Review Article

The Effect of Paricalcitol on Vascular Calcification and Cardiovascular Disease in Uremia: Beyond PTH Control

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Secondary hyperparathyroidism is a systemic disorder that associates with bone and cardiovascular disease, including arterial calcification. Treatment with calcitriol, the active form of vitamin D, reduces parathyroid hormone levels, but may result in elevations in serum calcium and phosphorus, increasing the risk of vascular calcification in dialysis patients. New vitamin D receptor activators (VDRAs) have been developed and investigated with the rationale to treat high serum PTH levels, with a reduced risk of hypercalcemia and hyperphosphatemia. Paricalcitol is a selective VDRA that suppresses PTH secretion with minimal increases on serum calcium and phosphate. Moreover, paricalcitol prevents vascular calcification in experimental models of renal failure, compared with calcitriol.

1. Introduction

Secondary hyperparathyroidism (SHPT) affects less than half of the approximately 320 000 haemodialysis (HD) patients in the US who suffer from stage-V chronic kidney disease (CKD) (also known as end-stage renal disease or end-stage kidney disease) [41]. SHPT is characterized by abnormally elevated serum concentrations of intact parathyroid hormone (PTH), and abnormalities of serum calcium, phosphorous, and vitamin D concentrations. Inadequate treatment of SHPT has been associated with the following conditions: skeletal abnormalities (renal osteodystrophy), cardiovascular complications [1], infections and immunoregulatory dysfunction [2], foot and extremity complications, and anaemia. Patients on HD are at increased risk for fracture (including hip fracture) and vascular calcification, which results in significant morbidity (including hospitalization) and mortality [3].

Diminished levels of vitamin D have been significantly associated with an increased risk of vascular calcification in patients with a moderate or high risk of coronary heart disease, even with normal renal function [4]. Age, race, diabetic history, and log 1,25-D have been related to arterial mass of coronary calcium and inversely correlated with calcium phosphate mass. Furthermore, a cross-sectional examination from NHANES (2001–2004) patient data demonstrated a significant graded, inverse correlation between serum 25D levels and the prevalence of peripheral arterial disease and was independent of gender, age, race, and multivariable adjustment [5].

Several studies in patients with CKD have now correlated arterial calcification with the presence of coronary artery disease [6], peripheral vascular disease [7], left ventricular hypertrophy [6] and mortality. Increased pulse pressure, left ventricular hypertrophy, and arrhythmias, resulting from arterial stiffness, have been suggested as potential effects of arterial calcification that may lead to cardiovascular disease and death.

CKD patients have a dramatically higher incidence of cardiovascular morbidity and mortality compared to the general population. Studies show that CVD mortality is 10 to 70 times greater in the dialysis population than in the general age-matched cohort [8].

In the last 10 years, several studies pointed out that vascular calcification is a major cause of cardiovascular disease in the dialysis population. In CKD patients, high levels of

plasma calcium, serum phosphate, and PTH play a critical role in the pathogenesis of cardiovascular events [9]. Nasri et al. [10] analyzed the influence of PTH on myocardial function. In their cross-sectional study in hemodialysis patients, they determined that excess PTH played a significant role in the development of LVH and reduced left ventricular ejection fraction. In a decade-long retrospective study, Dai et al. found a 52% prevalence of severe LVH among ESRD patients. Ha et al. [11] further extended the links between LVH and CKD, finding an 87% prevalence of concentric and eccentric LVH among predialysis patients. Foley et al. corroborated the results in a decade-long prospective study, finding that 80% of the 433 patients initiating dialysis presented with LVH on echocardiography. The relationship between elevated PTH and LVH was further explored in a retrospective study by Goto et al. [12] who determined that parathyroidectomy in CKD patients with advanced SHPT led to a significant improvement of left ventricular ejection, fraction, and function. Hyperphosphatemia and hypercalcemia have been shown to promote calcification of the vasculature, myocardium, and cardiac valves. Vascular calcification manifested in reduced vessel wall elasticity, increased intima-media layer thickness, and enhanced pulse-wave velocity—has been linked to LVH—and occurs with increased severity in dialysis patients versus non-CKD patients.

