

# Vitamin D receptor activation: cardiovascular and renal implications

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**The effects of vitamin D receptor activation on cardiovascular diseases, especially hypertension and cardiac dysfunction, are areas of active investigation. This article reviews the current state of knowledge about vitamin D receptor activation with respect to blood pressure, heart, and vascular health, as well as to chronic kidney disease and end-stage renal disease. Potential biological mechanisms, the role of vitamin D-binding protein, and data from observational and randomized controlled trials on this topic are summarized.**

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The prevalence of cardiovascular disease is 10–20 times greater in patients with chronic kidney disease (CKD) compared with people with normal kidney function. CKD is characterized by low circulating levels of 25-hydroxyvitamin D and its primary active metabolite (1,25-dihydroxyvitamin D), as well as vitamin D resistance.<sup>1</sup> Circulating 1,25-dihydroxyvitamin D, also known as the hormonal form of vitamin D, acts on target tissues such as heart and blood vessels through the nuclear vitamin D receptor (VDR).<sup>2</sup> The VDR interacts with vitamin D response elements to influence gene transcription and affects multiple downstream biological activities. Increasing evidence points to a role for vitamin D on the cardiovascular system. This article reviews the plausible biological mechanisms and human studies conducted to evaluate the effects of VDR activation on blood pressure, cardiac function, and cardiovascular disease. As multiple redundant pathways link cardiac and renal function, we extend the potential application of these cardiac findings to CKD and end-stage renal disease (ESRD).

## ANIMAL STUDIES AND BIOLOGICAL MECHANISMS

Animal studies have provided valuable clues for understanding the links between vitamin D and the cardiovascular system. Rats with experimentally induced vitamin D deficiency (exposed to a diet low in vitamin D and limited ultraviolet light) have been shown to develop hypertension and cardiomegaly.<sup>3,4</sup> Mice lacking the VDR develop a fourfold increase in renin expression and angiotensin II production compared with wild-type mice.<sup>5</sup> VDR-null animals develop hypertension and cardiac hypertrophy, and cardiac-specific VDR knockout models demonstrate cardiac hypertrophy.<sup>6</sup>

Supplementation with vitamin D has been shown to abrogate endothelin-induced hypertrophy and atrial natriuretic peptide production in cultured rat myocytes.<sup>7</sup> In a study by Wong *et al.*<sup>8</sup> of spontaneously hypertensive rats, 6 weeks of treatment with 1,25-dihydroxyvitamin D<sub>3</sub> reduced endothelium-dependent aortic contractions that were accompanied by a lowering of blood pressure and a reduction in reactive oxidative stress. In another study, Dahl salt-sensitive rats treated with the VDR activator, paricalcitol, demonstrated improved cardiac contractility.<sup>9</sup> Lower end-diastolic pressures and smaller heart weights were also noted in paricalcitol-treated animals when compared with

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untreated animals. Paricalcitol treatment was associated with reduced cardiac mRNA expression for renin and natriuretic peptides. Systemic blood pressures were not significantly affected by paricalcitol therapy, suggesting that the observed cardiac changes were due to direct effects on the myocardium. Bae *et al.*<sup>10</sup> recently examined the effects of paricalcitol on progression to heart failure after myocardial infarction in mice. Paricalcitol attenuated the development of heart failure after myocardial infarction and was associated with improvement in cardiac function and reduction in markers of inflammation and fibrosis.

Some evidence suggests that the observed effects on cardiac structure and function from animal studies may translate to humans. For example, improvements in cardiac hypertrophy, diastolic function, and septal and posterior wall thickness have been observed in a retrospective pilot study of hemodialysis patients treated with paricalcitol compared with no treatment.<sup>9</sup>

