Treatment Failure of Active Vitamin D Therapy in Chronic Kidney Disease: Predictive Factors

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Abstract
Background: In patients with chronic kidney disease (CKD), impaired renal function leads to decreased vitamin D levels, which causes an increase in parathyroid hormone (PTH) production and contributes to the development of secondary hyperparathyroidism (SHPT). This may result in adverse clinical effects such as bone disorders, vascular calcification, cardiovascular disease, and increased mortality. Current treatment practices and associated outcomes with active vitamin D treatment in patients with CKD were reviewed with the objective to assess parameters (such as PTH and serum calcium levels) that may be used to define the failure of vitamin D treatment. Summary: Reports based on observational data have noted improved outcomes with active vitamin D treatment (calcitriol, paricalcitol, alfacalcidol, or doxercalciferol) in patients with CKD. Criteria for the identification of active vitamin D treatment failure are unclear from current guidelines, although up to 50% of patients may experience treatment failure eventually because of development of hypercalcemia or resistant SHPT, characterized by an elevated intact PTH (iPTH) level despite treatment. We propose a definition of vitamin D treatment failure as iPTH >600 pg/ml after 6 months of intravenous active vitamin D treatment and corrected total calcium serum levels >10.2 mg/dl, and review factors that may predict the response to vitamin D treatment. Key Message: Active vitamin D treatment failure is an important challenge in clinical practice. The aim of the proposed definition is to suggest a possible framework for hypothesis generation and to encourage further research into this common problem.

Introduction

An estimated 10% of the US population has chronic kidney disease (CKD), which occurs most often as the consequence of other chronic illness, especially hypertension and diabetes [1]. Worldwide, the prevalence is thought to be between 8 and 16% of the population, although it is challenging to determine the actual number of individuals affected [2]. CKD is progressive, with the disease classified in stages by the presence of kidney injury or impaired glomerular filtration rate (GFR; measured in ml/min/1.73 m²).

Secondary hyperparathyroidism (SHPT), manifested by increased production of parathyroid hormone (PTH)
associated with parathyroid hyperplasia, is a common and serious consequence of declining kidney function [3, 4]. An analysis from the Study for the Evaluation of Early Kidney disease (SEEK) noted that the prevalence of SHPT (intact PTH [iPTH] >65 pg/ml) begins to increase during stage 3 kidney disease, when the GFR falls below 45 ml/min/1.73 m², and increases across the spectrum of GFR reduction to include almost all patients with GFR <20 ml/min/1.73 m² (fig. 1) [5].

SHPT results from a complex, multifactorial series of disturbances in mineral and bone metabolism, systems which normally exist in a finely tuned equilibrium [6]. The clinical implications of this disrupted balance may include renal osteodystrophy (bone loss, fragility fracture, bone deformity), vascular calcification [7, 8], cardiovascular disease [9], and increased mortality [4, 10].

A low level of vitamin D is among the key factors that may contribute to the development of SHPT, and vitamin D replacement is an important aspect of the treatment and prevention of SHPT [4]. The objective of this review is to describe the role of vitamin D replacement therapy in patients with advanced CKD, with a focus on identifying those patients most likely to experience active vitamin D treatment failure. We also propose a definition of vitamin D treatment failure as iPTH >600 pg/ml after 6 months of intravenous (IV) active vitamin D treatment and corrected total calcium serum levels >10.2 mg/dl.

Pathophysiology of SHPT

Under conditions of homeostasis, one of the key roles of the active form of vitamin D, 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃), is suppression of serum levels of PTH and parathyroid hyperplasia via parathyroid vitamin D receptors [4, 10]. With declining kidney function, 1,25(OH)₂D₃ levels decrease because of the reduced availability of 1α-hydroxylase, an enzyme found mainly in the kidney, which is required for the final step in the synthesis of active vitamin D from exogenous sources [11]. Levels of vitamin D decline early in CKD, suggesting that this event is important for the development of SHPT. In SEEK, 1,25(OH)₂D₃ levels were correlated with GFR and were deficient (defined in the study as <22 pg/ml) when GFR was approximately 45 ml/min/1.73 m²; this is the same level at which the prevalence of SHPT was observed to increase [5]. Another role of 1,25(OH)₂D₃ that is relevant to the development of SHPT is its stimulation of calcium absorption in the intestine. When the level of 1,25(OH)₂D₃ is low, intestinal absorption of calcium decreases, contributing to a hypocalcemic state [12].

