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Original Investigation

Association of Vitamin D Metabolites With Arterial Function in the Hemodialysis Fistula Maturation Study

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Background: Disturbances in vitamin D metabolism are common in patients with end-stage renal disease and may contribute to vascular dysfunction.

Study Design: Cross-sectional.

Setting & Participants: We evaluated 558 of 602 participants at baseline of the Hemodialysis Fistula Maturation (HFM) Study, a 7-center prospective cohort study of a cohort of patients with chronic kidney disease awaiting arteriovenous fistula (AVF) creation surgery.

Factor: 4 vitamin D metabolites measured with liquid chromatography–tandem mass spectroscopy from samples obtained within 4 weeks prior to AVF surgery.

Outcomes: Vasodilator functions and measurements of arterial stiffness.

Measurements: Trained HFM Study personnel measured brachial artery flow-mediated dilation, nitroglycerin-mediated dilation, and carotid-femoral and carotid-radial pulse wave velocities (PWVs) prior to AVF creation. We evaluated associations after basic adjustment for sex, age, and clinical site and more fully adjusted additionally for baseline education, smoking, body mass index, diabetes, dialysis status, and medication use.

Results: Mean participant age was 55 ± 13 (SD) years and 65% were receiving maintenance dialysis. None of the vitamin D metabolites were significantly associated with flow-mediated dilation, carotid-femoral PWV, or carotid-radial PWV in basic or fully adjusted analyses. Higher serum concentrations of bioavailable vitamin D and 1,25-dihydroxyvitamin D were associated with 0.62% and 0.58% greater nitroglycerin-mediated dilation values, respectively, in basic models; however, these associations were no longer statistically significant with full adjustment. There were no significant associations of vitamin D metabolites with carotid-femoral or carotid-radial PWV in fully adjusted analyses.

Limitations: Cross-sectional ascertainment of vitamin D metabolites and vascular functions late during the course of kidney disease.

Conclusions: Serum concentrations of vitamin D metabolites are not associated with vasodilator functions or vascular stiffness at baseline in a cohort study of patients with chronic kidney disease awaiting AVF creation surgery. Laboratory measurements of vitamin D metabolites are unlikely to provide useful information regarding vascular functions in this setting.

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INDEX WORDS: Vascular function; endothelial function; vitamin D metabolites; calcitriol; vasodilation; stiffness; arterial function; epidemiology; hemodialysis; arteriovenous fistula (AVF); flow mediated dilation (FMD); nitroglycerine-mediated dilation (NMD); pulse wave velocities (PWV); end-stage renal disease (ESRD).

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Vitamin D exerts a broad range of potentially favorable effects on vascular function. Calcitriol (1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$]), the biologically potent form of vitamin D, binds to its intracellular target receptor to regulate the transcription of target genes that play important roles in vasoregulation, inflammation, and thrombosis.[1,2] Calcitriol directly stimulates the production of nitric oxide in cultured endothelial cells and downregulates cyclooxygenase 1 expression.[3,4] In animal models, calcitriol suppresses renin expression, leading to subsequent reductions in angiotensin and aldosterone synthesis.[5] Calcitriol also exhibits broad immunomodulatory effects, including suppression of major inflammatory cytokines and differentiation of T-helper cell subsets.[6,7]

Chronic kidney disease (CKD) leads to multiple inter-related disturbances in vitamin D metabolism.[8] The kidneys are the primary site for converting 25-hydroxyvitamin D (25[OH]D) to its biologically potent 1,25-dihydroxylated form: 1,25-dihydroxyvitamin D ($1,25[OH]_2D$).[9] A decline in serum $1,25(OH)_2D$ concentrations and secondary hyperparathyroidism are among the earliest detectable metabolic disturbances of CKD.[10] A loss of functioning nephrons also leads to stagnant vitamin D catabolism, evidenced by a decline in serum concentrations of 24,25-dihydroxyvitamin D_3, ($24,25[OH]_2D_3$), the most abundant vitamin D metabolite.[11] Moreover, 25(OH)D substrate deficiency is common in CKD and other chronic disease populations. These aggregate disturbances in vitamin D metabolism may contribute to the high prevalence of vascular dysfunction and cardiovascular disease in the setting of end-stage renal disease (ESRD) and earlier stages of CKD.

