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Serum Vitamin D, Parathyroid Hormone Levels, and Carotid Atherosclerosis

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Abstract

Evidence suggests low vitamin D and elevated parathyroid hormone (PTH) concentrations may increase risk for cardiovascular disease. However, little is known about the association between vitamin D or PTH and subclinical atherosclerosis. This cross-sectional study included 654 community-dwelling older adults aged 55–96 years (mean age, 75.5 years) without a history of coronary heart disease, revascularization, or stroke enrolled in the Rancho Bernardo Study who completed a clinic examination in 1997–1999 and provided a blood sample for determination of serum 25-hydroxyvitamin D [25(OH)D], 1,25-dihydroxyvitamin D [1,25(OH)₂D], and PTH concentrations. Carotid artery intima-media wall thickness (IMT) was measured as an indicator of atherosclerosis at two sites with B-mode ultrasound. After adjusting for age, sex, smoking, alcohol intake, waist-to-hip ratio, exercise, season of blood draw, diabetes, and hypertension, geometric mean internal carotid IMT (p_{trend} 0.022), but not common carotid IMT (p_{trend} 0.834) decreased in a dose-dependent fashion with increasing concentration of 25(OH)D. There was no association of 1,25(OH)₂D or PTH with either measure of carotid IMT. In subgroup analyses, 1,25(OH)₂D was inversely associated with internal carotid IMT among those with hypertension (p for interaction 0.036). These findings from a population-based cohort of older adults suggest a potential role for vitamin D in the development of subclinical atherosclerosis. Additional research is needed to determine whether vitamin D may influence the progression of atherosclerosis, including the effects of supplementation on the atherosclerotic process.

Keywords

Atherosclerosis; Vitamin D; Parathyroid Hormone; Cardiovascular Diseases

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1. Introduction

Vitamin D and parathyroid hormone (PTH) are widely recognized for their important roles in maintaining extracellular calcium and phosphorous homeostasis and in regulating bone formation and bone resorption. Vitamin D, largely obtained from cutaneous exposure to ultraviolet B radiation (290–315 nm) and to a lesser extent from dietary and supplemental sources, is metabolized by the liver to 25-hydroxyvitamin D [25(OH)D], the primary circulating storage form of vitamin D. 1,25-dihydroxyvitamin D [1,25(OH)₂D], produced largely in the kidney following a second hydroxylation, is the tightly regulated activated molecule of vitamin D. PTH, on the other hand, is a peptide hormone secreted by the parathyroid gland in response to low circulating calcium and phosphorus concentrations. PTH stimulates the reabsorption of calcium in the kidney, the resorption of calcium from the skeleton, and enhances the renal production of 1,25(OH)₂D.

Evidence from several lines of scientific inquiry suggests vitamin D and PTH may also play a role in the pathogenesis of cardiovascular disease. Hypovitaminosis D has been independently associated with increased rates of hypertension [1], diabetes [2], peripheral arterial disease [3], myocardial infarction [4,5], and related mortality [6,7]. Numerous studies have shown patients with hyperparathyroidism experience an excess risk of mortality from cardiovascular disease [8,9]. High PTH levels have also been independently associated with higher rates of cardiovascular disease in the general population [10]. Vitamin D and PTH may influence cardiovascular risk through a shared association with atherosclerotic plaque formation and progression. However, both vitamin D and PTH have been inconsistently found to be associated with early signs of atherosclerosis, such as increased carotid intima-media wall thickness (IMT) determined with B-mode ultrasound [11–13]. Existing studies have been limited by small clinic-based samples and the failure to examine the combined influence of both vitamin D metabolites and PTH. Therefore, in the current study we aimed to determine the individual and combined associations of 25(OH)D, 1,25(OH)₂D, and PTH levels with the extent of carotid artery IMT in a population-based cohort of community-dwelling older adults from the Rancho Bernardo Heart and Chronic Disease Study.

