



# Kidney Research and Clinical Practice

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## Review Article

# Cardiorenal syndrome and vitamin D receptor activation in chronic kidney disease <sup>☆</sup>



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## A B S T R A C T

### Article history:

Received 13 October 2011

Received in revised form

22 November 2011

Accepted 22 November 2011

Available online 18 January 2012

### Keywords:

Cardio-renal syndrome

Chronic kidney disease

Vitamin D receptor

Vitamin D mimetic

Racial disparities

Paricalcitol

Cardiorenal syndrome (CRS) refers to a constellation of conditions whereby heart and kidney diseases are pathophysiologically connected. For clinical purposes, it would be more appropriate to emphasize the pathophysiological pathways to classify CRS into: (1) hemodynamic, (2) atherosclerotic, (3) uremic, (4) neurohumoral, (5) anemic-hematologic, (6) inflammatory-oxidative, (7) vitamin D receptor (VDR) and/or FGF23-, and (8) multifactorial CRS. In recent years, there have been a preponderance data indicating that vitamin D and VDR play an important role in the combination of renal and cardiac diseases. This review focuses on some important findings about VDR activation and its role in CRS, which exists frequently in chronic kidney disease patients and is a main cause of morbidity and mortality. Pathophysiological pathways related to sub-optimal or defective VDR activation may play a role in causing or aggravating CRS. VDR activation using newer agents including vitamin D mimetics (such as paricalcitol and maxacalcitol) are promising agents, which may be related to their selectivity in activating VDR by means of attracting different post-D-complex cofactors. Some, but not all, studies have confirmed the survival advantages of D-mimetics as compared to non-selective VDR activators. Higher doses of D-mimetic per unit of parathyroid hormone (paricalcitol to parathyroid hormone ratio) is associated with greater survival, and the survival advantages of African American dialysis patients could be explained by higher doses of paricalcitol (> 10 µg/week). More studies are needed to verify these data and to explore additional avenues for CRS management via modulating VDR pathway.

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<sup>☆</sup> **Funding sources:** Kamyar Kalantar-Zadeh is supported by a research grant from Abbott and a philanthropic grant from Mr. Harold Simmons.

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doi:10.1016/j.krcp.2011.12.006

## Introduction

Combined cardiac and renal dysfunction, referred to as cardiorenal syndrome (CRS), is common in people with primary cardiovascular disease and those with kidney function disorders. It is believed that the incidence and prevalence of CRS have increased in recent decades, not only because of increasing occurrence of cardiac or renal disease but also because of improved longevity of cardiac and renal patients. Pathophysiologically, heart and kidney diseases are connected to each other through a number of pathways, including, but not limited to, hemodynamic constellations, electrolyte disarrays, immunological disorders, metabolic dysfunctions, neurological derangement, and inflammatory and hormonal factors (Fig. 1).

## Definition and classification of CRS

Recently, CRS has been more systemically defined and classified into five different types [1]. CRS Types I and II are described as the primary occurrence of an acute cardiac event or chronic heart disease, respectively, leading to kidney disorders, whereas in Types III and IV CRS, the primary disease is acute kidney injury or chronic kidney disease (CKD), respectively, and the cardiovascular disease is a secondary phenomenon. Type V is any combination of the above.

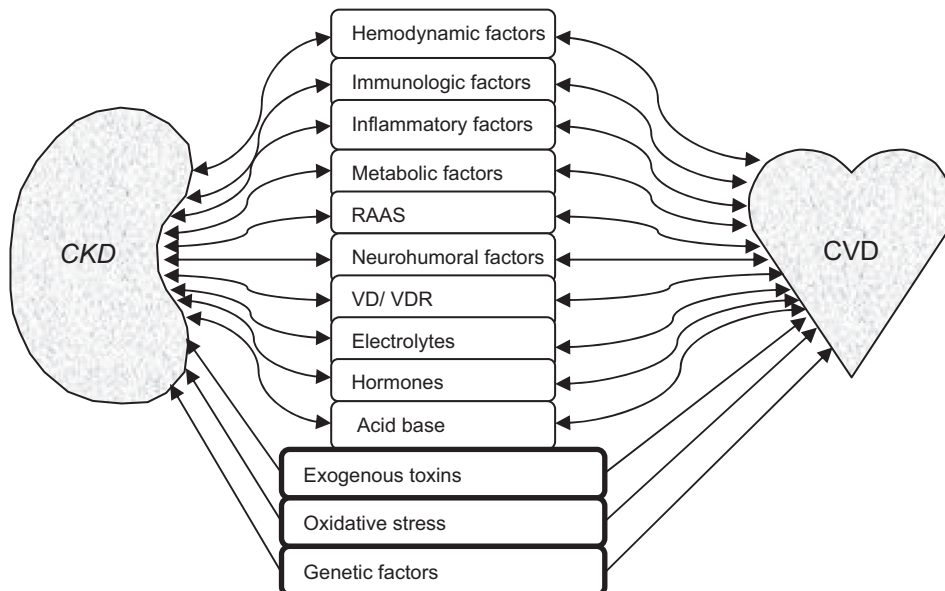
Despite the well-intended efforts in providing such novel definitions, the usefulness of this classification in clinical approaches and patient management is questionable. Perhaps, for clinical purposes, it would be more appropriate to emphasize the pathophysiological pathways, which are the main etiological role-players and which may have more clinical utility in patient management. We propose the following categories (Table 1): “hemodynamic CRS” (when heart failure leads to renal perfusion compromise and renal functional derangements, or when fluid retention due to primary kidney disease leads to decompensated heart failure); “atherosclerotic CRS”

(when both atherosclerotic cardiovascular disease and renal artery disease coexist); “uremic CRS” (when primary kidney disease leads to myocardial or pericardial dysfunction); “neurohumoral CRS” (when primary electrolyte or acid-base disorders in renal disease or heightened catecholamine release in cardiac disease or other hormonal derangements lead to cardiac or renal compromise); “anemic-hematologic CRS” (when anemia and/or iron deficiency lead to cardiac or renal compromise); “inflammatory CRS” (when proinflammatory pathways are activated in either organ and affect the other organ); and “vitamin D receptor (VDR)-related CRS” (when VDR activation is suboptimal, leading to a variety of combined heart and kidney diseases); and finally in situations where there are multiple pathophysiological connections, the term “multifactorial CRS” could be used.