Patients develop extensive medial calcification, which causes increased arterial stiffness and high morbidity and mortality due to cardiovascular events [13]. A variety of risk factors are associated with vascular calcification in dialysis patients (time on dialysis, uremic toxins, history of diabetes, inflammation), but abnormal ties in bone mineral metabolism may play a critical role [14]. In fact, elevated serum phosphate, calcium-phosphate product, and PTH levels contribute to vascular calcification, although their roles are incompletely understood [15, 16].

Elevations of serum phosphate and calcium-phosphate product levels may worsen cardiovascular events in the uremic population, through a progressive increase in calcium deposition in the coronary arteries and heart valves [8]. Furthermore, calcium-containing phosphate binders can increase calcium load [17]. In haemodialysis children and young adults, Goodman et al. [18] showed a correlation between coronary artery calcification detected by electron beam computed tomography (EBCT) and years on dialysis, serum phosphorus, calcium-phosphate product levels, and daily intake of calcium. Moreover, experimental observations in uremic rats [19, 20] and in dialysis patients [21] indicate that the calcium and aluminium-free phosphate binder, Sevelamer HCl, reduced the progression of cardiovascular calcification observed in a control group treated with calcium-based phosphate binders [20].

2. The Role of Paricalcitol on CKD-MBD Prevention and Treatment

Prevention and treatment of SHPT commonly requires control of both phosphate and $1,25(OH)_2D$ levels in serum. Phosphate levels are usually controlled by reducing dietary phosphate intake, by dialysis, and by using phosphate-binders. $1,25(OH)_2D$ effectively suppresses PTH production and improves bone histology in some patients [22].

The therapeutic use of $1,25(OH)_2D$ in CKD mainly aims to raise intestinal absorption of calcium, to protect bone against osteomalacia and to control parathyroid function. However, also the function of other organs expressing VDR, as kidney, pancreas, myocardium, and testis, might be improved by vitamin D administration. $1,25(OH)_2D$ inhibitory effect on PTH synthesis and parathyroid hyperplasia is well established in CKD. Vitamin D analogues with a lower hypercalcemic and hyperphosphatemic activity, are now available as an efficient alternative to $1,25(OH)_2D$ treatment. Furthermore, normal serum levels of $25(OH)D$ are relevant for the prevention or treatment of SHPT, due to the capacity of $25(OH)D$ to support renal 1α-hydroxylase activity or the synthesis of active vitamin D metabolites different from $1,25(OH)_2D$.

Clinical targets for serum concentrations of phosphate, calcium, and PTH have been proposed in the 2003 guidelines proposed by the Kidney Dialysis Outcomes Quality Initiative (K/DOQI) Work Group [23]. Target for plasma concentrations of PTH increases according to creatinine clearance because patients develop a progressive tissue resistance to PTH explained by a diminished expression of PTH receptors and by $1,25(OH)_2D$ deficiency or resistance [24, 25]. The low target for calcium concentrations aims to avoid calcium overload and excessively high calcium x phosphate product.

A particular bone complication of the therapy with vitamin D metabolites occurs in case of excessive parathyroid suppression. As defined in the K/DOQI guidelines, the target for PTH concentration is 150–300 pg/mL in end-stage CKD. The new K/DIGO guidelines proposed a new target for serum PTH levels [26], but if the values of circulating PTH are suppressed below these limits, bone cells become quiescent and bone remodelling is far slowed [27]. The histology pattern of these functional alterations is adynamic bone disease, characterized by decreased number of bone cells, bone metabolic inactivity, and reduced bone formation rate [25]. The mechanism of adynamic bone disease is unknown. The clinical consequences of adynamic bone disease may be an increased fracture risk while its relationship with osteoporosis is still debated [28]. At the opposite, osteomalacia may develop in case of $1,25(OH)_2D$ deficiency, even though the toxic effect of aluminum overload has been the most frequent cause of osteomalacia in dialysis population till some years ago [29, 30].

