Mineral Metabolism and Arterial Functions in End-Stage Renal Disease: Potential Role of 25-Hydroxyvitamin D Deficiency

Gérard M. London,* Alain P. Guérin,* Francis H. Verbeke, † Bruno Pannier,* Pierre Boutouyrie, ‡ Sylvain J. Marchais,* and Fabien Métivier*

*Hôpital F.H. Manèhes, Fleury-Mérogis, France; † University Hospital, Gent, Belgium; and ‡ INSERM U652, Hôpital Européen Georges-Pompidou, Paris, France

In ESRD, arterial function is abnormal, characterized by decreased capacitive function (arterial stiffening) and reduced conduit function, shown by diminished flow-mediated dilation (FMD). The pathophysiology of these abnormalities is not clear, and this cross-sectional study analyzed possible relationships among arterial alterations and cardiovascular risk factors, including mineral metabolism parameters, such as serum parathormone, and vitamin D “nutritional” and “hormonal” status by measuring serum 25-hydroxyvitamin D [25(OH)D₃] and 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃] levels. Aortic stiffness (pulse wave velocity), brachial artery (BA) distensibility (echotracking; n = 42), BA FMD (hand-warming; n = 37), and arterial calcification scores (echography and plain x-rays) were measured in 52 stable and uncomplicated patients who were on hemodialysis. 25(OH)D₃ and 1,25(OH)₂D₃ serum levels were low and weakly correlated (r = 0.365, P < 0.05). After adjustment for BP and age, multivariate analyses indicated that 25(OH)D₃ and 1,25(OH)₂D₃ were negatively correlated with aortic pulse wave velocity (P < 0.001) and positively correlated with BA distensibility (P < 0.01) and FMD (P < 0.001). Arterial calcification scores were not independently associated with 25(OH)D₃ and 1,25(OH)₂D₃ serum concentrations. These results suggest that nutritional vitamin D deficiency and low 1,25(OH)₂D₃ could be associated with arteriosclerosis and endothelial dysfunction in patients who have ESRD and are on hemodialysis.


Cardiovascular complications are the leading cause of death of patients with ESRD (1), and the results of epidemiologic and clinical studies showed that large artery damage is a major factor that contributes to the mortality of these patients (2,3). The arterial system has two distinct, interrelated functions: To deliver an adequate blood supply from the heart to peripheral tissues (i.e., the conduit function) and to dampen blood flow and pressure oscillations that are caused by intermittent ventricular ejection (i.e., the cushioning function). Conduit function depends primarily on the diameter of the arterial lumen. It is highly efficient, and its physiologic adaptability is mediated through acute arterial diameter changes, which depend in large part on the endothelium response to alterations of shear stress, a phenomenon called flow-mediated dilation (FMD) (4). Conduit function disorders result from the narrowing of the arterial lumen or the diminished ability of the artery to dilate in response to shear stress changes. The cushioning function is altered by diminished distensibility that is caused by stiffening of arterial walls. Arterial stiffening results from fibroelastic intima thickening, increased collagen accumulation, and fragmentation of elastic lamellae with secondary fibrosis and calcification of the media (5).

In patients with ESRD, both aspects of arterial functions are abnormal, characterized by arterial outward remodeling (6,7), increased arterial stiffening (6,7), and decreased FMD (8,9). These anomalies are enhanced further with aging, but these age-related effects are accelerated in uremic patients, in whom they are predictive of all-cause and cardiovascular mortality (3,10). The pathogenesis of these dysfunctions is not entirely clear. Conventional risk factors, such as aging and hypertension, only partly explain arterial abnormalities in patients with ESRD. Intimal and medial arterial calcifications (AC) are frequent in patients with ESRD (11); they result in arterial stiffening and abnormal conduit function and are associated with poor outcome (12). Several mineral metabolism disorders have been associated with increased AC and cardiovascular risk, including hyperphosphatemia, hyperparathyroidism, and increased calcium-phosphate product (13). Patients with chronic kidney disease and ESRD have vitamin D deficiency that is characterized by low serum 25-hydroxyvitamin D [25(OH)D₃] levels (14). With the decreased capacity of 1-α-hydroxylase to synthesize calcitriol (1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃]), the serum levels of the “hormonal” form of vitamin D also are low. Results of studies on the general population indicate that poor vitamin D status, characterized by low serum 25(OH)D₃ levels, is associated with higher prevalences of chronic heart failure, hypertension, and hyperparathyroidism (15–18), all fre-
quent complications of ESRD. The purpose of this study was to analyze potential relationships among arterial and mineral metabolism disorders, including the vitamin D system, in stable patients who had ESRD and were on hemodialysis.

