disease, knee osteoarthritis, hip osteoarthritis). For the number of cardiovascular and arthritic diseases, a numerical value (range 0–4), representing the number of comorbidities within each category, was entered into analyses.

Vitamin D and parathyroid hormone levels

Levels of 25-hydroxyvitamin D were measured from blood obtained at the same visit at which functional performance, muscle, and nerve measures were obtained. We used the direct, competitive chemiluminescence immunoassay (CLIA) with the DiaSorin LIAISON® 25-OH Vitamin D TOTAL assay.^{20,21} The coefficient of variation percent for measurement of vitamin D among 81 split sample specimens was 3.74. Levels of parathyroid hormone were measured using the FDA approved DiaSorin intact PTH-specific immunoradiometric assay (IRMA). The coefficient of variation percent for measurement of PTH among 81 split sample specimens was 11.87. We observed minor variations in 25-hydroxyvitamin D levels by season. Therefore, we normalized 25-hydroxyvitamin D values to adjust for seasonal variation.

Other measures

Height and weight were measured. Body mass index (BMI) was calculated as weight (kg)/(height (m))². Cigarette smoking history and alcohol consumption were based on self-report. Physical activity was measured using patient-reported blocks walked in the past week.^{22,23}

Statistical analyses

Baseline 25-hydroxyvitamin D levels were categorized using definitions from the Institute of Medicine.²⁴ The Institute of Medicine defined deficient vitamin D as 25-hydroxyvitamin D levels < 30 nmol/L, indicated that vitamin D status may be inadequate at levels of 30–50 nmol/L, defined sufficient levels as 50 nmol/L or greater, and stated that levels > 75 nmol/L are not associated with additional benefit.²⁴ Therefore, we defined the following four categories of vitamin D levels: vitamin D < 30 nmol/L, vitamin D 30 to < 50 nmol/L, vitamin D 50 to < 75 nmol/L, and vitamin D 75–125 nmol/L. Differences in continuous variables between the vitamin D groups were evaluated using analyses of variance. Rates for dichotomous variables across groups were compared using chi-squared tests.

Each measure of functional performance, calf muscle characteristic, peripheral nerve function, and leg strength was compared across vitamin D categories using general linear models, adjusting for age, race, and sex (Model I). Analyses were repeated with additional adjustment for comorbidities, ABI, smoking, BMI, physical activity and study cohort (WALCS vs WALCS II) (Model II). Analyses of muscle cross-sectional area were additionally adjusted for tibia length.⁸ Analyses of NCV were additionally adjusted for alcohol consumption (Model II).¹⁰ When calculating the *p* trend value across vitamin D groups, the 25-hydroxyvitamin D level was entered into analyses. Model I was repeated with stepwise adjustment for the additional variables in Model II, to identify the covariates that were responsible for the model attenuation and loss of statistical significance between Model I and Model II. Pairwise comparisons in outcomes were made between the group with 25-hydroxyvitamin D level < 30 nmol/L (reference group) and each remaining group. Analyses were performed using SAS Statistical Software (SAS Inc., Cary, NC, USA).

Results

Among 478 WALCS II participants with PAD, 402 had stored blood available for vitamin D measurement and complete data for multivariable analyses. Among 351 participants without PAD, 305 had stored blood available for vitamin D measurement and complete data for multivariable analyses. Among PAD participants, 20.4% of PAD participants had 25-hydroxyvitamin D levels < 30 nmol/L and 196 (48.8%) had levels < 50 nmol/L. Among non-PAD participants, 15.4% had 25-hydroxyvitamin D levels < 30 nmol/L and 46.9% had levels < 50 nmol/L. Mean 25-hydroxyvitamin D levels were 53.7 nmol/L $\pm$ 24.9 and 54.6 nmol/L $\pm$ 23.7 among participants with and without PAD, respectively ($p = 0.63$).

Table 1 shows associations of clinical characteristics with vitamin D levels in the cohort. Among PAD participants, lower 25-hydroxyvitamin D levels were associated with higher BMI values and higher prevalences of women, African Americans, diabetes mellitus, and current smoking. Among participants without PAD, lower 25-hydroxyvitamin D levels were associated with higher BMI, lower physical activity, and higher prevalences of diabetes mellitus and heart failure.