2. Methods

2.1 Study population

The Rancho Bernardo Study has been described in detail elsewhere [14]. Briefly, between 1972 and 1974, 82% of all adults living in the southern California community of Rancho Bernardo were enrolled in a study of heart disease risk factors as part of the Lipid Research Clinics Prevalence Study. Nearly all were white and middle to upper-middle class, as assessed by Hollingshead's index [15]. Between 1997 and 1999, 89% of the local surviving community-dwelling members attended a clinic visit when a medical evaluation was performed and a blood sample was obtained. Of these, approximately 70% agreed to participate in the current study involving the measurement of carotid artery IMT. Sub-study participants were generally older and more likely to be male than non-participants; however, no differences were observed in 25(OH)D, 1,25(OH)₂D, or PTH levels between participants and non-participants.

Because this analysis focused on the role of vitamin D and PTH early in the atherosclerotic process, those with a history of clinical cardiovascular disease, including coronary heart disease, coronary revascularization, or stroke were excluded ($n = 103$). After further excluding 1 participant who did not have a blood sample adequate for measurement of vitamin D and PTH levels, there remained 654 participants for these analyses. All participants had serum calcium concentrations within the reference range and no participant reported a history of thyroid or parathyroid surgery. The University of California, San Diego Human Subjects

Protections Program approved this study and all participants provided written informed consent prior to participation.

2.2 Clinical evaluation

Participants were evaluated at the University of California, San Diego Rancho Bernardo Research Clinic. During the clinic visit, standardized questionnaires were used to obtain demographic information, medical history, and lifestyle behavior information. Data on alcoholic beverage consumption (g/wk during the previous 2 weeks) [16], cigarette smoking (current, former, never), and participation in strenuous exercise three or more days per week (yes/no) were obtained. Current use of diabetes and blood pressure medications as well as vitamin D and calcium supplement use was validated by the examination of pills and prescriptions brought to the clinic for that purpose.

Two morning blood pressure readings were recorded and averaged in seated subjects after a five-minute rest using a mercury sphygmomanometer according to the Hypertension Detection and Follow-up Program protocol [17]. Hypertension was defined by meeting any of the following 4 criteria: systolic blood pressure ≥ 140 mmHg, diastolic pressure ≥ 90 mmHg, previous physician's diagnosis, or medication use. Height and weight were measured with a standard physician's scale and stadiometer while participants were wearing light clothing and no shoes. Waist circumference was measured at the bending point (the natural indentation when bending side-wards) and at the narrowest circumference. The correlation between these two measures was 98% and the bending point measure was used in these analyses. Hip circumference was measured at the widest circumference below the waist.

2.3 Laboratory methods

Blood was obtained by venipuncture after an overnight fast and placed into tubes that were protected from sunlight. Serum was separated and stored at -70°C within 30 minutes of collection. Serum 25(OH)D [25(OH)D₂ + 25(OH)D₃] was measured in the research laboratory of M. Holick, using vitamin D competitive binding protein recognition and chemiluminescence detection (Nichols Institute Diagnostics, San Clemente, CA) as described by Chen et al. [18]. The rat serum vitamin D binding protein has high affinity for 25(OH)D. The intra- and inter-assay coefficients of variation were 8% and 10%, respectively. The limit of detection was 5.0 ng/mL and the reference range was 10–55 ng/mL. Serum 1,25(OH)₂D was measured in the same laboratory using a radioreceptor assay (Nichols Institute Diagnostics, San Clemente, CA) as described previously [19]; intra- and inter-assay coefficients of variation were 10% and 15%, respectively, with a reference range of 20–45 ng/L. The PTH assay was performed in the same laboratory using a chemiluminescence assay for the measurement of intact PTH (Nichols Institute Diagnostics, San Clemente, CA); intra- and inter-assay coefficients of variation were both 6% with a reference range of 10–65 ng/L.