Materials and Methods

Fifty-two stable and uncomplicated patients who had ESRD and were on hemodialysis for at least 3 mo (median 46; range 3 to 364 mo) were included. ESRD resulted from chronic glomerulonephritis (n = 23), interstitial nephritis (n = 10), polycystic kidney disease (n = 6), hypertensive nephroangiosclerosis (n = 7), and other (n = 6). Patients were eligible for inclusion when they had no clinical cardiovascular complication, including coronary or peripheral artery disease, chronic heart failure, or atrial fibrillation, and they agreed to participate in the study, which was approved by our institutional review board. Patients underwent dialysis 4 to 6 h three times weekly to control body fluids and blood chemistries. Twenty-four patients with ESRD received anti-hypertensive therapy (angiotensin-converting enzyme inhibitor and/or calcium channel blocker), which was stopped 10 d before the determinations were made. Three patients were current smokers. Patients were naive to vitamin D supplementation (oral or active vitamin D) or calcimetics. Sevelamer was used as the phosphate binder. Erythropoietin was administered to 43 patients to maintain hemoglobin at ≥110 g/L.

Arterial Measurements

Measurements were obtained in a temperature-controlled (23 ± 1°C) room before the first hemodialysis of the week. BP was measured with a mercury sphygmomanometer after 15 min of recumbency using phases I and V of the Korotkoff sounds, respectively, as the systolic BP (SBP) and diastolic BP.

Cushioning Function of Arteries

The arterial system is heterogeneous in its structure and function. The cushioning function is ensured principally by the functional and geometric properties of the aorta, whereas peripheral arteries, such as the brachial artery (BA), fulfill more conduit function. For these reasons, we analyzed separately the cushioning properties of the aorta and the BA.

Aortic Stiffness Assessed as Aortic Pulse Wave Velocity. Aortic pulse wave velocity (PWV) was determined automatically with a dedicated device (CompliorSP; Artech Medical, Pantin, France), as described previously and validated (19). Simultaneously recorded pulse waveforms were obtained transthoracically over the common carotid artery and femoral artery in the groin. PWV was calculated as the distance between recording sites measured over the surface of the body, length from the suprasternal notch to the groin (L), divided by the time interval (t) between the feet of the flow waves (PWV = L/t), which was averaged over 15 cardiac cycles.

BA Distensibility and FMD. BA distensibility was measured in 42 patients. BA wall motions were measured independently with a high-resolution B-mode (7.5-MHz transducer) echotracking system (Wall-Track System, Maastricht, The Netherlands), which was described previously in detail (6,7). Briefly, vessel walls are identified ultrasonographically as described previously (23). Arteries were scanned longitudinally and transversely to detect the presence of calcified plaques (those that produce bright white echoes with shadowing). This assessment was completed with lateral fine-detail radiographs of the abdomen, posteroanterior radiographs of the pelvis, and soft-tissue images of the femorotibial axis. AC in specific regions were assigned as a binary value, absent (0) or present (1). The final overall score, obtained by adding the AC scores from all studied regions, ranged from 0 (no visible calcium deposits) to 4 (generalized calcifications present in all arterial segments examined).

Blood Chemistries

All blood chemistries were determined on samples that were drawn before hemodynamic study and included serum albumin, serum high-sensitivity C-reactive protein, blood lipids, serum phosphates, and Ca²⁺. Serum parathormone (iPTH 1-84) was measured by RIA. Winter serum 25(OH)D was determined with the LIAISON 25 OH Vitamin D assay (D₂ and D₃; DiaSorin, Stillwater, MN) on the LIAISON analyzer according to the manufacturer’s instructions (24). Serum 1,25(OH)₂D₃ was determined by RIA (1,25-Dihydroxyvitamin D 125I RIA KIT; DiaSorin) for 40 patients.