In recent years, there have been a preponderance data indicating that vitamin D and VDR play an important role in the combination of renal and cardiac diseases. This review focuses on some important findings about VDR activation and its role in CRS.

## Biological characteristics of vitamin D and VDR

Usually about 50–90% of required vitamin D for the body is engendered in the skin under the sunshine by converting dehydro-cholesterol into cholecalciferol (vitamin D<sub>3</sub>), and the remainder comes from ingested food in the form of natural or added cholecalciferol, mostly animal origin, or ergocalciferol (vitamin D<sub>2</sub>), mostly plant origin. In the liver, 25-hydroxylase converts the latter to 25-OH vitamin D (which is usually measured in the blood as a screening test), and 1- $\alpha$ -hydroxylase in the kidneys converts the latter to 1,25 di-hydroxy-cholecalciferol, which is also known as active vitamin D and which is the most potent activator of VDR (Fig. 2). Although small amounts of 1- $\alpha$ -hydroxylase also exist in peripheral (extrarenal) tissues, > 90% of vitamin D activation occurs in



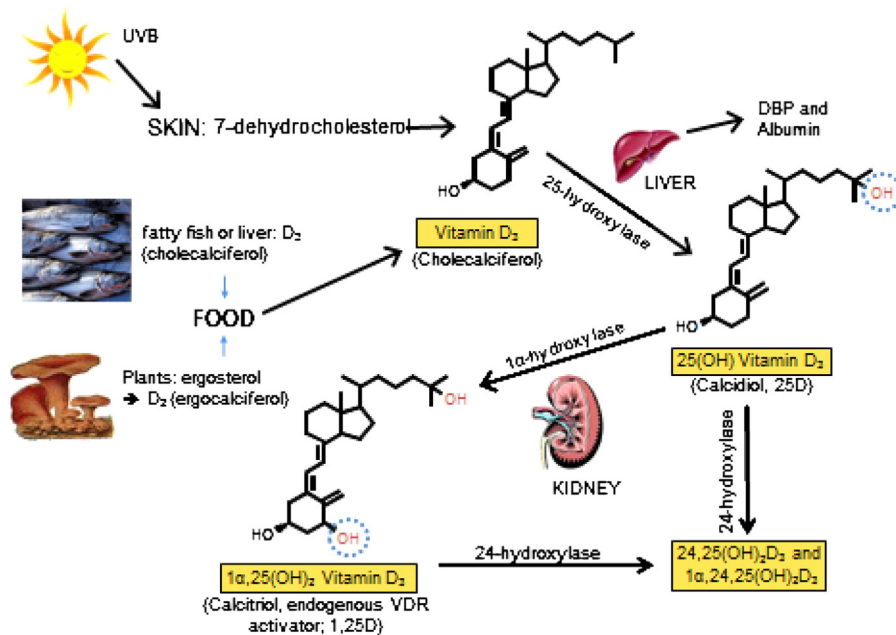
**Figure 1. Putative pathophysiological connections in cardiorenal syndrome.**

RAAS, renin-angiotensin-aldosterone system; VD/VDR, vitamin D/vitamin D receptor.

**Table 1. Suggested Classification of CRS According to Pathophysiology and Clinical Utility**

Suggested CRS category	Definition	Equivalent of current definition	Comments
Hemodynamic CRS	Heart failure leads to renal perfusion compromise leading to renal functional derangements, or when fluid retention due to primary kidney disease leads to decompensated heart failure	All types	Can be subclassified as primary heart or kidney hemodynamic CRS. Functional subtypes may include acute, chronic and recurrent
Atherosclerotic CRS	Both atherosclerotic cardiovascular disease and renal artery disease coexist	Mostly types I or II	
Uremic CRS	Primary kidney disease and uremic toxins leads to myocardial or pericardial dysfunction (e.g., myocardial dysfunction or uremic pericarditis)	types III or IV	Functional subtypes may include acute, chronic and recurrent
Neurohumoral CRS	Primary electrolyte or acid–base disorders (mostly renal disease) or heightened catecholamine release (mostly cardiac) or other hormonal derangements lead to cardiac or renal compromise	All types	Functional subtypes may include acute, chronic and recurrent
Anemic–hematologic CRS	Anemia and/or iron deficiency lead to cardiac or renal compromise	Mostly types III or IV	Functional subtypes may include acute, chronic and recurrent
Inflammatory CRS	Proinflammatory pathways are activated in either organs and affect the other organ	All types	Functional subtypes may include acute, chronic and recurrent
VDR-related CRS	VDR activation is suboptimal leading to a variety of combined heart and kidney diseases such as LVH and proteinuria	All types	A direct impact of FGF-23 on myocardium is possible
Multifactorial CRS	Situations where there are multiple pathophysiological connections	All types	

CRS=cardiorenal syndrome; LVH=left ventricular hypertrophy; VDR=vitamin D receptor.

**Figure 2. Sources of vitamin D and its metabolism in the body.**

the kidneys, hence explaining the main pathophysiological reason behind inadequate VDR activation in CKD patients.

Most, if not all, biological effects of the hormonal secosteroid ligand 1,25-(OH)<sub>2</sub>-D<sub>3</sub> (D-hormone) are mediated by the VDR, which can also be called D-hormone receptor (DHR). VDR is a member of the super-family of nuclear receptors that regulate gene expression. The transcriptional activity of this receptor is modulated by ligands, such as steroids, retinoids and other lipid-soluble compounds, and by nuclear proteins acting as coactivators and co-repressors [2,3]. The genomic organization of the *DHR* at locus 12q13.1 shows that the *VDR* gene itself is large (> 100 kb) and has an extensive promoter region capable of generating multiple

tissue-specific transcripts [4]. Activated vitamin D is a highly flexible molecule, the structure of which can be manipulated synthetically; hence, many vitamin D analogs have been synthesized for research or clinical purposes, and some providing important therapeutic effects with varying degrees of calcemic activity [5].