Plasma total and HDL-cholesterol were measured in a Centers for Disease Control-certified Lipid Research Clinic laboratory. Total cholesterol was measured by enzymatic techniques using an ABA-200 biochromatic analyzer (Abbott Laboratories, Irving, TX). HDL-cholesterol was measured after precipitation of the other lipoproteins with heparin and manganese chloride according to standardized procedures of the Lipid Research Clinics manual [20]. Fasting plasma glucose was measured by the glucose oxidase method. Serum creatinine levels were measured by Smith Kline Beecham clinical laboratories. Glomerular filtration rate, a measure of kidney filtration function, was estimated with the abbreviated Modification of Diet in Renal Disease Study equation, calculated as $175 \times (\text{serum creatinine, mg/dL})^{-1.154} \times (\text{age, years})^{-0.203} \times 0.742$ (if female) [21]. Diabetes was defined by history, use of diabetes medications, or a fasting blood glucose level ≥ 126 mg/dl.

2.4 Carotid artery intima-media thickness (IMT)

B-mode ultrasonography of the left and right common carotid arteries and the internal carotid artery was performed, and IMT was determined, as described by O'Leary et al. [22] Four standardized images were obtained bilaterally for each subject: 1 of the common carotid artery, 1 cm proximal to the dilation of the carotid bulb at a lateral angle and 3 of the internal carotid artery at the site of maximal thickness in 3 angles (anterior, posterior, and lateral). Ultrasound measurements were sent to a central reading facility (DH O'Leary, Principal Investigator) where data were processed in a blinded fashion. The common carotid artery IMT score was calculated as the mean of the left and right measurements of the common carotid artery IMT. The internal carotid artery IMT score was determined as the mean of the 6 internal carotid artery IMT measurements.

2.5 Statistical analyses

All analyses were conducted with SAS version 9.1 (SAS Institute, Cary, NC). Carotid IMT and PTH concentrations were positively skewed and were therefore log-transformed or categorized as appropriate, depending upon the type of analysis conducted; geometric means and 95% confidence intervals were calculated. Analysis of covariance was used to examine the association of 25(OH)D, 1,25(OH)₂D, and PTH with log-transformed common carotid and internal carotid IMT. Models adjusted for potential confounding factors based upon a review of the relevant literature, including age, sex, smoking status, alcohol intake, waist-to-hip ratio, exercise, and season of blood draw. Additional models adjusted further for potential intermediate factors, including diabetes and hypertension. Tests for a linear trend were performed by entering the quintile categories of 25(OH)D, 1,25(OH)₂D, and PTH into the model as an ordinal term. We also examined the association of 25(OH)D, 1,25(OH)₂D, and PTH with log-transformed common carotid and internal carotid IMT according to high or low levels of the other vitamin D metabolite and PTH (two categories, defined by the sample median); factors that are thought to influence the concentration of 25(OH)D, 1,25(OH)₂D, or PTH; and diabetes or hypertension status. We tested for the presence of interaction by including a product term with the respective stratification variable and the continuous exposure variable in the model. Statistical significance was defined at $p < 0.05$ using two-sided tests.

3. Results

The demographic, anthropometric, and clinical characteristics of the study population are presented in Table 1. On average, the 654 adults included in this analysis were aged 75.5 ± 8.5 (range 55–96) years, 64% were women, and the mean body mass index was 25.6 ± 4.1 kg/m². Most reported a healthy lifestyle, with current smoking in only 4.2%, regular exercise in 74.6%, calcium supplement use in 46.1%, and vitamin D supplement use in 23.6%. Mean 25(OH)D, 1,25(OH)₂D, and geometric mean (95% CI) PTH levels were 41.5 ± 14.1 ng/mL, 32.4 ± 17.3 ng/L, and 44.7 (44.2, 47.3) ng/L, respectively. The prevalence of 25(OH)D levels >20 or >30 ng/mL was 96.8% and 83.3%, respectively.