A progressive decline in kidney function also results in high plasma levels of phosphorus. Hyperphosphatemia promotes PTH production directly, and together with decreased 1,25(OH)₂D₃–mediated calcium absorption, result in hypocalcemia. Hypocalcemia, in turn, also stimulates PTH production and secretion (fig. 2) [13]. Fibroblast growth factor 23 (FGF23), a peptide produced by osteocytes, further contributes to the pathophysiology of SHPT. FGF23 levels have been shown to increase as renal
function deteriorates. It is theorized that the rise in FGF23 levels reflects a homeostatic response to reduced phosphate excretion, which occurs as renal mass declines. FGF23 inhibits 1α-hydroxylase, thereby suppressing 1,25(OH)2D3. In addition, PTH itself appears to further stimulate FGF23 production [14, 15]. Ultimately, in the setting of declining GFR, a cascade of adaptive changes within a tightly regulated system leads to highly disordered mineral metabolism, with salient features including decreased 1,25(OH)2D3 levels, hyperphosphatemia, hypocalcemia, and increased FGF23 and SHPT, with associated bone disease, vascular calcification, cardiovascular disease, and increased morbidity and mortality.

It should be noted that knowledge of this complex, multifactorial process is still evolving. Decreased expression of vitamin D and calcium-sensing receptors, as well as FGFR-Klotho have also been associated with parathyroid hyperplasia [16–19], and it is likely that other mediators (e.g. sclerostin [20, 21]) also play a role in the deterioration of bone and vascular health in patients with CKD. However, a full discussion of these factors is beyond the scope of this review.

Vitamin D Replacement Therapy in CKD

Correction of low levels of vitamin D (deficiency or insufficiency, defined as 25-hydroxy-vitamin D levels <30 and <15 ng/ml, respectively) with vitamin D replacement therapy is one of the cornerstones of treatment for patients with CKD. Guidelines suggest that patients who have PTH levels that are rising persistently and are consistently above the upper limit of normal may receive treatment with active vitamin D or analogs (calcitriol, paricalcitol, alfalcacidol, or doxercalciferol) as part of an effort to prevent or slow the progression of SHPT [10]. Unfortunately, there are limited reports of well-designed, randomized, controlled studies of these agents, or for comparisons of the efficacy of active vitamin D or analogs, conducted in patients with CKD [10]. In one recently published (2014) trial in patients with CKD who were not undergoing dialysis, calcifediol for 6 weeks has been shown to significantly increase serum 25-hydroxyvitamin D and decrease plasma iPTH (≥30% in >60% patients treated with 60 or 90 μg/day) levels compared with placebo [22]. In pre-dialysis patients with CKD stage 3 or 4, treatment with cholecalciferol for 12 weeks has been shown to significantly increase serum vitamin D compared with placebo; however, effects on plasma PTH levels were not statistically significant (−31 vs. −7% for placebo) [23]. In a single-blinded (to investigators), randomized 3-month trial of high-dose cholecalciferol vs. doxercalciferol, vitamin D levels were significantly increased from baseline in the cholecalciferol group, but not in the doxercalciferol group; the between-group difference was also significant [24]. The differences between the treatment groups for changes in iPTH levels were not significant, although in the doxercalciferol group, the decrease from baseline was significant (−27%; p = 0.002). A prospective nonrandomized, observational study of ergocalciferol in patients with stage 3 or 4 CKD (mean duration, approximately 7 months) found that PTH level reductions were associated with kidney function, with significant decreases in PTH levels noted in patients with stage 3 CKD (−13.1%, p = 0.041), but no statistically significant effects on PTH levels were found in patients with stage 4 CKD [25]. It should be noted that in many of these studies, outcomes are typically characterized by changes in biochemical measures (e.g. PTH, calcium, phosphorus, and markers of bone turnover) [26, 27], rather than those that may be most relevant to patients, such as quality of life, fracture incidence, cardiovascular events, or death [10].

Relationships between Active Vitamin D Treatment and Mortality

Evidence for the effects of active vitamin D treatment on hard clinical outcomes, such as mortality, has generally come from observational studies. Although such data provide associational support rather than definitive evidence, they suggest that active vitamin D treatment may improve survival in patients with CKD. Several retrospective studies have evaluated active vitamin D therapy in patients with stage 5 CKD undergoing hemodialysis (HD) and identified an association between decreased mortality in patients who received vitamin D therapy compared with those who did not [28, 29]. Other retrospective studies of patients with stages 3 to 5 CKD not yet on dialysis identified lower risks for mortality and for initiation of dialysis in patients treated with calcitriol, compared with untreated patients, suggesting the apparent benefit of active vitamin D treatment in this patient population as well [30, 31]. Prospective, controlled studies are needed to confirm the apparent benefits of calcitriol treatment observed in these retrospective analyses.