#### Biological effects of VDR

VDR activation inhibits cell differentiation and proliferation while promoting cell maturation and regulation of apoptosis. The widespread tissue distribution of VDR suggests that the D-hormone endocrine system has additional physiological

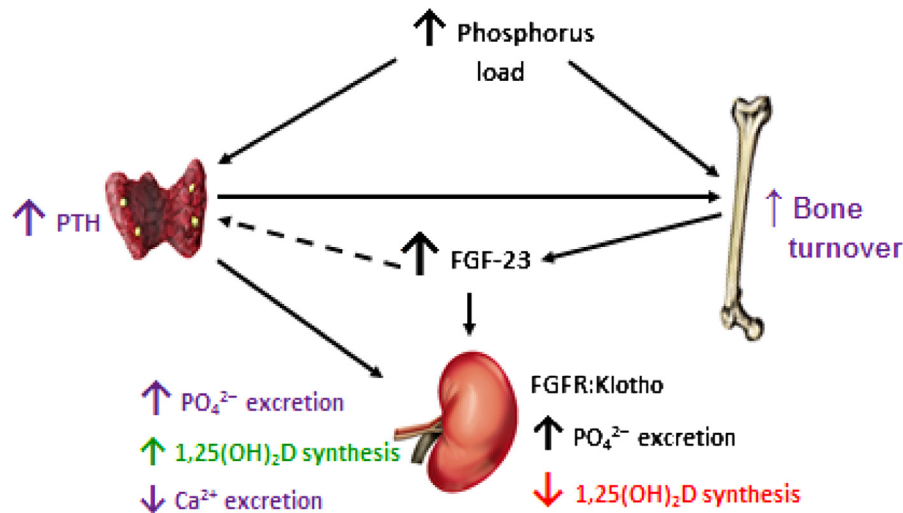


Figure 3. Interaction between vitamin D regulation and fibroblast growth factor-23.

functions beyond calcium homeostasis including, but not limited to, skin [6] and hair follicles [7], immune system [8,9], cell growth in gastrointestinal tract, prostate and mammary cancer [10–15], lung and production of surfactant [16,17], Alzheimer's disease [18], cardiovascular system, and even male fertility [19]. Nowadays, it has been revealed that > 60 types of cells possess VDRs, 2776 genomic positions are occupied by the VDR, and 229 genes show significant changes in expression in response to VDR activation. VDR binding sites are considerably enriched near autoimmune and cancer-associated genes identified from genome-wide association studies [20]. It has been demonstrated that many tissues not only express the VDR but also may possess small amounts of 1- $\alpha$ -hydroxylase, and are therefore, capable of the production of paracrine 1,25-(OH)<sub>2</sub>-D<sub>3</sub>, which may act locally. However, VDR multiple polymorphisms have also been described in association with different malignant and nonmalignant diseases.

An important function of the VDR complex is to regulate the level of renal 1,25-(OH)<sub>2</sub>-D<sub>3</sub> biosynthesis. 1,25-(OH)<sub>2</sub>-D<sub>3</sub> appears to affect a short feedback loop to repress 1- $\alpha$ -hydroxylase [21], and is also a potent suppressor of the synthesis and secretion of parathyroid hormone (PTH), the primary hormone stimulating 1- $\alpha$ -hydroxylase. The mechanism by which 1,25(OH)<sub>2</sub>-D<sub>3</sub> reduces PTH production involves a VDR-mediated silencing of PTH gene transcription [22–25].

Similar constellations of feedbacks and modulations also exist for fibroblast growth factor (FGF)-23, which may be even more involved with phosphorus regulation including its renal excretion (Fig. 3).

### Circulating vitamin D

#### Definition and measurement methods

Measuring serum level of 25-(OH) vitamin D concentration is the most commonly used assessment of vitamin D status. Acceptable levels are not known exactly but the

general recommendations are between 30 and 60 ng/mL (70–150 nmol/L). Vitamin D insufficiency is defined when the levels are between 20 ng/mL and 29 ng/mL and at levels of  $\leq 20$  ng/mL (or < 15 ng/mL according to some guidelines such as Kidney Disease Outcomes Quality Initiative; KDOQI), the patient is considered to be vitamin D deficient. It is important to note that besides the definition of vitamin D insufficiency and deficiency variations, methods of 25-(OH)-D assessment vary between studies. Also, it is important to know that 25-(OH)-D has higher affinity for vitamin D binding protein (VDBP) than 1,25-(OH)<sub>2</sub>-D<sub>3</sub>; whereas, 1,25(OH)<sub>2</sub>-D<sub>3</sub> has the highest affinity for VDR when compared to 25-(OH)-D, which may have no meaningful affinity to VDR at physiological concentrations. Hence, 25-(OH)-D is much less potent than 1,25-(OH)<sub>2</sub>-D<sub>3</sub> [26], suggesting that without adequate 1- $\alpha$ -hydroxylation in the kidneys, as is the case in most terminal CKD patients, examining the level of 25-(OH)-D may be of little significance for optimal health and well-being of these patients. It is also important to note that methods for measuring 25(OH)-D levels vary widely. Especially at lower vitamin D levels, some commonly used assays show up to 80% differences [27]. These assays include competitive protein-binding assay, radioimmunoassay, enzyme immunoassay, chemiluminescence immunoassays, high-performance liquid chromatography, and liquid chromatography–mass spectrometry; and each of them have a number of advantages and disadvantages beyond the scope of this review. There is significant interassay and interlaboratory variability in measurements even at usual levels [28]. Furthermore, some assays measure both D<sub>2</sub> and D<sub>3</sub>, whereas some measure only D<sub>3</sub> or differentially and each separately. Therefore, comparing vitamin D status between studies is not reliable unless the exact same definition and assay and type of D (D<sub>2</sub> vs. D<sub>3</sub>) are clarified adequately. The assays should be appropriately cross-calibrated in clinical studies and patient management [29]. Finally, most of these studies are in non-CKD patients, and there is virtually no study to examine

the reliability of these assays in the uremic milieu of CKD patients.