Table 2 displays the demographic, anthropometric, and clinical predictors of 25(OH)D, 1,25(OH)₂D, and PTH levels. Individuals with the highest 25(OH)D levels were younger, had lower systolic blood pressure and body mass index levels, and were more likely to be male, physically active, drink alcoholic beverages more frequently, and use calcium and vitamin D supplements. Those with the highest 1,25(OH)₂D levels were also younger and drank alcohol more frequently, but were more likely to be female, have a lower waist-to-hip ratio and total cholesterol:HDL ratio, and higher kidney function. On the other hand, participants with the lowest PTH levels had a lower body mass index and total cholesterol:HDL ratio, and were more likely to exercise regularly as well as use calcium and vitamin D supplements.

Table 3 displays the adjusted geometric mean common carotid IMT and internal carotid IMT according to quintiles of 25(OH)D, 1,25(OH)₂D, and PTH. Lower geometric mean internal carotid IMT was observed across increasing quintiles of 25(OH)D. These results were independent of age, sex, smoking status, alcohol use, waist-to-hip ratio, physical exercise, and season of blood draw. Further adjustment for potential mediators of this association, including diabetes and hypertension, did not explain these findings. Adjustment for body mass index as opposed to waist-to-hip ratio or systolic blood pressure rather than hypertension status had little influence on these results. No association was observed between 25(OH)D levels and common carotid IMT, or between 1,25(OH)₂D or PTH and the common carotid or internal carotid IMT.

There was no evidence the inverse association between 25(OH)D and internal carotid IMT differed significantly by age, sex, adiposity, exercise, kidney function, hypertension, diabetes, 1,25(OH)₂D, or PTH levels (p for interaction > 0.1 , for all). An inverse association between 1,25(OH)₂D and internal carotid IMT was observed only among those with hypertension (p for interaction 0.036); for each 1-SD increase in the concentration of 1,25(OH)₂D, multivariable-adjusted log-transformed carotid IMT decreased by 0.050 (0.005, 0.095). PTH showed no association with the internal or the common carotid IMT in subgroups defined by age, sex, adiposity, exercise, kidney function, hypertension, diabetes, 25(OH)D, or 1,25(OH)₂D (p for interaction > 0.1 , for all). In stratified subgroup analyses, 25(OH)D and 1,25(OH)₂D showed no association with common carotid IMT.

4. Discussion

In this community-based cohort, we found a significant inverse stepwise association between serum 25(OH)D levels and internal carotid IMT, but no association with common carotid IMT. The association with internal carotid IMT was independent of age, sex, and multiple other potential confounding factors. There was no evidence of an association between 1,25(OH)₂D, the activated metabolite of vitamin D, or PTH with either common carotid or internal carotid IMT. In only one of several subgroup analyses, an inverse association was found between 1,25(OH)₂D and internal carotid IMT among those with hypertension.

The results of previous studies seeking an association between vitamin D and atherosclerosis have been inconsistent. Targher et al. [13] reported an inverse association between 25(OH)D and IMT among 390 diabetic patients, but no association was observed in another study of 109 postmenopausal women [23]. Arad et al. [11] found no evidence of an association between 1,25(OH)₂D levels and the extent of coronary artery calcification among 50 patients who had recently undergone coronary angiography for the evaluation of coronary artery disease, valvular heart disease, or both. On the other hand, Watson et al. [12] observed a weak but statistically significant inverse association between 1,25(OH)₂D concentrations and coronary artery calcium mass ($r = -0.18$) among 153 subjects at moderate risk for developing coronary heart disease according to Framingham Study estimates. Doherty et al. [24] later confirmed this finding among 283 asymptomatic adults at high risk of coronary disease.

Differences in the selection criteria and demography of the study populations may be responsible for the contradictory findings. Factors that contribute to carotid IMT may also be different from coronary artery calcification. The inconsistent findings of studies measuring 1,25(OH)₂D may also be due to its tight physiologic control, reported biological half-life of only 4–6 hours, and concentration within the normal range even in the presence of vitamin D deficiency [25]. On the other hand, 25(OH)D has been widely recommended as the best indicator of vitamin D status in individuals without chronic kidney disease because it has a reported half-life of 12–19 days and its levels are closely associated with the amount of sunlight to which the epidermis is exposed as well as dietary intake of vitamin D [25].