Adjusting for age, sex, and race, lower vitamin D levels were associated with a poorer 6-minute walk performance (p trend = 0.002), slower usual-paced 4-meter walking velocity (p trend = 0.0307), slower fast-paced 4-meter walking velocity (p trend = 0.043) and lower SPPB scores (p trend = 0.031) in PAD participants (Figures 1 and 2, Model I). These associations were not statistically significant after additional adjustment for BMI, smoking, comorbidities, physical activity, ABI and WALCS cohort (Figures 1 and 2, Model II).

Adjusting for age, sex, and race, lower vitamin D levels were associated with lower calf muscle density among participants with PAD (eTable 1, Model I). This association was not statistically significant after adjusting for BMI, smoking, comorbidities, physical activity, ABI, and WALCS cohort (eTable 1, Model II). Among PAD participants, there were no significant associations of lower vitamin D levels with calf muscle characteristics, lower extremity isometric strength, or knee extension power (eTables 1 and 2).

Among participants with PAD, lower vitamin D levels were associated with lower peroneal NCV (p trend = 0.003) and poorer ulnar NCV (p trend = 0.014) (Table 2, Model I). After additional adjustment for BMI, smoking, comorbidities, ABI, height, alcohol consumption, physical activity, and WALCS cohort, the associations of low vitamin D levels with peroneal NCV (p trend = 0.013) and sural NCV (p trend = 0.039) remained statistically significant, but the association of vitamin D levels with ulnar NCV (p trend = 0.166) was not statistically significant (Table 2).

Among participants with PAD, additional stepwise analyses demonstrated that statistical adjustment for BMI and diabetes mellitus largely accounted for the loss of statistical significance between Model I and Model II in the association of vitamin D levels with functional performance and calf muscle density. Associations of lower vitamin D levels with a poorer 6-minute walk (p trend = 0.002) and slower usual-paced 4-meter walking velocity (p trend = 0.031) in Figure 1, Model I were no longer statistically significant after additional adjustment for diabetes mellitus and BMI (p values = 0.093 and 0.255, respectively).

Significant associations of lower vitamin D levels with slower fast-paced 4-meter walking velocity (p trend = 0.043) and lower SPPB scores (p trend = 0.031) in Figure 1, Model I were no longer statistically significant after additional adjustment for diabetes mellitus and BMI (p values = 0.387 and 0.380, respectively). Adjusting for physical activity levels did not substantially alter the significant associations of lower vitamin D levels with poorer functional performance shown in Figures 1 and 2.

Among participants without PAD, lower vitamin D levels were associated with poorer 6-minute walk performance and slower usual-paced 4-meter walking velocity, adjusting for age, race, and sex (eTable 3). However, these associations were not statistically significant after additional adjustment for comorbidities, smoking, BMI, physical activity, and study cohort (eTable 3). Among participants without PAD, there were no significant associations of lower vitamin D levels with muscle outcomes (data not shown) or peripheral nerve function (eTable 4). Results for participants with and without PAD were not substantially changed after additionally adjusting associations for para-thyroid hormone level (data not shown). In post hoc analysis of participants with PAD, there were no differences in functional performance measures between those with a vitamin D level < 30 nmol/L and those with a vitamin D level > 30 nmol/L, adjusting for age, sex, race, comorbidities, smoking, BMI, ABI, physical activity, and study cohort (data not shown). In post hoc analyses of participants with PAD, findings were generally similar among those with versus without diabetes mellitus.

Discussion

Among 402 participants with PAD identified from Chicago-area medical centers, 20.4% had 25-hydroxyvitamin D levels < 30 nmol/L, recently designated by the Institute of Medicine as consistent with vitamin D deficiency.²⁴ Among 305 non-PAD participants, 15.4% had levels of vitamin D < 30 nmol/L. These results document a high prevalence of vitamin D deficiency in people with and without PAD identified from clinical practice settings.

Among participants with PAD, we found that lower vitamin D levels were associated with poorer 6-minute walk performance, slower walking velocity at usual and fastest pace, lower SPPB scores, and lower calf muscle density after adjusting for age, sex, and race. After adjusting for additional covariates, particularly diabetes and BMI, vitamin D levels were no longer associated with functional performance measures or calf muscle density among participants with PAD. Our data do not allow us to determine whether higher BMI and diabetes mellitus were confounders of the associations of low vitamin D levels with poorer functional performance or whether they are on a causal pathway linking low vitamin D levels with greater functional impairment in PAD.