Statistical Analyses

Data are expressed as means ± SD or (medians), depending on the distribution. Serum 25(OH)D and PTH were log₁₀ transformed. Univariate Pearson correlation coefficients were used to assess the relationship among biochemical, clinical, and arterial parameters. P < 0.05 after Bonferroni correction for the number of tested relationships was considered significant. Multiple regression analysis was performed using the subset of univariate analysis–selected independent variables. Serum 25(OH)D and 1,25(OH)₂D₃ levels between the various AC scores were compared using Kruskal-Wallis one-way ANOVA and multiple comparison z scores with Bonferroni correction. All tests were performed using NCSS 2000 (Gerry Hintze, Kaysville, UT).
Results

Patient Characteristics

The baseline clinical and biochemical characteristics are reported in Table 1. Serum albumin and total cholesterol were within their normal ranges, and serum C-reactive protein was increased moderately. Mineral disorders were characterized by normal serum total and ionized calcium levels, elevated serum PO₄ and intact PTH, and low serum 25(OH)D and 1,25(OH)₂D₃. Serum 25(OH)D₃ and 1,25(OH)₂D₃ were weakly correlated ($r = 0.365, P < 0.05$). Serum 25(OH)D₃ was below the recommended sufficiency values in 90% of our patients with ESRD (Figure 1). Serum 25(OH)D₃ was negatively correlated with age ($r = -0.346, P < 0.05$) but not with BP ($r = -0.239; NS$). 1,25(OH)₂D₃ was not correlated with age ($r = -0.234; NS$) but was inversely correlated with SBP ($r = -0.360; P < 0.05$). No correlation was observed between vitamin D parameters and PTH, serum phosphate, or calcium.

Arterial Characteristics

The principal arterial parameters are given in Table 1. Univariate associations between arterial and blood chemistry parameters are shown in Table 2. As classically observed, aortic stiffness and BA distensibility were correlated with age and SBP. FMD was positively correlated with 25(OH)D₃ and 1,25(OH)₂D₃. Independent of age or SBP, we observed negative correlations between serum 25(OH)D or 1,25(OH)₂D₃ and aortic PWV and positive correlations between 25(OH)D₃ or 1,25(OH)₂D₃ and BA distensibilities and FMD (Table 3, Figures 2 and 3). Serum 25(OH)D₃ was lower in patients with higher arterial calcification scores ($r = -0.419, P < 0.01$; Figure 4), but calcification score was strongly age dependent ($r = 0.646, P < 0.0001$), and, after adjustment for age, arterial calcification score no longer was correlated with serum 25(OH)D₃ ($P = 0.151$). No association was found between arterial calcification scores and serum 1,25(OH)₂D₃ (Figure 4).

Discussion

The principal results of this study indicate that, in addition to aging and BP pressure as major factors that influence arterial functional and mechanical properties, arterial dysfunction in patients with ESRD was significantly associated with vitamin D deficiency and low 1,25(OH)₂D₃ levels. Arterial stiffening and decreased FMD are well documented in patients with ESRD, and some of these abnormalities also were observed previously in patients with mild to moderate chronic kidney disease (3,6,7). Although some of these changes are the consequence of mechanical load, reflecting flow or pressure changes, nonhemodynamic factors might be implicated. Aging and hypertension are the principal factors associated with arterial stiffening and also are associated with arterial abnormalities in patients with ESRD. Many vasoactive and metabolic factors and growth promoters can modulate the properties of arterial walls, and nonconventional risk factors, including inflammation, malnutrition, and mineral-metabolism disorders, have been associated with arterial dysfunctions and cardiovascular death (13,25–27). Although some of these changes are the consequence of mechanical load, reflecting flow or pressure changes, nonhemodynamic factors might be implicated. Aging and hypertension are the principal factors associated with arterial stiffening and also are associated with arterial abnormalities in patients with ESRD. Many vasoactive and metabolic factors and growth promoters can modulate the properties of arterial walls, and nonconventional risk factors, including inflammation, malnutrition, and mineral-metabolism disorders, have been associated with arterial dysfunctions and cardiovascular death (13,25–27).