Some studies have suggested that 25(OH)D and 1,25(OH)₂D are only weakly correlated and therefore might provide unique prognostic information regarding cardiovascular risk. Dobnig et al. [7] recently showed that low levels of 25(OH)D and 1,25(OH)₂D were each associated with higher rates of all-cause mortality, even after adjustment for the other vitamin D metabolite and PTH. Furthermore, the mortality risk was greatest among those in the bottom quartile of 25(OH)D and 1,25(OH)₂D, suggesting a possible synergistic effect for those deficient in both vitamin D metabolites. We found that the inverse association of 25(OH)D on internal carotid IMT did not differ between those with high or low levels of 1,25(OH)₂D or PTH.

We observed an independent association between serum 25(OH)D levels and internal carotid, but not common carotid IMT. The IMT of both the internal and common carotid arteries is strongly associated with incident atherosclerotic cardiovascular disease events even after adjustment for major cardiovascular risk factors [22,26]. However, recent evidence suggests a higher internal carotid IMT may reflect greater atherosclerotic plaque burden, whereas a higher common carotid IMT may be the result of vascular changes in response to shear stresses [27–29]. Thus, the overwhelming effects of endothelial shear stress may mask any potential role that vitamin D may play in regulating the IMT of the common carotid artery.

In subgroup analyses, higher 1,25(OH)₂D levels were associated with lower internal carotid IMT values only among those with high blood pressure. We are unsure as to why this association appeared limited to persons with hypertension. Furthermore, we could not confirm a modifying influence of hypertension on the association of the circulating metabolite of vitamin D [25(OH)D] with either internal carotid or common carotid IMT. Admittedly, we cannot rule out that this finding may be due to chance, since we performed numerous subgroup analyses. As discussed earlier, the measurement of the activated metabolite of vitamin D and its interpretation in clinical research studies among apparently healthy persons is complicated by many its physiologic parameters, namely its inability to provide an indication of usual vitamin D status.

There is accumulating evidence that vitamin D may influence vascular function and the development or progression of atherosclerosis. Vitamin D receptors have a broad tissue distribution which includes vascular smooth muscle cells [30,31], macrophages [32], and lymphocytes [33]. Vascular smooth muscle and endothelial cells possess the enzyme 25(OH)D-1 α -hydroxylase, which is responsible for the conversion of 25(OH)D to 1,25(OH)₂D [34–36]. Vitamin D induces prostacyclin in vascular smooth muscle cells, which prevents thrombus formation, cell adhesion, and smooth muscle cell proliferation [37]. Furthermore, vitamin D regulates the expression of a number of other proteins relevant to the arterial wall, including vascular endothelial growth factor, matrix metalloproteinase type 9, myosin, elastin, type I collagen, and γ -carboxyglutamic acid, a protein that protects against arterial calcification [38,39]. Vitamin D suppresses pro-inflammatory cytokines, including interleukin-6 and tumor necrosis factor- α in vitro and in vivo [40]. In mice, vitamin D is an inhibitor of the renin-angiotensin system [41], and vitamin D receptor knock-out mice develop cardiac hypertrophy [42]. Furthermore, a transgenic rat model which constitutively expresses vitamin D-24-hydroxylase, an enzyme responsible for breaking down an activated form of vitamin D thereby causing deficiency, develops aortic atherosclerosis and hyperlipidemia [43].

We found no evidence of an association between PTH concentrations and internal carotid or common carotid IMT in either the entire cohort or in subpopulations. A role for PTH in the development of cardiovascular disease has been suggested by several studies [8–10]. In a recent report, Choi et al. [23] observed a direct association between PTH and carotid IMT independent of established cardiovascular risk factors among postmenopausal women attending an endocrine clinic. Patients with primary hyperparathyroidism have been reported to have increased arterial stiffness, altered vascular reactivity, left ventricular hypertrophy, and

valvular calcification [8]. Furthermore, receptors for PTH and PTH-related peptide have been located in the arterial endothelium as well as vascular smooth muscle cells [30].