#### Prevalence and risk factors of vitamin D deficiency

Low-level vitamin D status is a common problem in the general population. Levels of 25-(OH)-D below 30 ng/mL are prevalent in every region studied, whereas very low levels below 10 ng/mL are also common in regions such as South Asia and the Middle East. Factors that are significantly associated with lower vitamin D levels include older age, female sex, higher latitude, winter season, darker skin pigmentation, less sunlight exposure, dietary habits, and absence of vitamin D fortification [29].

Vitamin D deficiency is a common problem among CKD patients. In one prospective study of 140 CKD patients, it has been revealed that about 42% and 34% of patients suffered from vitamin D deficiency and insufficiency, respectively [30]. In a recent cross-sectional analysis of 1026 adult patients across all stages of non-dialysis-dependent CKD, the prevalence of 25-(OH)-D deficiency was associated inversely with glomerular filtration rate (GFR), ranging from 28% and 51% for GFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> and  $< 15$  mL/min/1.73 m<sup>2</sup>, respectively. The vitamin D deficiency was higher in patients of African origin, those with obesity, diabetes, hypertension, macroalbuminuria and hypoalbuminemia, and also during winter [31].

#### Role of vitamin D in CKD

##### Effect of low vitamin D level on mortality

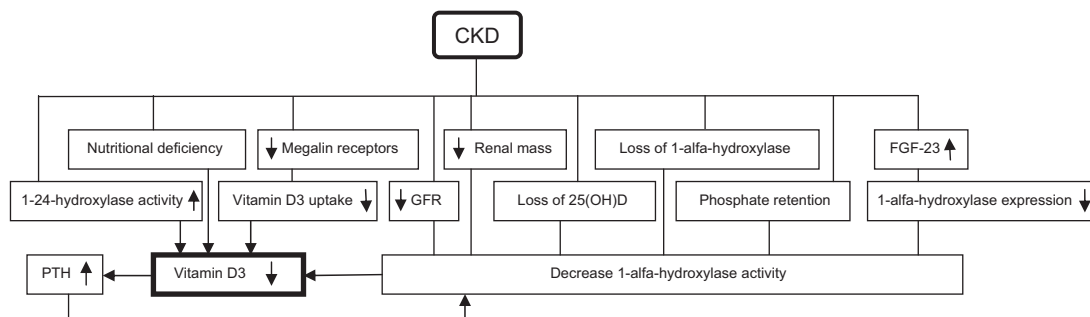
A recent meta-analysis has revealed that the relative risk of mortality per 10-ng/mL (25-nmol/L) increase in 25-(OH)-D level was 0.86 [95% confidence interval (CI): 0.82–0.91], suggesting 14% greater survival benefit across each 10-ng/mL higher level [32]. In patients with very low levels of vitamin D ( $< 16.7$  ng/mL) mortality rate was significantly higher. Multivariate adjustments (including for age, sex, diabetes, arterial pressure, CKD stage, phosphorus, albumin, hemoglobin, aortic calcification score, and pulse wave velocity) confirmed 25-(OH)-D level as an independent predictor of all-cause mortality. As a result

of decreased level of vitamin D, hypoparathyroidism occurs. The combination of persistently high PTH and low 1,25-(OH)<sub>2</sub>-D<sub>3</sub> is associated with bone loss, cardiovascular disease, immune suppression and increased mortality in patients with end-stage kidney failure [30]. CKD stage 5 patients are at a higher risk for cardiovascular disease and stroke as leading causes of mortality, which is about 10–20-fold higher than the age- and sex-matched general population [33].

#### Mechanisms of vitamin D deficiency in CKD

Hydroxylation by cytochrome P450 27B1 (CYP-27B1) is the rate-limiting step in the activation of vitamin D and production of 1,25-(OH)<sub>2</sub>-D<sub>3</sub> [34]. Another hydroxylase, CYP24A1, represents the first step in the inactivation of 1,25-(OH)<sub>2</sub>-D<sub>3</sub> [6,25]. Generally, 25-OHD-1 $\alpha$ -hydroxylase (CYP27B1), which is expressed as the highest concentration in the kidney, is positively regulated by calcium, PTH, calcitonin, growth hormone, and insulin-like growth factor-I, and negatively regulated by phosphate, FGF-23, and 1,25-(OH)<sub>2</sub>-D<sub>3</sub> itself [35]. There seem to be several mechanisms involved in the decreased levels of 1,25-(OH)<sub>2</sub>-D<sub>3</sub> that occur in the course of kidney disease (Fig. 4).

1. Maintaining circulating level of 25-(OH)-D is an important key factor for nonrenal calcitriol synthesis. In CKD, progressive loss of this substrate, besides the lower capacity for conversion of it to circulating calcitriol, has been observed [36].
2. A decrease in renal mass (independent of renal function) limits substantially the quantities of 1- $\alpha$ -hydroxylase that are available for production of active vitamin D metabolites.
3. GFR reduction limits substrate delivery to the 1- $\alpha$ -hydroxylase sites, which further decreases the ability of the kidney to synthesize 1,25-(OH)<sub>2</sub>-D<sub>3</sub>.
4. The progressive decline in kidney function (independent of renal mass) is associated with loss of renal 1- $\alpha$ -hydroxylase (CYP27B1), resulting in gradual decline in circulating 25-hydroxyvitamin D and 1,25-(OH)<sub>2</sub>-D<sub>3</sub>.
5. Decrease in uptake of vitamin D<sub>3</sub> bound to vitamin D binding protein by megalin receptors in the proximal



**Figure 4.** Putative mechanisms involve in the decreased levels of 1,25(OH)<sub>2</sub>-D<sub>3</sub> in the course of kidney disease progression in chronic kidney disease patients.