In contrast, we found significant associations of low vitamin D levels with slower peroneal and sural NCV, even after adjusting for BMI, diabetes, smoking, and other covariates. These results are consistent with basic research and animal data demonstrating that vitamin D receptors exist on peripheral nerves and Schwann cells, and that vitamin D promotes production of nerve growth factor and axon regeneration in peripheral nerves.^{25–29} Few data on the association of vitamin D levels and peripheral nerve function are available from

humans. However, among 51 patients with Type 2 diabetes and neuropathy, vitamin D supplementation resulted in significant decreases in neuro-pathic pain scores.³⁰ Data from NHANES demonstrated that low vitamin D levels were associated with higher neuropathic pain scores among participants with diabetes mellitus.³¹ The combination of ischemia and low vitamin D levels may be particularly important for development of peripheral neuropathy, since we identified significant associations of low vitamin D levels with impaired peripheral nerve function only among participants with PAD but not among those without PAD. However, our data are cross-sectional and further study is needed.

Data from 406 participants with PAD and 4433 without PAD in the community dwelling NHANES cohort demonstrated that participants with PAD had significantly lower vitamin D levels than those without PAD ($53.8 \text{ nmol/L} \pm 1.5$ vs $61.5 \text{ nmol/L} \pm 1.3$; $p < 0.001$).⁶ Our results demonstrate that levels of vitamin D among PAD and non-PAD patients identified from clinical practices are similar to those of community-dwelling individuals with PAD in the NHANES cohort. The non-PAD participants identified from clinical settings in our cohort had lower vitamin D levels than the community-dwelling NHANES participants without PAD, perhaps because of a higher prevalence of chronic disease among non-PAD participants identified from a clinical setting.

This study has limitations. First, data are cross-sectional. Further study is needed to identify longitudinal associations of vitamin D levels with outcome measures reported here. Second, our data were collected from participants in Chicago, IL, where colder winter climates may contribute to lower vitamin D levels as compared to PAD patients in southern latitudes. However, vitamin D levels among the PAD patients in our cohort are similar to those of PAD participants from the nationally representative sample of participants in the NHANES cohort. Third, vitamin D levels were measured from blood samples collected between 2002 and 2004. It is conceivable that typical levels of vitamin D levels in patients with and without PAD may have increased or decreased over time. Fourth, we cannot rule out the possibility of a threshold effect between very low vitamin D levels and adverse outcomes in people with and without PAD.

In conclusion, low vitamin D levels are common among patients with and without PAD recruited from Chicago medical centers. However, low vitamin D levels are not associated with poorer functional performance or more adverse lower extremity skeletal muscle characteristics in individuals with PAD, after adjusting for BMI and diabetes. Further study is needed to confirm our findings regarding low vitamin D levels and peripheral nerve function among participants with PAD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Adjusted associations of vitamin D levels with 6-minute walk and usual-paced walking velocity in peripheral artery disease. (Model I: adjusts for age, sex, and race; Model II: adjusts for covariates in Model I and body mass index, smoking, comorbidities, and study cohort.)

Figure 2.

Adjusted associations of vitamin D levels with fast-paced 4-meter walking velocity and the short physical performance battery in peripheral artery disease. (Model I: adjusts for age, sex, and race; Model II: adjusts for covariates in Model I and body mass index, smoking, comorbidities, and study cohort.)

Table 1. Baseline characteristics associated with vitamin D levels among participants with and without peripheral artery disease ($n = 707$)