Table 1. Baseline clinical and biochemical and arterial parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with ESRD (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>58.0 ± 1.9</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>138.0 ± 3.0</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>76.0 ± 1.6</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>116.0 ± 1.9</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>4.8 ± 0.5 (4.0)</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>38.0 ± 0.40</td>
</tr>
<tr>
<td>Total cholesterol (mMol/L)</td>
<td>4.42 ± 0.16</td>
</tr>
<tr>
<td>Serum calcium (mMol/L)</td>
<td>2.31 ± 0.02</td>
</tr>
<tr>
<td>Serum Ca²⁺ (mMol/L)</td>
<td>1.17 ± 0.08</td>
</tr>
<tr>
<td>Serum phosphate (mMol/L)</td>
<td>1.58 ± 0.06</td>
</tr>
<tr>
<td>Ca × PO₄ product (mMol²/L²)</td>
<td>3.94 ± 0.03</td>
</tr>
<tr>
<td>Serum 25(OH)D₃ (µg/L)</td>
<td>14.2 ± 1.0 (13.5)</td>
</tr>
<tr>
<td>Serum 1,25(OH)₂D₃ (ng/L)</td>
<td>17.4 ± 1.0 (17.0)</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>345 ± 37 (256)</td>
</tr>
<tr>
<td>Aortic PWV (m/s)</td>
<td>10.30 ± 0.37</td>
</tr>
<tr>
<td>BA distensibility (kPa10⁻¹ × 10⁻³)</td>
<td>2.75 ± 0.20</td>
</tr>
<tr>
<td>FMD (ΔBA diameter % of baseline)</td>
<td>2.76 ± 0.40</td>
</tr>
</tbody>
</table>

*Data are means ± SEM and sometimes (median). 1,25(OH)₂D₃, 1,25-dihydroxyvitamin D₃; 25(OH)D₃, 25-hydroxyvitamin D; BA, brachial artery; CRP, C-reactive protein; DBP, diastolic BP; FMD, flow-mediated dilation; PTH, parathormone; PWV, pulse wave velocity; SBP, systolic BP.*
existence of a role of increased PTH levels in the arterial abnormalities in patients with ESRD remains unclear, with some authors indicating that PTH as associated with stiffening (28,29) but not observed by others (23,30) and not found in the present population despite the wide scatter of PTH levels. The only age- and SBP-independent factors that were associated with arterial stiffening and abnormal FMD were low serum levels of 25(OH)D3 and 1,25(OH)2D3.

Vitamin D intoxication or pharmacologic doses of active vitamin D are associated with increased microvascular resistance and AC (31). Pharmacologic doses usually are applied in experimental studies, and vitamin D is associated with other substances, such as nicotine or antivitamin K, which potentiate its toxic effects (31). However, AC could be linked to hypercalcemia and not only to the action of vitamin D. In the general population, the circulating 1,25(OH)2D3 levels were not or were inversely correlated with coronary calcifications (32). In our study, serum 25(OH)D3 was lower in patients with high calcification scores, but 1,25(OH)2D3 levels were comparable for all calcification scores. Nevertheless, because arterial disease usually progresses with age whereas vitamin D serum levels decline, the absence of an association between AC and vitamin D does not exclude the latter’s role in the pathogenesis of calcifications.

Because 1-β-Hydroxylase converts 25(OH)D3 into its active hormonal form, 1,25(OH)2D3, and because we observed a weak

<p>| Table 2. Univariate relationships of arterial hemodynamics parametersa |</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Aortic PWV (n = 52)</th>
<th>BA Distensibility (n = 42)</th>
<th>FMD (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>0.568</td>
<td>&lt;0.0001</td>
<td>-0.423</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.448</td>
<td>&lt;0.01</td>
<td>-0.562</td>
</tr>
<tr>
<td>Serum Ca2+ (mMol/L)</td>
<td>-0.064</td>
<td>NS</td>
<td>0.042</td>
</tr>
<tr>
<td>Serum PO4 (mMol/L)</td>
<td>-0.036</td>
<td>NS</td>
<td>-0.021</td>
</tr>
<tr>
<td>Log10 PTH (pg/ml)</td>
<td>-0.174</td>
<td>NS</td>
<td>-0.039</td>
</tr>
<tr>
<td>Log10 25(OH)D3 (μg/L)</td>
<td>-0.535</td>
<td>&lt;0.0001</td>
<td>0.616</td>
</tr>
<tr>
<td>1,25(OH)2D3 (ng/L)</td>
<td>-0.616 (n = 40)</td>
<td>&lt;0.0001</td>
<td>0.632 (n = 30)</td>
</tr>
</tbody>
</table>

aP values are corrected for the number of tested relationships.