CKD, chronic kidney disease; FGF-23, fibroblast growth factor-23; GFR, glomerular filtration rate; PTH, parathyroid hormone.

tubules is another potential cause for vitamin D deficiency presenting in CKD [37,38].

6. Another factor that may be involved in decreased vitamin D in CKD is phosphorus retention that causes a decrease in activity of 1- $\alpha$ -hydroxylase (Fig. 3) [39].
7. Northern blot analysis has revealed that FGF-23 decreases 1- $\alpha$ -hydroxylase expression and increases 24-hydroxylase expression, starting as early as 1 h after administration. In CKD subjects, FGF-23 levels rise in parallel with declining renal function long before a significant increase in serum phosphorus concentration can be detected [40].
8. An additional factor that may be involved is the potential for N-terminally truncated PTH fragments or C-terminal PTH fragments to decrease activity of 1- $\alpha$ -hydroxylase [41].
9. Few foods contain vitamin D, therefore, humans including CKD patients depend on sun exposure to satisfy their requirements for vitamin D. High incidence of nutritional vitamin D insufficiency or deficiency, in parallel with uremic malnutrition (including anorexia and protein-energy wasting), and sun exposure deprivation could be additional important factors for low levels of vitamin D in CKD patients.
10. Serum levels of 25-(OH)-D is the main determinant of 1,25-(OH)<sub>2</sub>-D<sub>3</sub> tissue levels in various organs. Furthermore, 24-hydroxylation of 25-(OH)-D or 1,25-(OH)<sub>2</sub>-D<sub>3</sub> is considered the main degradation process and produces ineffective vitamin D metabolites [24,25-(OH)<sub>2</sub>-D or 1,24,25-(OH)<sub>3</sub>-D], which are converted to water-soluble inactive calcitroic acid [39]. The decline in circulating 1,25-(OH)<sub>2</sub>-D<sub>3</sub> in CKD might be a consequence of increased inactivation (24-hydroxylation) rather than of reduced production (1 $\alpha$ -hydroxylation) of 1,25-(OH)<sub>2</sub>-D<sub>3</sub> [42].

#### *Risk factors for vitamin D deficiency in CKD*

Aging, diabetes and obesity are generally the major risk factors for hypovitaminosis D in the general population as well as in non-dialysis-dependent CKD patients [43]. Additionally, in patients with CKD stage 5 undergoing hemodialysis, lower values of 25-(OH)-D seem to be associated with female sex, increased body mass index, and worse functional class of CKD [44].

#### **Vitamin D and CRS**

Cardiovascular mortality is the leading cause of death in the entire spectrum of CKD, including dialysis and transplanted patients, with mortality 10–30 times higher than in the general population, despite stratification for sex, race, and presence of diabetes. Similarly, cardiovascular mortality is 2–5 times higher than in the general population in patients with a functioning renal transplant [33]. However, cross-sectional studies have demonstrated that the Framingham risk equation is insufficient to capture the extent of cardiovascular disease in CKD subjects, implying the presence of additional risk factors [45].

Expression of the VDR and vitamin D metabolizing enzymes in the myocardium and endothelial system suggests a role for vitamin D in the cardiovascular system. Many precursor states of heart failure, such as hypertension, atherosclerosis, and diabetes are more prevalent in subjects with low vitamin D levels. Furthermore, vitamin D deficiency leads to secondary hyperparathyroidism and both primary and secondary hyperparathyroidism are associated with cardiovascular pathologies [46]. In CKD, vitamin D plays a prominent role in the progression of heart failure, hypertension, myocardial hypertrophy and an increased prevalence of cardiovascular risk factors and related morbidity and mortality (see below) [47–49].

#### *Role of PTH in CRS*

An increased risk of cardiovascular diseases in patients with primary hyperparathyroidism without CKD has been reported [50]. In the line with this, hypertension, impaired glucose tolerance and chronic inflammation have been associated with primary hyperparathyroidism [51–54]. One study has suggested the possible role of PTH in the difference in adipose tissue gene expression. Many of those most upregulated genes have been implicated in inflammatory diseases, whereas many of the downregulated genes play roles in lipid and carbohydrate metabolism that suggest that downregulation of metabolic genes in primary hyperparathyroidism patients may confer, or at least reflect, metabolic dysregulation and may be contributed in cardiovascular disease [55]. Elevated PTH has been shown to play a role in abnormal vasodilatation [56]. In patients with primary hyperparathyroidism, parathyroidectomy significantly improves endothelial vasodilatory function [57]. In one recently published article, highly significant differential cardiovascular disease prevalence/incidence rates for most cardiovascular risk factors, disease, diagnoses, and mortality were noted for PTH > 75 pg/mL (by 1.25–3-fold). PTH is correlated weakly with 25-(OH)-D and moderately with GFR. In this study, 25(OH)-D level, standard risk factors, and renal dysfunction variably attenuated PTH risk associations, but the risk still persisted after full multivariable adjustment [46].

#### *Renin–angiotensin system and blood pressure*

Associations of minerals and bone and blood pressure have been the focus of many studies. In most of these studies, there has been no or little difference in mean blood pressure (BP) between the group of patients who took calcium supplements and the control (placebo) group. Heterogeneity between trials could not be explained by dose of calcium or baseline BP [58–60]. However, a recent study in rats has revealed significant elevation in BP and heart rate in association with low vitamin D level [61]. Also, a relationship between cutaneous vitamin D photosynthesis and BP has been confirmed experimentally by Krause et al. [62] who have found UV-B irradiation not only significantly increased 25-(OH)-D concentrations but also lowered BP; an effect not seen with exposure to UV-A radiation.