Animal studies evaluating effects of active vitamin D compounds on uremic vascular calcification offer additional two insights into the actions of these compounds: one related to the dose–response relationship and the other related to differential effects of different active vitamin D compounds on the biology of vascular calcification independent of their potential to increase serum calcium. Mathew *et al.*<sup>11</sup> reported that low doses of calcitriol and paricalcitol (dosages sufficient to correct secondary hyperparathyroidism) were protective against aortic calcification in a mouse model of CKD and higher doses were noted to stimulate further calcification. In uremic rats, comparable doses of calcitriol, paricalcitol, and doxercalciferol have been reported to have significant differences in mRNA expression of Runx2 and osteocalcin in aortic tissues (calcitriol and doxercalciferol treatments resulted in marked increases in these expressions where as paricalcitol did not).<sup>12</sup> These dose–response and differential effects need evaluation in observational and randomized studies in humans. It is notable that risk of calciphylaxis, one of the most severe forms of vascular calcification seen in patients with ESRD, was recently reported to be increased in patients treated with calcitriol but not in patients treated with selective vitamin D analogues such as paricalcitol or doxercalciferol.<sup>13</sup> These findings are preliminary and need confirmation in larger cohorts and also in patients with other forms of vascular calcification. We encourage readers to refer to comprehensive discussion of vitamin D and vascular calcification by Dr Gerard London in this supplement of *Kidney International*.

## EPIDEMIOLOGICAL STUDIES

As early as the 1980s, a number of studies have reported higher blood pressure in patients with low 25-hydroxyvitamin D levels.<sup>14,15</sup> One systematic review that extracted data from 14 cross-sectional and 4 prospective studies representing 78,028 participants reported that 25-hydroxyvitamin D levels were inversely associated with hypertension.<sup>15</sup> The pooled odds ratio of hypertension was 0.73 (95% confidence

interval (CI) 0.63–0.84) for the highest versus lowest categories of 25-hydroxyvitamin D concentration. A dose–response relationship was observed such that, for every 16 ng/ml increment in blood 25-hydroxyvitamin D concentration, the odds ratio of hypertension was 0.84 (95% CI 0.78–0.90).

Observational studies have also detected associations between vitamin D and left ventricular hypertrophy and incident cardiovascular disease. Pilz *et al.*<sup>16</sup> reported a negative correlation between 25-hydroxyvitamin D levels and impaired left ventricular function in a cross-sectional study of patients referred for coronary angiography. Comparing patients with severe vitamin D deficiency (<10 ng/ml) to patients with normal 25-hydroxyvitamin D levels ( $\geq 30$  ng/ml), adjusted hazard ratios for heart failure mortality and sudden cardiac death were 2.84 (95% CI 1.20–6.74) and 5.05 (95% CI 2.13–11.97), respectively. In the Framingham Offspring Study that included 1739 Caucasian subjects,<sup>17</sup> vitamin D deficiency was found to be associated with incident cardiovascular disease. Subjects with 25-hydroxyvitamin D levels below 15 ng/ml had a multivariable-adjusted hazard ratio of 1.62 (95% CI 1.11–2.36) for incident cardiovascular events (including myocardial infarction, coronary insufficiency, angina, stroke, transient ischemic attacks, peripheral claudication, or heart failure) compared with subjects whose 25-hydroxyvitamin D levels were  $\geq 15$  ng/ml.

Vitamin D deficiency is highly prevalent in the CKD and ESRD populations, with estimates as high as 70–80% in some studies. Several observational studies have noted links between vitamin D deficiency and poor cardiovascular outcomes in patients with renal disease.<sup>1</sup> When reviewed systematically, studies suggest that survival in patients with CKD and ESRD is positively correlated with increasing 25-hydroxyvitamin D levels. Each 10 ng/ml increment in serum 25-hydroxyvitamin D level was associated with a 14% reduction in mortality (relative risk, 0.86; 95% CI 0.82–0.91).<sup>18</sup> It is noteworthy that the majority of deaths were attributed to cardiovascular causes. In an analysis of data from the NECOSAD (Nederland Cooperative Study on the Adequacy of Dialysis) cohort, significantly higher cardiovascular mortality was observed in patients with severe 25-hydroxyvitamin D deficiency ( $\leq 10$  ng/ml) compared with those with 25-hydroxyvitamin D levels above 10 ng/ml.<sup>19</sup> Although 1,25-hydroxyvitamin D levels were not reported in this study, the association with cardiovascular mortality was most prominent in patients with high parathyroid hormone levels suggesting that low conversion from 25-hydroxyvitamin D to 1,25-hydroxyvitamin D may predispose patients to the highest risks from adverse consequences of 25-hydroxyvitamin D deficiency.<sup>19,20</sup>

## FACTORS INFLUENCING OBSERVED OUTCOMES IN CLINICAL STUDIES OF VITAMIN D

Observational studies fall short in their ability to establish a causal relationship between serum 25-hydroxyvitamin D and blood pressure lowering or reduction of cardiac disease risk. This is largely due to the inability of such trials to adjust for possible confounding factors. It is not surprising, therefore,

that results suggesting favorable associations between 25-hydroxyvitamin D levels and cardiovascular outcomes have been inconsistent. Study design-related factors, population differences, and variations in definitions are also often invoked to explain discrepant results.