Previous studies have suggested associations of vitamin D metabolites with endothelial function and arterial stiffness in ESRD populations with ESRD or earlier stages of CKD.[12,13] However, these studies are limited by small sample sizes, differing procedures for measuring vascular function, and evaluation of limited numbers of vitamin D metabolites. We addressed these shortcomings by measuring a comprehensive set of inter-related vitamin D metabolites, including vitamin D−binding globulin, for estimation of bioavailable vitamin D, and determining associations with arterial vasodilator functions and vascular stiffness in the Hemodialysis Fistula Maturation (HFM) Study, a prospective cohort study designed to identify predictors of arteriovenous fistula (AVF) maturation failure outcomes.[14] We hypothesized that higher serum concentrations of vitamin D metabolites would be associated with greater vasodilatory responses and reduced arterial stiffness.

METHODS

Study Population

The HFM Study recruited 602 patients with CKD prior to their undergoing AVF creation surgery at one of 7 clinical sites across the United States: Boston University, University of Cincinnati, University of Alabama−Birmingham, University of Florida, University of Texas Southwestern, University of Utah, and University of Washington. Patients were eligible if they were either currently receiving maintenance hemodialysis or expected to initiate dialysis therapy within 3 months. Study participants were recruited from nephrology and vascular surgery clinics, dialysis units, interventional radiology and nephrology practices that perform vascular access procedures, and hospitals that provide CKD care. Exclusion criteria were age younger than 18 years, age older than 80 years if not yet on maintenance hemodialysis therapy, inability to provide informed consent, anticipated life expectancy less than 9 months, or inability to meet protocol requirements in the judgment of the study investigators. All participants gave written informed consent, and the protocol was approved by the institutional review boards/ethics committees of the participating sites and is in accordance with the Declaration of Helsinki.

We excluded 44 HFM participants from our analysis; 40 did not provide a baseline blood sample and 4 had indeterminate values of vitamin D−binding globulin. Among the remaining 558 participants, technically acceptable measurements of flow-mediated dilation, nitroglycerin-mediated dilation, and pulse wave velocity (PWV) were obtained for 510, 423, and 422 participants, respectively.

Vitamin D Metabolites

The HFM Study coordinators collected blood samples typically within 3 weeks prior to vascular function testing. Coordinators shipped samples to the National Institute of Diabetes and Digestive and Kidney Diseases Biosample Repository, where they were stored until shipment to the University of Washington Nutrition Obesity Research Center. Personnel from this research center measured serum concentrations of 1,25-dihydroxyvitamin D_2 ($1,25[OH]_2D_2$), $1,25(OH)_2D_3$, $24,25(OH)_2D_3$, 25-hydroxyvitamin D_2 ($25[OH]D_2$], 25-hydroxyvitamin D_3 ($25[OH]D_3$), vitamin D−binding globulin mass, and vitamin D−binding globulin isoform using liquid chromatography−tandem mass spectroscopy on an Xevo TQ tandem mass spectrometer (Waters).[11,15] Interassay coefficients of variation for these vitamin D metabolite assays across a range of measured concentrations are 3.5% to 10.4% (Table S1, available as online supplementary material). We calculated total $1,25(OH)_2D$ as the sum of $1,25(OH)_2D_2$ and $1,25(OH)_2D_3$ and calculated total 25(OH)D as the sum of 25(OH)D_2 and 25(OH)D_3. We estimated bioavailable 25(OH)D based on measured serum 25(OH)D, vitamin D−binding globulin mass, vitamin D−binding globulin isoform, and serum albumin level according to published equations.[16] For participants who had heterozygous vitamin D−binding globulin isoforms (2 different alleles), we averaged the binding affinity of the 2 alleles to estimate bioavailable vitamin D.[17]

Vascular Function Tests

Vascular function measurements included flow-mediated and nitroglycerin-mediated brachial artery dilation to assess endothelium-dependent and endothelium-independent functions and carotid-femoral and carotid-radial PWVs to assess arterial stiffness of the aorta and peripheral arteries. The HFM Study vascular function personnel were trained by the HFM Study Vascular Function Core laboratory at Boston University before the