Some clinical studies have suggested an inverse relationship between the plasma  $1,25\text{-(OH)}_2\text{-D}_3$  concentrations and BP and/or plasma renin activity in both normotensive men and patients with essential hypertension [63–67]. However, at least one study has shown no difference in systolic and mean BP after 6 months, and even a decrease in mean systolic pressure after 9 months in VDR knockout (VDR-KO) mice. In this study, heart weight/body weight ratio was 41% greater in the VDR-KO mice than wild-type (WT) mice ( $p < 0.003$ ). Interestingly, other VDR-KO mouse tissues did not display hypertrophy. Trichrome staining of heart tissue showed marked increase in fibrotic lesions in the VDR-KO mice. Analysis of plasma showed elevated renin activity and angiotensin II and aldosterone levels in VDR-KO compared with WT mice [68].

#### *Role of nitric oxide pathway in VDR–CRS link*

Calcium is required for the activity of nitric oxide (NO) synthase, and thus, increasing extracellular or intracellular calcium concentrations may stimulate NO production. An increase in serum calcium may also alter the intracellular calcium level, leading to opening of endothelial calcium-sensitive potassium channels, and vessel relaxation. Aortic endothelial NO synthase expression and urinary NO<sub>x</sub> excretion appear to be reduced in hypocalcemic VDR-KO mice but not in normocalcemic VDR-KO mice [69]. Whether NO pathways are involved in the VDR–CRS link remains to be determined in additional studies.

#### *Thrombogenicity and platelet pathway*

It seems that platelet aggregatory threshold in association with VDR activity is partly related to calcium level. In one study, platelet aggregatory index values in hypocalcemic VDR-KO mice were increased markedly compared with those in WT mice ( $p < 0.01$ ). In contrast, platelet aggregatory threshold index values in normocalcemic VDR-KO mice were significantly lower than those in WT mice ( $p < 0.05$ ). These results demonstrate that hypocalcemia is responsible for the suppression of platelet aggregation in VDR-KO mice fed a regular diet, and that VDR itself has a suppressive effect on platelet aggregability [70]. The gene expression of antithrombin in the liver and that of thrombomodulin in the aorta, liver and kidney was downregulated in hypo- and normocalcemic VDR-KO mice [65]. However, VDR-KO mice manifest normal prothrombin time and activated partial thromboplastin time as in WT mice. These results demonstrate that the loss of VDR function does not lead to impaired blood coagulation and is consistent with the fact that VDR-KO mice do not show a bleeding tendency [66].

#### *Lipid metabolism and VDR*

The exact role of VDR in lipid metabolism is not clear. In one study, uncoupling protein-1, which mediates dissociation of cellular respiration from energy production, was elevated by > 25-fold in VDR-KO mouse white adipose tissue. Consistent with this elevation in uncoupling protein-1, VDR-KO mice were resistant to high-fat-diet-induced weight gain [71].

In contrast, several cross-sectional studies have reported a strong inverse association between 25-OH-D level and prevalence of obesity (body mass index, waist circumference, waist: hip ratio, total body fat percentage and total body fat mass); a direct association between PTH and obesity has also been described [72,73]. In another cross-sectional study in overweight adult African Americans, depressed 25-OH-D and elevated PTH levels were both linked to body composition, fat distribution and anthropometric measures [74].

#### *Coronary artery calcification*

Coronary artery calcification may be present even in the early phases of CKD; the prevalence is greater in patients with renal dysfunction than in controls, but less than that in dialysis patients [75]. Up to 80% of all dialysis patients have vascular calcification [76]. This means at least 2–5-fold more frequent coronary artery calcification than age-matched individuals with angiographically proven coronary artery disease [77]. Serum concentrations of calcium, phosphorus, PTH, and inflammatory markers may or may not predict the risk of pre-existing or progressive coronary artery calcification [75]. Although serum alkaline phosphatase > 120 U/L does so [78]. In another study on 81 patients on hemodialysis, older age and higher PTH and serum calcium were associated with higher coronary calcium score, which is a predictor of higher mortality in dialysis patients [79]. In a study by Mizobucchi et al., higher risk of vascular calcification in uremic rats was seen upon exposure to calcitriol or doxercalciferol (a  $1\text{-}\alpha\text{-OH-vitamin-D}_2$ ) but not with paricalcitol ( $19\text{-nor-dihydroxy-D}_2$ ).

#### *African American race and vitamin D link*

Vitamin D deficiency is more common among African Americans, whose dark skin makes vitamin D photosynthesis inefficient. Most Africans and others with deep skin pigmentation live at or near the equator. Compared with those living at more northern or southern latitudes, native Africans and other people of color living near the equator have a lower prevalence of hypertension. It has been demonstrated that for each  $10^\circ$  north or south of the equator, BP increases by 2.5 mmHg and hypertension prevalence by 2.5%, which may indicate the link with the VDR activation pathway [80,81]. Moreover, about half of the BP difference noted between African Americans and European Americans could be explained by vitamin D deficiency. Although these statistical associations may suggest associations, they do not prove causality.

#### *Vitamin D and diabetes*

In a study of disease-free adults in the National Health and Nutrition Examination Survey (NHANES) 2001–2006, mean vitamin D concentration was significantly lower in adults with pre-diabetic status or undiagnosed diabetes compared with those with normoglycemia ( $p = 0.004$  and  $p = 0.0002$ , respectively). Mean serum vitamin D concentrations in those with desirable BP (< 120/80 mmHg),

pre-hypertensive status (systolic BP 120–139 mmHg and/or diastolic BP 80–89 mmHg), and untreated hypertension (BP  $\geq$  140/90 mmHg) were 67.9 nmol/L, 61.5 nmol/L and 62.4 nmol/L, respectively. Compared with those with desirable BP, adults with pre-hypertensive BP ranges had significantly lower mean vitamin D concentration ( $p < 0.001$ ) [82]. In another prospective study, those who developed diabetes had lower serum 25-OH-D (mean: 58 nmol/L vs. 65 nmol/L;  $p < 0.001$ ) and calcium intake (mean: 881 mg/day vs. 923 mg/day;  $p = 0.03$ ) compared with those who remained free of diabetes. Each 25-nmol/L increment in serum 25 (OH) D was associated with a 24% reduced risk of diabetes (odds ratio: 0.76; 95% CI: 0.63–0.92) after adjusting for age, waist circumference, ethnicity, season, latitude, smoking, physical activity, family history of diabetes, dietary magnesium, hypertension, serum triglycerides, and fasting plasma glucose. Dietary calcium intake was not associated with reduced diabetes risk [83]. Animal and human studies have indicated that vitamin D can have a direct (via activation of the VDR on pancreatic  $\beta$ -cells and insulin-sensitive organs) and indirect (via regulation of calcium homeostasis) positive effect on insulin secretion and sensitivity [84,85].