Several new vitamin D analogues have been developed and investigated with the rationale to treat secondary HPT with a reduced risk of hypercalcemia and hyper-phosphatemia in CKD patients. Vitamin D analogues have variable affinity for the components of the vitamin D system, including the vitamin D-binding protein and the nuclear VDR. Some of the effects are genomic and mediated through changes in the structural configuration of the vitamin D-VDR complex or in the affinity of the vitamin D-VDR complex for the key response elements in various target genes. There are currently 3 vitamin D analogues approved for use in CKD patients with secondary HPT in the US,

1,25-dihydroxy-22-oxavitamin D_3 (22-oxacalcitriol, OCT), 1,25-dihydroxy-19-norvitamin D_2 (19-norD_2, paricalcitol), and 1α-hydroxyvitamin D_2 (1αOHD_2).

Three identical, 12-week studies determined that paricalcitol was safe and effective in suppressing serum PTH levels in 78 HD patients without significantly increasing serum calcium and phosphorus levels. The mean percentage decrease in iPTH was 60%, and calcium levels rose slightly but remained within the normal range. Changes in phosphate from baseline to study end were not significantly different between the group treated with paricalcitol and the group treated with placebo.

First, Martin et al. [31] reported the outcomes of up to 1 year of therapy with paricalcitol in 164 HD patients. Paricalcitol rapidly suppressed PTH, with the mean iPTH reaching a target of 150–300 pg/mL by month 5. Furthermore, 19-norD_2 had minimal effects on calcium and phosphate. Most (70%) of the episodes of hypercalcemia (>11.5 mg/dL) that occurred did so when iPTH was suppressed below 150 pg/mL.

Second, a 12-week study by Martin et al. [32] compared PTH suppression and calcium/phosphate outcomes when 125 HD patients were given doses of paricalcitol that were based on the patient's dry weight or on the serum level of iPTH. Both regimens were effective in reducing iPTH to the target of four consecutive weeks of 30% or greater reductions from baseline. The patients receiving the dosing regimen based on iPTH level reached this target significantly faster than those on the weight-based regimen (31 versus 45 days, $P = .0306$). No incidences of hypercalcemia occurred in either group.

Third, Llach and yudd [30] proved that 19-norD_2 is effective in suppressing PTH in 37 HD calcitriol-resistant patients. This study showed that using 3 mcg of paricalcitol for each 1 mcg of calcitriol that the patient had previously received (a 1 : 3 ratio) resulted in a decline in mean iPTH from 836 to 341 pg/mL after 2 months. Clearly the above studies establish that 19-norD_2 rapidly suppresses PTH with no significant difference in the incidence of hyperphosphatemia or hypercalcemia compared to placebo.

Paricalcitol has also been directly compared with calcitriol in an international study involving HD 263 patients. This study showed that paricalcitol reduced iPTH 50% or more from baseline and did so significantly faster than calcitriol. Patients receiving paricalcitol had significantly fewer sustained episodes of hypercalcemia and/or increased Ca × P product [33]. In addition, a historical study examined the records of 67,399 patients who had been treated exclusively with calcitriol or paricalcitol. Patients were evaluated over a 2-year period until one of the following occurred: death, a switch to another vitamin D formulation, renal transplantation, or transfer to another facility. This study showed a statistically significant difference in survival rate in favor of paricalcitol over calcitriol [34]. Furthermore, in patients taking 19-norD_2 a reduced hospitalization rate was observed [35]. These findings will need to be supported by prospective trials before definitive conclusions can be made.

The mechanism for paricalcitol's low calcemic effect is due to reduced stimulation of intestinal calcium transport
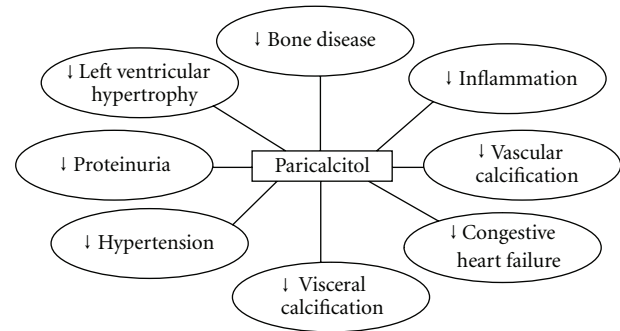

Figure 1

proteins (e.g., calbindin, CAT, and PMAT) compared to calcitriol, [36, 37] thus conferring a selective activator function [38].