	Vitamin D level < 30 nmol/L	Vitamin D level 30 to < 50 nmol/L	Vitamin D level 50 to < 75 nmol/L	Vitamin D level 75 to < 120 nmol/L	p trend
Participants with peripheral artery disease ($n = 402$)	$n = 82$	$n = 114$	$n = 114$	$n = 92$	
Age (years)	73.1 ± 7.71	75.3 ± 7.59	76.2 ± 8.6	75.1 ± 7.7	0.066
Ankle-brachial index	0.62 ± 0.16	0.62 ± 0.14	0.64 ± 0.18	0.63 ± 0.16	0.720
Male sex (%)	47.6	51.8	52.6	63.0	0.036
Body mass index (kg/m ²)	28.9 ± 5.7	28.0 ± 5.0	28.3 ± 4.6	26.4 ± 4.3	0.007
Current cigarette smoking (%)	30.5	12.3	11.4	13.0	0.003
Diabetes mellitus (%)	52.4	34.2	24.6	20.7	<0.001
Myocardial infarction (%)	29.3	24.6	19.3	32.9	0.539
Angina (%)	34.2	38.9	27.2	41.1	0.495
Heart failure (%)	36.6	28.9	28.9	25.0	0.195
Pulmonary disease (%)	45.1	47.4	43.9	42.4	0.547
Knee or hip osteoarthritis (%)	20.7	14.0	14.9	12.0	0.190
Spinal stenosis or spinal disk disease (%)	43.9	46.5	45.6	39.1	0.495
No. of city blocks walked in the past week	25.2 ± 40.8	23.61 ± 36.3	30.7 ± 69.3	42.4 ± 89.1	0.084
Taking vitamin D supplement or a multi-vitamin (%)	2.4	3.5	8.8	6.5	0.105
Participants without peripheral artery disease ($n = 305$)	$n = 47$	$n = 96$	$n = 99$	$n = 63$	
Age (years)	70.2 ± 7.2	72.6 ± 7.9	71.3 ± 7.6	72.4 ± 7.8	0.464
Ankle-brachial index	1.06 ± 0.10	1.09 ± 0.11	1.09 ± 0.09	1.08 ± 0.10	0.409
Male sex (%)	38.3	54.2	48.5	47.6	0.883
Body mass index (kg/m ²)	32.1 ± 7.1	30.2 ± 7.1	28.8 ± 5.7	27.6 ± 4.7	<0.0001
Current cigarette smoking (%)	14.9	7.3	3.0	6.4	0.070
Diabetes mellitus (%)	42.6	25.0	15.2	20.6	0.034
Myocardial infarction (%)	21.3	24.0	14.1	20.6	0.242
Angina (%)	34.8	21.9	19.4	24.2	0.297
Heart failure (%)	19.2	24.0	11.1	6.4	0.009
Pulmonary disease (%)	42.6	30.2	40.4	30.2	0.386

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	Vitamin D level < 30 nmol/L	Vitamin D level 30 to < 50 nmol/L	Vitamin D level 50 to < 75 nmol/L	Vitamin D level 75 to <120 nmol/L	p trend
Knee or hip osteoarthritis (%)	29.8	27.1	15.2	23.8	0.210
Spinal stenosis or spinal disk disease (%)	68.1	61.5	51.5	66.7	0.348
No. of city blocks walked in the past week	18.6 ± 23.9	29.8 ± 49.6	57.8 ± 81.0	46.7 ± 63.3	0.0007
Taking vitamin D supplement or a multi-vitamin (%)	6.4	6.3	5.1	9.5	0.769

Data shown are means ± standard deviations.

Table 2.

Associations of vitamin D levels with peripheral nerve function in participants with peripheral artery disease

Peroneal NCV	Vitamin D (VD) categories (nmol/L)	<i>n</i>	Model I		Model II	
			Least-square mean	mean <i>p</i> trend	Least-square mean	<i>p</i> trend
	Group 1 (VD < 30)	75	34.41	<i>p</i> = 0.0029	34.80	<i>p</i> = 0.013
	Group 2 (30 VD < 50)	107	39.22 ^{<i>b</i>}		39.58 ^{<i>a</i>}	
	Group 3 (50 VD < 75)	105	39.31 ^{<i>b</i>}		38.88	
	Group 4 (75 VD < 120)	86	41.72 ^{<i>c</i>}		41.46 ^{<i>b</i>}	
Sural NCV	VD categories (nmol/L)	<i>n</i>	Model I		Model II	
			Least-square mean	<i>p</i> trend	Least-square mean	<i>p</i> trend
	Group 1 (VD < 30)	44	41.91	<i>p</i> = 0.0855	41.80	<i>p</i> = 0.039
	Group 2 (30 VD < 50)	75	41.78		41.60	
	Group 3 (50 VD < 75)	65	41.85		41.94	
	Group 4 (75 VD < 120)	63	43.92		44.12	
Ulnar NCV	VD categories (nmol/L)	<i>n</i>	Model I		Model II	
			Least-square mean	<i>p</i> trend	Least-square mean	<i>p</i> trend
	Group 1 (VD < 30)	76	48.98	<i>p</i> = 0.0138	49.73	<i>p</i> = 0.166
	Group 2 (30 VD < 50)	108	50.70		50.79	
	Group 3 (50 VD < 75)	106	51.30 ^{<i>a</i>}		50.94	
	Group 4 (75 VD < 120)	86	51.64 ^{<i>b</i>}		51.30	

^{*a*} *p* < 0.05^{*b*} *p* = 0.01^{*c*} *p* = 0.001.

Model I: adjusts for age, sex, and race; Model II: adjusts for covariates in Model I and body mass index, smoking, comorbidities, height, alcohol consumption, physical activity, and study cohort.