<p>| Table 3. Multiple correlations between arterial hemodynamic parameters and dependent variables |</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>β Coefficient</th>
<th>T</th>
<th>P</th>
<th>R² (Adjusted for Rest)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dependent variable aortic PWV (m/s)</td>
<td>age (yr)</td>
<td>0.08</td>
<td>3.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>SBP (mmHg)</td>
<td>0.04</td>
<td>2.79</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>log10 25(OH)D3 (μg/L)</td>
<td>-3.97</td>
<td>-2.91</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>R² = 0.504</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age (yr)</td>
<td>0.07</td>
<td>3.11</td>
<td>&lt;0.01</td>
<td>0.226</td>
</tr>
<tr>
<td></td>
<td>SBP (mmHg)</td>
<td>0.04</td>
<td>2.84</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>1,25(OH)2D3 (ng/L)</td>
<td>-0.17</td>
<td>-3.14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>R² = 0.597</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dependent variable BA distensibility (kPa 10⁻¹ × 10⁻³)</td>
<td>age (yr)</td>
<td>-0.09</td>
<td>-0.63</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>SBP (mmHg)</td>
<td>-0.024</td>
<td>-2.79</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>log10 25(OH)D3 (μg/L)</td>
<td>2.61</td>
<td>3.18</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>R² = 0.509</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age (yr)</td>
<td>-0.02</td>
<td>-1.51</td>
<td>NS</td>
<td>0.083</td>
</tr>
<tr>
<td></td>
<td>SBP (mmHg)</td>
<td>-0.03</td>
<td>-3.13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>1,25(OH)2D3 (ng/L)</td>
<td>0.07</td>
<td>-2.63</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>R² = 0.612</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BA FMD</td>
<td>log10 25(OH)D3 (μg/L)</td>
<td>5.36</td>
<td>4.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>R² = 0.340</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,25(OH)2D3 (ng/L)</td>
<td>0.28</td>
<td>5.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>R² = 0.548</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
but significant correlation between the two forms of vitamin D, the question is whether the observed relationships indicate an association with 25(OH)D₃ or 1,25(OH)₂D₃. The correlations between arterial parameters were observed with both metabolites, suggesting that not only 1,25(OH)₂D₃ but also its precursor are linked to arterial dysfunction. 25(OH)D₃ is able to activate the vitamin D receptor directly (33), albeit with low affinity, but partially compensated by >1000 times higher serum 25(OH)D₃ concentrations (33).

Active vitamin D and its receptor ligands have several non-calcemic actions, including antiproliferative, prodifferentiating, and immunomodulatory activities (34), and vitamin D deficiency is associated with a higher risk for development of several diseases, including cancers, type 1 diabetes, cardiovascular disease, and osteoporosis (15,16,18). Results of experimental studies showed that active vitamin D regulates cardiomyocyte proliferation and hypertrophy (35), improves cardiac function, and induces left ventricular hypertrophy regression in patients with ESRD (36,37). 1,25(OH)₂D₃ is a negative regulator of the renin-angiotensin system (38) and might be involved in

**Figure 2.** Correlations in patients with ESRD between 25-hydroxyvitamin D [25(OH)D₃] and 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃] serum concentrations and aortic pulse wave velocity and brachial artery (BA) distensibility.

**Figure 3.** Correlations between BA flow-mediated dilation (FMD) and serum 25(OH)D₃ concentration (left) and serum 1,25(OH)₂D₃ concentrations (right).
the pathogenesis of hypertension and hypertension-associated cardiac and arterial disorders (17). In this study, the association between arterial stiffening and 25(OH)D$_3$ or 1,25(OH)$_2$D$_3$ serum concentrations was independent of age and arterial BP. According to cross-sectional human studies, vitamin D deficiency was associated with increased circulating concentrations of matrix metalloproteinase-9, which controls vascular wall remodeling and is increased in unstable angina, and vitamin D supplementation was associated with decreased serum matrix metalloproteinase-9 concentrations (39). Hypovitaminosis D is associated with decreased levels of HDL cholesterol–associated apolipoprotein A-I (40,41), and vitamin D supplementation had a beneficial effect on the elastic properties of the arterial wall in a randomized, placebo-controlled interventional study in postmenopausal women (42).