An alternative and biologically relevant explanation for the inconsistent observations may be based on the free hormone hypothesis.<sup>21</sup> Vitamin D is a highly protein-bound hormone with <1% of circulating 25-hydroxyvitamin D existing in its free form.<sup>22</sup> The majority of circulating 25-hydroxyvitamin D (85–90%) is tightly bound to its specific vitamin D-binding protein and a smaller amount (10–15%) is loosely bound to albumin (Figure 1a). Levels of bioavailable 25-hydroxyvitamin D, comprised of the free fraction plus albumin-bound hormone (Figure 1b), have been shown to be more strongly associated with serum calcium and parathyroid hormone levels than total 25-hydroxyvitamin D in ESRD patients.<sup>22</sup> Whether the strength of association between bioavailable 25-hydroxyvitamin D and cardiovascular diseases is also improved needs to be investigated, since most studies to date have reported total 25-hydroxyvitamin D levels and not its bioavailable form.

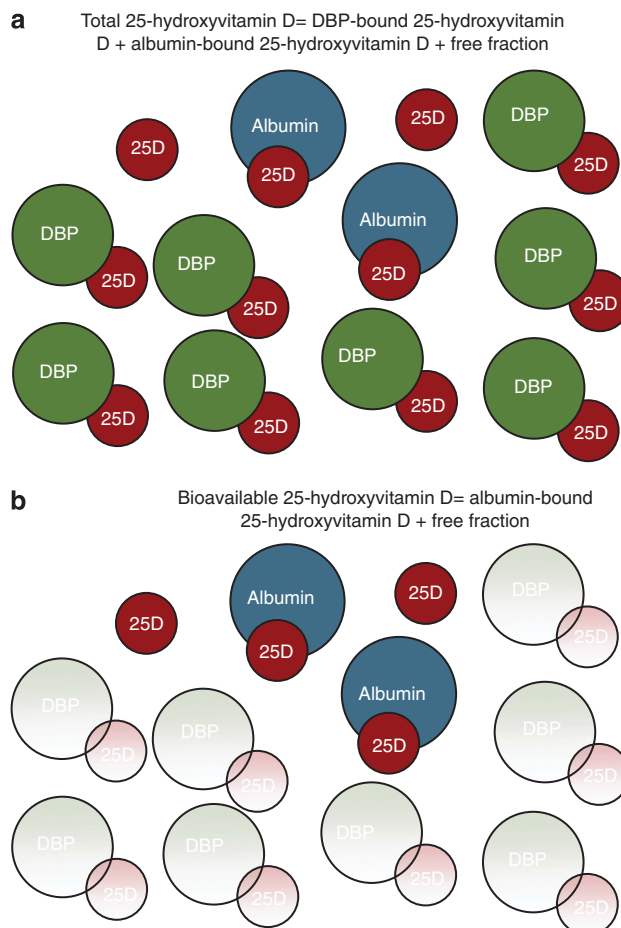
Genetic studies demonstrate that vitamin D-binding protein levels are dictated by common genetic polymorphisms. For example, GC suballele frequencies vary considerably by race and are notably different in white subjects compared with non-whites.<sup>23,24</sup> How circulating vitamin D-binding protein levels and their polymorphisms impact the thresholds used currently to define vitamin D deficiency, and perhaps more importantly, what levels of vitamin D should be targeted in future trials of vitamin D repletion remains open for debate.

Considering the associations observed between vitamin D deficiency and poor cardiovascular outcomes, a natural question is whether supplementation with vitamin D will provide clinical benefits. A number of observational studies, at least in patients with CKD and ESRD, have been supportive and provide rationale for vitamin D therapy in these populations;<sup>25–27</sup> however, all have potential limitations that apply to any observational study and this question can only be addressed by randomized controlled trials.