A recent meta-analysis evaluating the effect of active vitamin D treatment found a significantly lower (27%) all-cause mortality risk, and that the reduction in risk ap-
peared to be greater with longer follow-up. A reduction of 37% was observed in the relative risk of cardiovascular mortality. Further, a survival advantage was demonstrated in patients in the early stages of CKD, as well as in patients with CKD undergoing HD [32].

Prospective observational data from the Italian FARO survey [9] suggested that patients who received treatment for SHPT (calcitriol, paricalcitol, or cinacalcet with/without active vitamin D treatment) had reduced overall and cardiovascular-related risk of mortality versus untreated patients (p < 0.001). Interestingly, a more recent analysis of the FARO study showed that active vitamin D treatment was associated with decreased all-cause mortality, even among patients with low iPTH levels (≤150 pg/ml; p < 0.01), who do not typically receive active vitamin D therapy in an attempt to avoid adynamic bone disease [33]. Again, controlled studies are necessary to determine if patients with low iPTH levels might indeed gain benefit from active vitamin D treatment.

Guidelines for Treatment of Patients with Abnormal PTH Levels

Two principal guidelines have been published on the prevention and management of disturbances in mineral and bone metabolism in patients with CKD. The first, published in 2003, was from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) [4]. These guidelines provide a US perspective and are based on expert evaluation of clinical evidence from a range of study types, including randomized, matched controlled, prospective, retrospective, and uncontrolled cross-sectional studies [4]. The second set of guidelines was developed by KDIGO (Kidney Disease: Improving Global Outcomes) in 2009. These guidelines provide a global perspective and were based only on randomized, controlled studies of at least 6 months' duration and with sample sizes of 50 or more patients [10]. The KDIGO guidelines have subsequently been endorsed by European Renal Best Practice and form the basis of care in countries across the globe [34, 35].

A commentary from a KDOQI working group on the KDIGO guidelines puts them in the context of US-delivered care and summarizes important differences between the 2 guidelines. Notably, the KDOQI expert group suggests that the KDIGO guidance, because it is based on more recent evidence, should supplant the 2003 KDOQI guidelines [36]. However, because the KDIGO guidelines included only randomized studies, definitive recommendations could not be made for widely and currently used treatment. Therefore, the KDOQI guidelines advocate flexibility in developing treatment goals and for weighing the benefits and risks of the approaches used in individual patients. Guidelines pertinent to the treatment of patients with SHPT, with relevant commentary from the KDOQI working group, are included in table 1 [4, 10].

Active Vitamin D Treatment Failure: Definition

Active vitamin D treatment is not effective in all patients. A primary cause of treatment discontinuation is hypercalcemia, which is observed in approximately 20 to 30% of patients whether they have end-stage renal disease and are undergoing HD [37], or have CKD and are not undergoing HD [38]. Concern for hypercalcemia is greater with 2 standard treatments for SHPT, calcitriol and alfalcacidol, which are non-selective activators of VDRs in other calcium-regulating organs, such as intestine and bone [39, 40]. Preclinical studies provided robust evi-

<table>
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<tr>
<th>Table 1. Recommendations for SHPT testing and treatment targets in KDOQI [4] and KDIGO [10] guidelines</th>
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<tr>
<td>KDOQI</td>
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<tr>
<td>PTH target ranges, pg/ml</td>
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<tr>
<td>CKD stage 3, 35–70</td>
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<td>CKD stage 4, 70–110</td>
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<td>CKD stage 5, 150–300</td>
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<tr>
<td>CKD stages 3–5: in patients not undergoing dialysis with PTH levels above the URL, evaluate for hyperphosphatemia, hypocalcemia, and vitamin D deficiency</td>
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<tr>
<td>In CKD stage 5D, consider maintenance of PTH levels within ~2–9 × the URL of the assay</td>
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<td>Marked PTH changes within this range require treatment initiation or modification</td>
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<td><strong>5D</strong> = Stage 5 on dialysis; <strong>URL</strong> = upper reference limit.</td>
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Recognizing and Defining Vitamin D Failure
ence that these 2 agents have greater potential than other similar agents to induce hypercalcemia [39, 40]; however, evidence for this effect has been difficult to determine in humans. A randomized study in patients with SHPT who were undergoing HD found that alfalcaldol and paricalcitol were equally effective in lowering PTH levels, and no differences between the agents were observed with regard to hypercalcemia [41]. A recent randomized trial in patients with stages 3 to 4 CKD found that the incidence of hypercalcemia was low and was similar with calcitriol and paricalcitol. Both agents were effective in lowering PTH levels, although a higher percentage of patients achieved PTH reduction ≥40% or PTH suppression >60%, as calculated versus baseline, when treated with paricalcitol as compared with calcitriol. A 40% reduction from baseline in PTH was also achieved more rapidly in patients who received paricalcitol than in those who received calcitriol [42]. Another prospective randomized trial, conducted in a small population of patients undergoing continuous ambulatory peritoneal dialysis (n = 26), found that the incidence of hypercalcemia was similar with paricalcitol (33%) or calcitriol (29%) treatment; likewise, suppression of iPTH by ≥50% from baseline was achieved by similar percentages of patients in each treatment group [43]. Whether one agent is superior to another remains to be determined in large controlled studies. A second cause of treatment failure (observed in approximately 20 to 30% of patients) is treatment resistance, whereby active vitamin D treatment becomes less effective over time in inhibiting parathyroid cell proliferation and PTH production, despite increasing doses [44]. Altogether, it may be expected that active vitamin D treatment will fail in 40 to 50% of patients.