### Heart failure

Vitamin D<sub>3</sub> deficiency and insufficiency are associated with the etiology and pathogenesis of congestive heart failure [86]. Ablation of the VDR in mice and vitamin D deficiency in rats leads to cardiac hypertrophy and fibrosis [87]. An increase in c-myc protein levels observed in the hearts of the vitamin D<sub>3</sub>-deficient rats suggests that 1,25-(OH)<sub>2</sub> D regulates c-myc expression [88]. The proto-oncogene c-Myc (Myc) has been shown to be increased in many different types of heart disease, including hypertrophic cardiomyopathy, before any signs of the disease are present; c-Myc (Myc) is highly expressed in fetal and proliferating cardiomyocytes. However, soon after birth, cardiomyocytes cease to divide, corresponding with the downregulation of Myc [89]. c-Myc proto-oncogene is induced in the ventricular myocardium within 1 hour after imposition of pressure overload [90]. Myc also plays a role in the maintenance of mitochondrial function [91]. A 2-week induction of Myc resulted in an approximately twofold increase in gravimetric cardiac mass normalized to body weight compared with Myc-OFF mice, and the expression of both atrial and brain natriuretic peptides was significantly increased after 1 week induction and then decreased after 2 weeks induction [92]. Myc overexpression for 2 weeks produced decompensated hypertrophic cardiomyopathy characterized by impaired systolic and diastolic function.

### Stroke, sudden cardiac death and myocardial infarction

25-(OH)-D was measured in 1108 diabetic hemodialysis patients, who participated in the German Diabetes Dialysis Study (4D) and were followed for a median of 4 years; patients with severe vitamin D deficiency tended to have a 2.8-fold nonsignificant increased risk of stroke

compared with those with normal levels [adjusted hazard ratio (HR): 2.83, 95% CI: 0.82–9.80], but the risk of fatal and nonfatal myocardial infarction did not increase at lower levels of 25-(OH)-D. Sudden cardiac death was threefold higher in patients with severe vitamin D deficiency as compared with those with sufficient 25(OH)-D levels (HR: 2.99, 95% CI: 1.39–6.40). This association was virtually unchanged after controlling for potential confounders and seasonal variation of 25-(OH)-D (HR: 2.95, 95% CI: 1.35–6.46) [93].

## Management of CRS

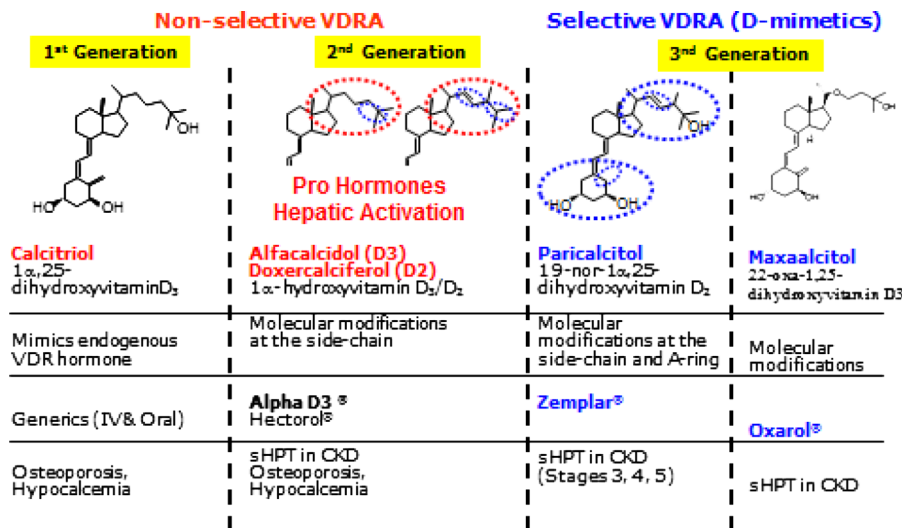
### Vitamin D supplement therapy

Some guidelines suggest correcting reduced 25-(OH)-D concentrations in CKD patients with an estimated GFR  $<$  60 mL/min/1.73 m<sup>2</sup>. Calcitriol and its analogs including vitamin D mimetics that activate VDR directly are commonly used to manage hyperparathyroidism secondary to CKD [94]. It has been shown that vitamin D<sub>3</sub> supplementation reduces BP in patients with essential hypertension [95,96]. Similarly, in hyperparathyroidism, plasma renin activity and angiotensin II levels are different [97,98]. In one study, subjects who received calcitriol experienced a 9% decrease in mean systolic BP compared to that in the matched placebo group. However, after 1 week, BP returned to pretreatment levels, suggesting at least an effective short-term intervention for reducing BP [99]. In a recent study, 15 out of 94 (16%) infants with severe left ventricular dysfunction had severe hypocalcemia due to vitamin D deficiency; vitamin D levels were at lower limit of normal, but definitely low for that degree of hypocalcemia. All these infants except for one responded dramatically to therapeutic doses of vitamin D and calcium [100].