### RANDOMIZED CONTROLLED TRIALS

In a meta-analysis of 10 randomized trials in healthy adults, supplementation with nutritional vitamin D did not reduce systolic blood pressure (weighted mean difference,  $-1.9$  mm Hg ( $-4.2$  to  $0.4$  mm Hg)) or diastolic blood pressure (weighted mean difference,  $-0.1$  mm Hg ( $-0.7$  to  $0.5$  mm Hg)).<sup>28</sup> The dose of vitamin D preparations (either cholecalciferol or ergocalciferol) varied considerably among these trials (from 400 to 8500 units/day) and may explain the discrepancy between the outcomes reported in observational and these prospective interventional trials.

Albuminuria, an indirect measure of cardiovascular and endothelial health, was significantly reduced upon administration of oral paricalcitol  $2\ \mu\text{g}$  daily when compared with placebo in patients with diabetic nephropathy.<sup>29</sup> Paricalcitol



**Figure 1 | Concept of bioavailable 25-hydroxyvitamin D.** (a) Shows total 25-hydroxyvitamin D comprising of vitamin D-binding protein (DBP)-bound 25-hydroxyvitamin D, free fraction, and albumin-bound 25-hydroxyvitamin D. (b) Shows bioavailable 25-hydroxyvitamin D comprising of free fraction plus albumin-bound 25-hydroxyvitamin D.

was also associated with lowering of systolic blood pressure (range  $-3$  to  $-9$  mm Hg;  $P=0.033$  vs. placebo) during the trial period. A recent meta-analysis of six randomized clinical trials with active vitamin D analogs in CKD patients in which an effect of proteinuria or albuminuria was reported ( $n=688$ ), treatment with either paricalcitol or calcitriol reduced proteinuria (weighted mean difference from baseline to last measurement was  $-16\%$  (95% CI  $-13\%$  to  $-18\%$ )) compared with controls ( $+6\%$  (95% CI  $0\%$  to  $+12\%$ );  $P<0.001$ ).<sup>30</sup> Whether the improvements in proteinuria seen with active vitamin D therapy correspond with improved clinical outcomes needs further investigation.

Significant insights into the effects of active vitamin D administration on cardiac structure and function have been provided by the Paricalcitol Capsule Benefits in Renal Failure-Induced Cardiac Morbidity (PRIMO) trial.<sup>31</sup> This multinational double-blind placebo-controlled trial was designed to examine the effects of paricalcitol on left ventricular mass index over a period of 48 weeks in stages 3 and 4 CKD patients ( $n=227$ ) who had mild-to-moderate

left ventricular hypertrophy at baseline. Changes in left ventricular mass index were determined by cardiovascular magnetic resonance imaging and in left ventricular diastolic function were determined by cardiac echocardiography. Paricalcitol therapy did not alter left ventricular mass index, nor did changes in pre-specified measures of diastolic function or systolic blood pressure differ significantly between the paricalcitol and placebo groups. Interestingly, paricalcitol treatment was associated with fewer cardiovascular-related hospitalizations and also appeared to attenuate the increase in brain natriuretic peptide levels. In a *post-hoc* analysis of data from PRIMO, paricalcitol treatment reduced left atrial volume index, a marker for diastolic dysfunction that has been associated with significant cardiovascular risks.<sup>32</sup> Although encouraging, these results need further assessment in large randomized trials. One such trial, the Japan Dialysis Active Vitamin D trial (J-DAVID), is ongoing and the results are expected in the year 2015.<sup>20</sup>

## CONCLUSION

Biological evidence strongly supports the notion that heart structure can be remodeled and function improved with vitamin D intervention. Observational studies in humans have stimulated interest and provided important insights into vitamin D therapy, and have been generally supportive, especially with active vitamin D analogs in CKD and ESRD populations. However, potential confounding of observational data, limitations of available randomized controlled trials in terms of their sample size, and low intervention doses are possible explanations for discrepancies between observational and experimental data on blood pressure and cardiovascular outcomes. Whether future investigations should shift their attention to bioavailable rather than total 25-hydroxyvitamin D also needs to be carefully considered.

## DISCLOSURE

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