With the ubiquitous presence of the VDR in many tissues, it is of little wonder that the role of the VDR is multifaceted in providing tissue-specific responses. The impact of selective VDR activators on vascular calcification is multifaceted in that in vivo and clinical outcomes show variable results depending on the clinical circumstance and dose of VDR activator administered [39]. Although VDR activation may mitigate the effects of uremia-induced arterial calcification, emerging data support a potential role for VDR activation in preventing or ameliorating the pathogenesis of atherosclerosis.

These are a number of examples of many selective VDR activator effects on cardiovascular structure and function that, if borne out in humans, have the potential to improve clinical outcomes in CKD-MBD (Figure 1).

Low or clinically relevant doses of VDR activators correlate with decreased deposition of calcium and improved therapeutic outcomes, whereas high doses may actually induce vascular calcification. In 28-week-old mice, therapeutically relevant doses of calcitriol and paricalcitol reduced aortic calcium levels and aortic gene expression of osterix, Msx2, core binding factor (alpha)1 (Cbfa1/Runx-2), and osteocalcin, markers for progression of vascular calcification; while an elevated dose of 1,25-D or paricalcitol actually stimulated vascular calcification [40]. In a study of uremic rats, doxercalciferol produced marked increases in aortic calcification and aortic mRNA and protein expression of Runx2 and osteocalcin, whereas paricalcitol had no effect on these endpoints [41].

VDR activation has been shown to have a number of potential ameliorative effects on both inhibitors and inducers of calcification. The addition of VDR activators suppresses calcification inducers type I collagen, bone sialoprotein, IL-1β, and tumor necrosis factor (TNF)-α, as well as bone morphogenetic protein (BMP)-2 [42]. In addition, calcification inhibitors matrix Gla protein (MGP), osteopontin, and osteocalcin were upregulated by VDR activator treatment [43]. The same is true for type IV collagen.

Another hypothetical mechanism of VDR activation impact on cardiovascular outcome is an inappropriate activation of the renin-angiotensin-aldosterone system (RAAS),

which plays a central role in the regulation of blood pressure, electrolyte, and volume homeostasis and may represent a major risk factor for hypertension, heart attack, and stroke. Evidence from clinical studies has demonstrated an inverse relationship between circulating vitamin D levels and the blood pressure and/or plasma renin activity [44].

3. Conclusions

The modern strategies to prevent SHPT in CKD patients give great relevance to vitamin D replacement therapy. A sound approach to treatment requires taking into account many factors, including stage of CKD, underlying renal disorder, levels of circulating PTH, bone status, vitamin D deposits, and serum calcium and phosphate levels. The aim of vitamin D replacement therapy is to prevent SHPT from the early stages of CKD, because once parathyroid hyperplasia and osteodystrophy develop, they cannot be completely reverted. Because nephrologists have largely focused their attention on dialysis patients, unfortunately few studies have analyzed the outcome of vitamin D therapy in nonuremic patients.

The therapeutic strategies for SHPT are now changing. The availability of selective VDRAs may warrant inhibition of parathyroid glands with lower effect on calcium and phosphate levels and perhaps reduces mortality of dialysis patients. Paricalcitol is a selective VDRA with minor impact on serum Ca and P levels. Paricalcitol is growly used in dialysis patients for its efficacy and safety in the treatment and prevention of SHPT in this population. Recent studies demonstrated that therapy with paricalcitol injection is associated with improved survival, fewer hospitalizations, and shorter hospital stays in HD patients compared with calcitriol, even if prospective clinical trials are ongoing. Additionally, subjects on HD who did not receive active vitamin D had higher all-cause and cardiovascular mortality compared with subjects who received any form of active vitamin D.

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