Endothelial function is altered in patients with ESRD, as shown by decreased vasodilator responses of the macro- and microcirculations (8–10). FMD, as assessed by BA diameter changes, enables examination of the arterial response to local flow, independent of the maneuver that is used to induce flow changes (20). Factors that are known to contribute to endothelial dysfunction in ESRD include reduced bioactivity of the nitric oxide pathway with decreased endothelial nitric oxide synthase activity or inhibition via accumulation of endogenous inhibitors (25). Endothelial cells also respond to flow changes by releasing other vasodilating factors, such as prostacyclin or endothelium-dependent hyperpolarizing factor (acting on Ca$^{2+}$-activated K$^+$ channels). Mullen et al. (20) showed that the FMD response to hand warming is not attenuated by N-monomethyl-$L$-arginine, cyclooxygenase inhibition, or local autonomic nervous blockade. In patients who were on dialysis, vein relaxation was inhibited by tetraethylammonium chloride (inhibitor of Ca$^{2+}$-activated K$^+$ channels) but not N-monomethyl-$L$-arginine or asymmetrical dimethylarginine (43).

In our study, serum 25(OH)D$_3$ and 1,25(OH)$_2$D$_3$ levels were age- and SBP-independently and positively associated with FMD (Tables 2 and 3). Vitamin D receptors and 1$\alpha$-hydroxylase activity are present in endothelial and vascular smooth muscle cells, and 1,25(OH)$_2$D$_3$ stimulates vascular endothelial growth factor (44). It was shown experimentally that exposure to cholecalciferol improved the relaxation response of spontaneously hypertensive rat arteries to acetylcholine (45) and that this effect was mediated by recovery of impaired Ca$^{2+}$-activated K$^+$ channels (46). Finally, it was reported that vitamin D$_3$ stimulated prostacyclin production by vascular smooth muscle cells (47).

Increased arterial stiffness and decreased reactive hyperemia are independent predictors of all-cause and cardiovascular mortality in patients with ESRD (2,10). The results of a recent study showed that patients who were on long-term hemodialysis and receiving active injectable vitamin D benefited from significant survival advantages (48). Whether these associations could be related to vitamin D–induced improvement of arterial functions remains to be demonstrated in prospective, controlled studies.

Our study has two principal limitations. First, the studied patients were clinically stable with normal lipid status, the absence of pronounced inflammation and malnutrition, and relatively satisfactorily controlled calcium and phosphate status. These conditions may obscure the contributions of these factors in less well-controlled populations. Nevertheless, the arterial disorders were those that classically are observed in patients with ESRD, and the association with serum 25(OH)D$_3$ was strong and independent of age and SBP. Another limitation is that we studied nonsupplemented patients with vitamin D deficiency, which is not a situation that is associated with high, pharmacologic doses of vitamin D or high or eventually toxic serum concentrations, all conditions that could have different impacts on the arterial system. Finally, another limitation is the observational nature of the study. Although such observation is hypothesis generating, an association does not indicate a cause-and-effect relationship.

**Conclusion**

The results of this study indicate that the majority of patients with ESRD are vitamin D deficient, and this deficiency is inde-
pendently associated with abnormal conduit and capacitive functions of large arteries. Whether vitamin D supplementation could improve arterial function and whether this improvement could contribute to better outcomes remains to be investigated in controlled, prospective studies.

Acknowledgments
This work was funded by unrestricted grants from Ortho-Biotech Biopharmaceuticals EMEA, CKD Steering Committee Project 124026, and Groupe d’Étude de la Physiopathologie de l’Insuffisance Rénale. We express special thanks to Dr. Dieter Frei for support.

Disclosures
None.