Although hypercalcemia and resistant or refractory SHPT are recognized issues [4], they are not defined in published guidelines as a single concept that could serve to generate a hypothesis for clinical research and, eventually, to guide clinical practice. The KDOQI guidelines define hypercalcemia as serum levels of corrected total calcium >10.2 mg/dl [4]. In the literature, hypercalcemia has been variously defined, ranging from serum calcium levels >10 to >11.5 mg/dl [10]. In the context of active vitamin D treatment, the KDOQI guidelines suggest that treatment should be withheld when serum levels of corrected total calcium are >10.2 mg/dl [4].

Similarly, various definitions of treatment resistance have been used, primarily in studies examining the efficacy of IV paricalcitol in patients with SHPT resistant to IV calcitriol. Llach and Yudd [45], for instance, defined treatment resistance as iPTH values >600 pg/ml despite 6 months of treatment with IV calcitriol. Tonbul et al. [46] described treatment resistance as elevated serum iPTH (>300 pg/ml) despite treatment with calcitriol at a dosage of up to 9 μg/week for 6 months. In a study by Vulpio et al. [47], this phenomenon was defined as iPTH >300 pg/ml after patients received IV calcitriol therapy for at least 6 months. Kazama et al. [48] defined it as iPTH 300 pg/ml despite treatment with doses of up to 4.5 μg of IV calcitriol per week for 24 weeks, whereas Capuano et al. [49] described treatment resistance as patients with iPTH >300 pg/ml who had received pulse IV calcitriol for at least 1 year.

On the basis of the varying definitions, and to advance the recognition of this important clinical problem, we propose a unifying definition for active vitamin D treatment failure in patients with stage 5 CKD on dialysis that encompasses the concepts of hypercalcemia and resistance: iPTH >600 pg/ml after 6 months of active IV vitamin D treatment (e.g. calcitriol) and serum calcium levels >10.2 mg/dl. Selection of these cut-off values for iPTH and calcium is based on expert opinion and should be confirmed by studies. Strong data are lacking that a lower iPTH cut-off value (i.e. >300 pg/ml) would be preferred, particularly because of the known high incidence of adynamic bone disease in patients undergoing HD, even when iPTH values are approximately 400 pg/ml or greater. Further, there have been no trials supporting a cut-off value for serum calcium levels >9.5 mg/dl, and the upper limit of the normal range for serum calcium is 10.2 mg/dl [4]. The values in the proposed definition of active vitamin D failure are meant to only to generate a hypothesis, and the definition can be refined as clinical data become available.

**Vitamin D Treatment Failure: Associated Features**

Several clinical features may be associated with vitamin D treatment failure. Identification of these characteristics in conjunction with individual laboratory parameters for serum calcium, phosphorus, and PTH may help predict poor patient response to active vitamin D treatment. In a 12-month prospective, open-label study, the number and size of the parathyroid glands of patients with a subclinical response to calcitriol were assessed before patients were switched to paricalcitol treatment [47]. A higher rate of treatment response (defined as iPTH <300 pg/ml) was observed at 6 (23.5%) and 12 months (41.2%) in patients with a smaller gland size (maximum...
longitudinal diameter [MLD] ≤9 mm) compared with responses at 6 and 12 months (7% at both time points) in patients with larger gland sizes (MLD >9 mm) [47]. This study suggests that a larger parathyroid gland size may predict a poor response to active vitamin D treatment. Another study has indicated that pre-treatment PTH levels were predictive of outcomes of calcitriol therapy; patients with lower baseline PTH values were more likely to achieve a response than patients with higher baseline PTH values [50].