The high prevalence of sufficient 25(OH)D levels observed in the current study sample are likely due to latitude and the southern California climate which includes an abundance of year-round sun exposure. However, the high 25(OH)D levels may also be due to the competitive binding protein assay used to measure circulating vitamin D levels. At the time the blood samples were measured, high-performance liquid chromatography was more costly and labor intensive. Recent laboratory comparison studies have shown that competitive binding protein assays may produce higher 25(OH)D levels than other available assay methods [44,45]; however, routine assays accurately rank individuals across the range of 25(OH)D levels [45]. Thus, the use of the competitive binding protein assay should not have influenced the association between 25(OH)D and carotid IMT reported here. The magnitude of the association may have been even greater if studied in a population that was predominantly vitamin D deficient, since epidemiologic studies have shown a non-linear association between 25(OH)D and cardiovascular risk and mortality, with the greatest risk conferred by 25(OH)D levels <15 ng/ml [6]. In addition, a single measurement of vitamin D or PTH may not be reflective of lifetime status and subclinical atherosclerosis progresses over many years. We acknowledge the cross-sectional design of our study limits causal inference. Furthermore, the external validity of our findings may be limited to apparently healthy middle- to upper-middle class white adults and may or may not be generalizable to other groups or other geographic areas. While the homogeneity of our sample may limit the external validity of our findings, it minimizes the potential for residual confounding by unmeasured characteristics.

In conclusion, in this population-based cohort of older adults, we found an inverse dose-response association between serum 25(OH)D levels, but not 1,25(OH)₂D or PTH levels, with internal carotid IMT, independent of traditional cardiovascular disease risk factors. These findings provide evidence that vitamin D may play a role in the development of atherosclerosis. Our results support additional investigation into whether vitamin D may influence the progression of atherosclerosis as well as the effects of supplementation on the atherosclerotic process.

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Table 1

Descriptive characteristics of the 654 participants: Rancho Bernardo, CA, 1997–1999.

Characteristic	Value
Age, mean (SD), years	75.5 (8.5)
Men, No. (%)	238 (36.4)
Body mass index, mean (SD), kg/m ²	25.6 (4.1)
Waist-to-hip ratio, mean (SD)	0.876 (0.085)
Alcohol intake, median (IQR), g/wk	29.9 (0–97.4)
Current smoker, No. (%)	27 (4.2)
Former smoker, No. (%)	323 (49.4)
Exercise > 3 times/wk, No. (%)	488 (74.6)
Calcium supplement user, No. (%)	301 (46.1)
Vitamin D supplement user, No. (%)	154 (23.6)
Systolic BP, mean (SD), mmHg	136.9 (19.9)
Diastolic BP, mean (SD), mmHg	74.1 (9.8)
Hypertension, No. (%)	395 (60.4)
Fasting glucose, mean (SD), mg/dL	103.5 (19.1)
Diabetes, No. (%)	70 (10.7)
Total cholesterol:HDL ratio, mean (SD)	3.72 (1.14)
eGFR, mean (SD), ml/min per 1.73 m ²	73.7 (18.3)
25-hydroxyvitamin D, mean (SD), ng/mL	41.5 (14.1)
1,25-dihydroxyvitamin D, mean (SD), ng/L	32.4 (17.3)
Parathyroid hormone, geometric mean (95% CI), ng/L	45.7 (44.2, 47.3)
Common carotid IMT, geometric mean (95% CI), mm	0.946 (0.931, 0.961)
Internal carotid IMT, geometric mean (95% CI), mm	1.325 (1.279, 1.373)

SD indicates standard deviation; IQR, interquartile range; CI, confidence interval; eGFR, estimated glomerular filtration rate; IMT, intima-media thickness.