References
27. London GM, Marchais SJ, Guerin AP, Metivier F, Adda H,
Pannier B: Inflammation, arteriosclerosis, and cardiovascu-
28. Mitsnefes MM, Kimball TR, Kartal J, Witt SA, Glascoek BJ, Khoury PR, Daniels SR: Cardiac and vascular adaptation in pedi-
29. Seyrek N, Balal M, Karayaylali I, Paydas S, Aikimbew K, Cetiner S, Seydaoglu G: Which parameter is more influen-
tial on the development of arteriosclerosis in hemodialysis
30. Suzuki T, Yonemura K, Maruyama Y, Takahashi T, Taka-
T, Furushashi M, Hishida A: Impact of serum parathyroid
hormone concentration and its regulatory factors on arte-
rial stiffness in patients undergoing maintenance hemodi-
nicotine diminishes arterial distensibility in rats. Am J
Physiol 266: H540–H547, 1994
32. Watson KE, Abrolat ML, Malone LL, Hoeg JM, Doherty T, Detrano R, Demer LL: Active serum vitamin D levels are
inversely correlated with coronary calcification. Circulation
96: 1755–1760, 1997
33. Ritter CS, Armbrecht HJ, Slatopolsky E, Brown AJ: 25-
dihydroxyvitamin D3 suppresses PTH synthesis and secre-
tion by bovine parathyroid cells. Kidney Int 70: 654–659,
2006
34. Nagpal S, Na S, Ratnachalam R: Non-calcemic actions of
35. O’Connell TD, Berry JE, Jarvis AK, Somerman MJ, Simpson
RU: 1,25-Dihydroxyvitamin D3 regulation of cardiac myo-
36. Lemmla S, Saha H, Virtanen V, Ala-Houhala I, Pasternack
A: Effect of intravenous calcitriol on cardiac systolic and
EJ, Chang YS, Bang BK: Calcitriol regresses cardiac hyper-
trophy and QT dispersion in secondary hyperparathyroid-
38. Li YC, Kong J, Wei M, Chen Z-F, Liu SQ, Cao LP: 1,25-
Dihydroxyvitamin D (D3) is a negative endocrine regulator
of the renin-angiotensin system. J Clin Invest 110: 229–238,
2002
39. Timms PM, Mannan M, Hitman GA, Noonan K, Mills PG, Syndercombe-Court D, Aganna E, Price CP, Boucher BJ: Cir-
culating MMP9, vitamin D and variation in the TIMP-1 respon-
sive with vitamin D receptor genotype: Mechanisms for
inflammatory damage in chronic disorders? Q J Med 95:
787–796, 2002
40. Auwerx J, Bouillon R, Kesteloot H: Relation between 25-
hydroxyvitamin D3, apolipoprotein A-I, and high density
lipoprotein cholesterol. Arterioscler Thromb 12: 671–674,
1992
41. John WG, Noonan K, Mannan N, Boucher BJ: Hypovi-
taminosis D is associated with reduction in serum apoli-
ipoprotein A-I and high density lipoprotein cholesterol. Am J
Clin Nutr 82: 517–522, 2005
42. Braam LA, Hoeks AP, Brouns F, Hamulyak K, Gerich-
hausen MJ, Vermeer C: Beneficial effects of vitamins D and
K on the elastic properties of the vessel wall in postmeno-
pausal women: A follow-up study. Thromb Haemost 91:
373–380, 2004
43. Martinez-Leon JB, Segarra G, Medina P, Vila JM, Lluch P,
Peiró M, Otero E, Lluch S: Calcium-phosphorus metabolism.
44. Yamamoto T, Kozawa O, Tanabe K, Akamatsu S, Matsuno
H, Dohi S, Hirose H, Uematsu T: 1,25-Dihydroxyvitamin
D3 stimulates vascular endothelial growth factor release in
aortic smooth muscle cells: Role of p38 mitogen-activated
protein kinase. Arch Biochem Biophys 398: 1–6, 2002
45. Borges ACR, Feres T, Vianna LM, Paiva TB: Effect of
cholecalciferol treatment on the relaxant responses of
spontaneously hypertensive rat arteries to acetylcholine.
Hypertension 34: 897–901, 1999
46. Borges ACR, Feres T, Vianna LM, Paiva TB: Recovery of
impaired K+ channels in mesenteric arteries from sponta-
neously hypertensive rats by prolonged treatment with
47. Wakasugi M, Noguchi T, Inoue M, Kazama Y, Tawara M,
Kanemaru Y, Onaya T: Vitamin D3 stimulates the produc-
tion of prostacyclin by vascular smooth muscle cells.
48. Teng M, Wolf M, Ofsthun NM, Lazarus JM, Hernan MA,
Camargo CA Jr, Thadhani R: Activated injectable vitamin
D and hemodialysis survival: A historical cohort study.