Another potential predictor of response to vitamin D treatment is FGF23 serum level. Elevated levels of FGF23 are detected in patients with SHPT, and FGF23 is part of a feedback loop that involves the upregulation of FGF23 and resultant downregulation of 1α-hydroxylase, which results in reduced vitamin D production [12]. Kazama et al. [48] conducted a study in which patients with iPTH levels >300 pg/ml despite treatment with IV calcitriol underwent a 4-week washout period and subsequent re-treatment with calcitriol for 24 weeks (n = 66). The overall rate of treatment success (defined as iPTH <300 pg/ml) was 41.9%. Patients with low iPTH (≤591 pg/ml) and FGF23 (≤9,860 ng/l) levels at the re-initiation of calcitriol had a treatment success rate of 88.2%. In contrast, only 4.2% of patients with high iPTH (>591 pg/ml) and FGF23 (≤9,860 ng/l) levels after re-initiation of calcitriol treatment (11 of 12 patients achieved iPTH levels <300 pg/ml within 1 month of treatment initiation); calcium levels were slightly but significantly higher; phosphorus values were slightly but significantly lower; and calcium × phosphorus product did not change. In a study of 37 patients with iPTH levels ≥600 pg/ml despite treatment with calcitriol, a mean (SD) decrease in iPTH levels from 901 (58) pg/ml at baseline to 165 (24) pg/ml after 16 months of treatment with paricalcitol was noted. Serum calcium and phosphorus levels did not change during the study [45]. A retrospective analysis in 73 HD patients evaluated the effects of switching from ≥6 months of treatment with calcitriol to 6 months of treatment with paricalcitol. At 6 months, iPTH levels were significantly lower (p = 0.03), as were calcium levels (p = 0.05) and the calcium × phosphorus product (p = 0.01) [51]. Vulpio et al. [47] conducted a switch study (described earlier) in 30 HD patients with iPTH levels >300 pg/ml, calcium levels from 8.0 to 10.5 mg/dl, and calcium × phosphorus product <70 mg²/dl² (5.6 mmol²/l²) after ≥6 months of treatment with calcitriol. Patients were divided into 2 groups, depending on the MLD of the largest parathyroid gland (≤9 vs. >9 mm). In patients with an MLD of ≤9 mm, a significantly higher percentage achieved iPTH levels <300 pg/ml after 6 and 12 months of treatment with paricalcitol than with treatment with calcitriol (p = 0.09). iPTH levels did not decrease significantly in patients with an MLD of >9 mm.

These ‘switch’ studies provide preliminary evidence that paricalcitol may be a viable option for active vitamin D failure; however, they do not imply that paricalcitol is superior to calcitriol. Indeed, these results may reflect the fact that some patients may respond better to 1 active vitamin D treatment than another, even though they belong to the same class of agents. It is important to assess the various agents available before confirming that active vitamin D treatment has failed in a patient. Furthermore, confirmation is needed because of the inherent variability in test results, as was observed when 41.9% of patients achieved success (i.e. iPTH <300 pg/ml) with calcitriol re-treatment after an earlier failure of the same therapy [48].

KDIGO guidelines recommend the use of calcimimetics alone or in combination with vitamin D treatment for patients with CKD stage 5 and elevated PTH [10]. Large clinical trials have demonstrated that in dialysis patients with SHPT, calcimimetics alone or in combination with vitamin D treatment substantially lowered levels of PTH, calcium, and phosphorus [52–54]. One randomized controlled trial to date has examined the use of calcimi-
Evaluation is needed to use of calcimimetics is currently not recommended for phosphorous increased ≥ 20% during the study. Therefore, the use of calcimimetics is currently not recommended for nondialysis patients with CKD stages 3–5, and further evaluation is needed.

Conclusions

SHPT in patients with severely compromised renal function is associated with profound negative consequences that may be alleviated with active vitamin D treatment. However, active vitamin D treatment is unsuccessful in some patients due to intolerance (hypercalcemia) or resistance (high PTH levels despite continued treatment). Here, we have provided a construct that incorporates the issues of treatment intolerance and resistance into one definition, that is, the construct of active vitamin D treatment failure (iPTH >600 pg/ml after 6 months of IV active vitamin D treatment and corrected total calcium serum levels >10.2 mg/dl). We hope that this proposed definition will encourage further research and provide a useful framework for recognizing and addressing this important problem in clinical practice.

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