### Vitamin D analogs and D-mimetics

Different types of VDR activators are shown in Fig. 5. In 1998, paricalcitol (19-nor-1,25-OH<sub>2</sub>-D<sub>2</sub>) was approved for the treatment of hyperparathyroidism in chronic renal failure. Reductions in PTH occurred more rapidly and with least calcemic effects in subjects administered with paricalcitol compared with calcitriol, whereas the percentage of subjects experiencing severe hyperphosphatemia (serum phosphorus  $>$  8.0 mg/dL) was greater in those administered calcitriol compared with paricalcitol [101]. Several clinical studies have shown that VDR activation therapy was successful in increasing survival in CKD patients. In this regard, paricalcitol revealed more benefits than calcitriol, and both of them were more effective than no VDR activation therapy; these results seemed to be independent of PTH and calcium levels [102–104]. Other VDR-activating compounds have been invented in an attempt to find the most appropriate treatment, such as doxercalciferol and alfacalcidol. In a study on 37 dialysis patients, paricalcitol was successful at controlling secondary hyperparathyroidism in patients resistant to calcitriol therapy, with minimal impact on calcium and phosphorus homeostasis [105]. In another double blind randomized study on 88 patients with secondary





**Figure 5. Different types of active vitamin D analogs including non-selective vitamin D receptor activators and vitamin D mimetics.** CKD, chronic kidney disease; sHPT, secondary hyperparathyroidism; VDR, vitamin D receptor; VDRA, VDR agonist.

hyperparathyroidism, 3 weeks administration of paricalcitol caused a significant decrease in PTH, with a mean 30% reduction [106]. In another study, compared to the uremic control group, paricalcitol treatment in uremic patients greatly reduced PTH levels ( $p < 0.01$ ) and partially inhibited the development of left ventricular hypertrophy. Four weeks treatment with paricalcitol significantly prevented decreased VDR expression in myocardial cells. Also, left ventricular fibrosis and vessel thickness, which are major causes of cardiomyopathy in uremic patients, significantly decreased [107]. The endothelial-dependent relaxation was enhanced in nephrectomized rats treated with paricalcitol for 2 weeks, whereas it did not affect BP or heart rate. PTH suppression alone did not improve endothelial function because cinacalcet, a calcimimetic, suppressed PTH without affecting endothelial-dependent vasorelaxation [103,108,109]. Hence, the effect of paricalcitol on improving endothelial function and left ventricular hypertrophy appears to be independent of BP control [110,111]. In another study, in spontaneously hypertensive rats with impaired endothelial function, oral cholecalciferol (vitamin D<sub>3</sub>) treatment significantly improved the endothelium-dependent vascular relaxation and hyperpolarization induced by acetylcholine [112]. A study by Freundlich et al. [113] has reported that plasma creatinine level, elevated in all groups with renal ablation, started to decline after 2 weeks of paricalcitol treatment.

Different vitamin D analogs have been compared in their effects and side effects by several studies. A randomized control trial has compared outcome of 16 weeks treatment with paricalcitol versus ergocalciferol. In 80 patients with CKD, low 25-OH-D<sub>3</sub> level and secondary hyperparathyroidism, for lowering PTH level, paricalcitol was more effective than ergocalciferol, and for increasing serum 25-(OH)-D levels, ergocalciferol was more effective [114]. In another study in NTX Cyp27b1-null mice, which completely lack endogenous calcitriol, effects of oral doxercalciferol (1-α-OH-D<sub>2</sub>) and paricalcitol have been examined. Doxercalciferol

at 100 pg/g or 300 pg/g normalized serum calcium and PTH levels. Paricalcitol at 300 pg/g or 1000 pg/g normalized serum calcium, but less so with PTH levels. Osteomalacia was corrected by 100 pg/g doxercalciferol or 1000 pg/g paricalcitol. The highest dose of doxercalciferol, but not of paricalcitol, significantly reduced osteitis fibrosa [115]. Several limitations of the study were noticeable, making the accuracy of these results somewhat questionable. In a multi-center randomized clinical trial in hemodialysis patients, effects of intravenous alfacalcidol (D<sub>3</sub>) and paricalcitol (D<sub>2</sub>) were compared for 16 weeks. Paricalcitol was more efficient at correcting low than high baseline PTH levels, whereas alfacalcidol was equally effective at all levels. There were no differences in the incidence of hypercalcemia and hyperphosphatemia [116]. This study should be qualified for its small sample size and several other limitations. In general, VDR activation mitigates the impact of uremia on endothelial function in uremic animal models [117].

#### Other possibilities for future management of CRS

The administration of exogenous pyrophosphate, a potent inhibitor of vascular calcification, usually deficient in CKD, can inhibit uremic vascular calcification without producing adverse effects on bone [118]. Inhibition of proto-oncogene Myc is becoming an attractive paradigm for prevention and treatment of cardiomyopathy and heart failure. The nuclear hormone 1,25-(OH)<sub>2</sub>-D<sub>3</sub> downregulates Myc expression, but the exact mechanism is still elusive [119]. Bone morphogenetic protein-7 may inhibit the progression of vascular calcification induced by conditions such as high levels of vitamin D or phosphate [120].

#### Epilogue

CRS exists frequently in CKD patients and is a main cause of morbidity and mortality. Pathophysiological pathways related to suboptimal or defective VDR

activation may play a role in causing or aggravating CRS. VDR activation using newer agents including vitamin D mimetics (such as paricalcitol and maxacalcitol) are promising agents, which may be related to their selectivity in activating VDR by means of attracting different post-D-complex cofactors. Some [103], but not all [121], studies have confirmed the survival advantages of D-mimetics as compared to nonselective VDR activators. Indeed, higher doses of D-mimetic per unit of PTH (paricalcitol to PTH ratio) is associated with greater survival [122], and the survival advantages of African American dialysis patients could be explained by higher doses of paricalcitol (> 10 µg/week). More studies are needed to verify these data and to explore additional avenues for CRS management via modulating VDR pathway.

### Conflict of interest

Kamyar Kalantar-Zadeh and Csaba Kovesdy are supported by research grants from Abbott.

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