Table 2

Characteristics of participants according to quintiles (Q) 1, 3, and 5 of 25-hydroxyvitamin D [25(OH)D], 1,25-dihydroxyvitamin D [1,25(OH)₂D], and parathyroid hormone concentration: Rancho Bernardo, CA, 1997–1999.

	25(OH)D (ng/mL)					1,25(OH) ₂ D (ng/L)					Parathyroid hormone (ng/L)				
	Q1 (<32.0)	Q3 (38.0–43.0)	Q5 (>49.0)	P _{trend}	Q1 (<20.0)	Q3 (27.0–34.0)	Q5 (>42.0)	P _{trend}	Q1 (<34.0)	Q3 (42.0–50.0)	Q5 (>64.0)	P _{trend}	Q1 (<34.0)	Q3 (42.0–50.0)	Q5 (>64.0)
No.	119	148	137	--	126	148	138	--	129	128	133	--	129	128	133
Age, years	77.8	76.0	73.7	<0.001	77.4	74.1	74.4	0.006	75.4	74.4	75.5	0.185	75.4	74.4	75.5
Men, (%)	21.0	39.2	41.6	<0.001	39.8	35.8	28.3	0.033	32.6	38.6	34.6	0.468	32.6	38.6	34.6
Body mass index, kg/m ²	26.6	25.8	25.0	0.027	24.7	25.8	25.6	0.213	25.2	25.2	26.6	0.005	25.2	25.2	26.6
Waist-to-hip ratio	0.862	0.880	0.875	0.075	0.885	0.874	0.858	0.012	0.867	0.880	0.875	0.332	0.867	0.880	0.875
Alcohol intake, g/wk	50.7	53.8	91.5	<0.001	53.6	66.5	72.5	0.038	65.9	64.8	64.0	0.772	65.9	64.8	64.0
Current smoker, (%)	5.0	2.7	5.1	0.942	4.4	4.1	3.6	0.462	8.5	2.3	3.8	0.083	8.5	2.3	3.8
Exercise > 3 times/wk, (%)	58.8	75.0	83.2	<0.001	75.2	77.0	80.4	0.146	82.2	70.5	67.7	<0.001	82.2	70.5	67.7
Calcium supplement user, (%)	39.0	44.6	50.4	0.040	49.1	46.6	43.5	0.354	59.7	43.2	39.1	<0.001	59.7	43.2	39.1
Vitamin D supplement user, (%)	14.4	24.3	29.9	0.010	22.3	25.7	20.3	0.352	34.1	16.7	24.8	0.037	34.1	16.7	24.8
Systolic BP, mmHg	142.8	134.0	136.5	0.044	140.0	134.3	136.6	0.148	137.8	134.7	136.9	0.593	137.8	134.7	136.9
Diastolic BP, mmHg	74.5	73.2	74.5	0.567	73.8	74.8	74.5	0.594	73.0	75.3	74.4	0.521	73.0	75.3	74.4
Hypertension, (%)	63.9	56.8	62.0	0.830	64.6	50.0	58.7	0.525	62.0	59.9	64.7	0.289	62.0	59.9	64.7
Fasting glucose, mg/dL	106.2	102.8	101.9	0.123	104.8	105.3	100.8	0.066	100.8	105.8	107.1	0.111	100.8	105.8	107.1
Diabetes, (%)	13.5	9.5	8.8	0.209	14.2	12.8	8.7	0.248	7.0	9.9	14.3	0.078	7.0	9.9	14.3
Total cholesterol:HDL ratio	3.702	3.782	3.613	0.783	3.898	3.695	3.606	0.037	3.623	3.685	3.948	0.045	3.623	3.685	3.948
eGFR, ml/min per 1.73 m ²	73.5	73.3	73.9	0.669	67.6	76.4	76.8	<0.001	72.9	74.7	72.8	0.748	72.9	74.7	72.8

Values presented are the mean unless otherwise indicated.

BP indicates blood pressure; eGFR, estimated glomerular filtration rate.

Table 3

Adjusted geometric mean (95% CI) common carotid artery IMT and internal carotid artery IMT according to quintiles (Q) of 25-hydroxyvitamin D [25(OH)D], 1,25-dihydroxyvitamin D [1,25(OH)₂D], and parathyroid hormone concentration: Rancho Bernardo, CA, 1997–1999.

Quintiles	Common Carotid Artery IMT (mm)		Internal Carotid Artery IMT (mm)	
	Model 1 [*]	Model 2 [†]	Model 1 [*]	Model 2 [†]
25(OH)D (ng/mL)				
Q1 (<32.0)	0.979(0.939, 1.021)	0.971 (0.928, 1.017)	1.530(1.389, 1.686)	1.577(1.421, 1.750)
Q2 (32.0–37.9)	0.953 (0.915,0.993)	0.946 (0.905, 0.989)	1.430(1.300, 1.573)	1.477(1.333, 1.638)
Q3 (38.0–43.0)	0.946 (0.909, 0.985)	0.941 (0.900, 0.983)	1.350(1.230, 1.481)	1.402(1.267, 1.552)
Q4 (43.1–49.0)	0.963 (0.922, 1.006)	0.956(0.912, 1.003)	1.364(1.233, 1.510)	1.417(1.270, 1.580)
Q5 (> 49.0)	0.978 (0.940, 1.018)	0.969(0.928, 1.013)	1.343 (1.225, 1.472)	1.383 (1.250, 1.530)
<i>P</i> _{trend}	0.795	0.834	0.023	0.022
1,25(OH) ₂ D (ng/L)				
Q1 (<20.0)	0.956 (0.916, 0.997)	0.950 (0.908, 0.994)	1.449(1.314, 1.599)	1.492(1.344, 1.656)
Q2 (20.0–26.9)	0.991 (0.952, 1.031)	0.983 (0.940, 1.028)	1.392(1.267, 1.529)	1.441 (1.298, 1.600)
Q3 (27.0–34.0)	0.951 (0.914,0.989)	0.949 (0.909, 0.990)	1.402(1.279, 1.537)	1.460(1.322, 1.612)
Q4 (34.1–42.0)	0.952 (0.913, 0.992)	0.944 (0.902, 0.988)	1.414(1.284, 1.556)	1.458 (1.412, 1.621)
Q5 (> 42.0)	0.970(0.931,0.992)	0.964(0.921, 1.009)	1.361 (1.237, 1.498)	1.404(1.265, 1.558)
<i>P</i> _{trend}	0.857	0.829	0.393	0.386
Parathyroid hormone (ng/L)				
Q1 (<34.0)	0.954(0.917,0.993)	0.946 (0.904, 0.989)	1.390(1.266, 1.527)	1.441 (1.299, 1.598)
Q2 (34.0–41.9)	0.939 (0.900, 0.979)	0.934 (0.892, 0.978)	1.317(1.195, 1.452)	1.370(1.234, 1.522)
Q3 (42.0–50.0)	0.978 (0.939, 1.019)	0.971 (0.928, 1.015)	1.429(1.300, 1.570)	1.478 (1.334, 1.639)
Q4 (50.1–64.0)	0.980(0.941, 1.020)	0.973 (0.931, 1.018)	1.440(1.310, 1.582)	1.494(1.348, 1.655)
Q5 (> 64.0)	0.969(0.931, 1.009)	0.961 (0.919, 1.004)	1.430(1.310, 1.572)	1.473 (1.330, 1.631)
<i>P</i> _{trend}	0.197	0.202	0.263	0.315

CI indicates confidence interval; IMT, intima-media thickness.

^{*} Model 1 adjusts for age, sex, smoking (current, former, never), alcohol intake (g/wk), waist-to-hip ratio (continuous), exercise ≥ 3 times/wk (yes/no), and season of blood draw (spring, summer, fall, winter).

[†] Model 2 adjusts for variables in Model 1 in addition to diabetes (yes/no) and hypertension (yes/no).