Review Article

Bioactive Vitamin D Therapy to Treat Secondary Hyperparathyroidism in Pre-Dialysis Chronic Kidney Disease: A Systematic Review - 🔓

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ABSTRACT

Background: Chronic kidney disease affects one in five adults ≥65 years old, over half of whom develop secondary hyperparathyroidism. In observational studies, secondary hyperparathyroidism is associated with low bone mineral density and excess vascular calcification, presumably leading to surplus fractures, more cardiovascular events and shortened lifespan. Several bioactive vitamin D analogs are FDA approved to treat secondary hyperparathyroidism and published algorithms direct their clinical use. However, whether such therapy improves patient outcomes is uncertain. The purpose of this review is to summarize evidence derived from clinical trials describing the benefits of treating secondary hyperparathyroidism in patients with pre-dialysis chronic kidney disease.

Methods: We performed a systematic review of the literature to identify trials using bioactive vitamin D (calcitriol, alfacalcidol, paricalcitol and doxercalciferol) to treat secondary hyperparathyroidism in chronic kidney disease patients. We focused on changes in bone mineral density, fractures, falls, vascular events and lifespan, resulting from treatment of secondary hyperparathyroidism.

Results: We found weak evidence that treating secondary hyperparathyroidism improved bone mineral density, based on two studies recruiting only 62 subjects. However, neither trial required baseline secondary hyperparathyroidism or followed published treatment algorithms. We found no randomized, placebo-controlled trials that tested the effect of treating secondary hyperparathyroidism on the risk of fractures, falls, vascular events or death.

Conclusions: Randomized, double-blind, placebo-controlled trials are needed to evaluate the potential harms and benefits of treating secondary hyperparathyroidism in pre-dialysis chronic kidney disease patients.

Keywords: Bone mineral density; Chronic kidney disease; Falls; Secondary hyperparathyroidism; Survival, Vitamin D

ABBREVIATIONS

CKD: Chronic Kidney Disease; SHPT: Secondary Hyperparathyroidism; BMD: Bone Mineral Density; FDA: Food and Drug Administration

INTRODUCTION

Chronic Kidney Disease (CKD) affects approximately 13% of adults, including roughly 1 in 5 adults over 65 years old [1]. Secondary Hyperparathyroidism (SHPT) occurs in over half of patients with stage 3 and 4 CKD [2,3] and is a risk factor for both cardiovascular events [4,5] and decreased bone mineral density (BMD) [6]. These observations suggest that treating SHPT would increase BMD and reduce vascular events.

Medicare spends an estimated 20% of its budget on care related to CKD [7], largely due to acute kidney injury, renal replacement therapy and co-morbid conditions including cardiovascular events [4,8] and fractures [9-12]. If treatment of SHPT improved musculoskeletal or vascular health, such therapy could reduce health care costs for CKD patients. Several bioactive vitamin D compounds are FDA approved to treat SHPT [13]. In 2003, the National Kidney Foundation published the Kidney Disease Outcome Quality Initiative (K/DOQI) SHPT treatment algorithms [14] which outlined specific PTH targets to achieve with vitamin D therapy, based on the degree of CKD. However, in 2017 the National Kidney Foundation recommended against routine use of vitamin D analogs to treat SHPT in CKD patients [15,16]. Instead, the 2017 guidelines suggest treatment only for patients with severe and progressive SHPT [15,16].

Since SHPT commonly affects older adults, including those with osteoporosis, we sought evidence that its treatment would improve musculoskeletal and vascular health. We performed a systematic review to summarize clinical trials data evaluating the clinical outcomes of treating SHPT in patients with pre-dialysis CKD.

Pathophysiology of secondary hyperparathyroidism

Vitamin D_3 is produced in the skin when 7-dehydrocholesterol interacts with ultraviolet radiation [6], and is then hydroxylated in the liver to $25(OH)D_3$. Within the kidneys, 1-α-hydroxylase converts $25(OH)D_3$ to $1,25(OH)_2D_3$, which promotes intestinal absorption of ingested calcium and phosphorus. Impaired renal function with reduced phosphorus excretion allows serum phosphorus to rise, triggering release of FGF-23. FGF-23 promotes renal phosphorus excretion, inhibits 1-α-hydroxylase and promotes 24,25 hydroxylase enzyme activity which together reduces $1,25(OH)_2D_3$ production. $1,25(OH)_2D_3$ levels also decline due to reduced renal mass and subsequently lower renal $1,25(OH)_2D_3$ synthesis. Over time, $1,25(OH)_2D_3$ deficiency reduces calcium absorption, leading to hypocalcemia. In response to hypocalcemia, calcium receptors in the parathyroid glands trigger increased secretion of Parathyroid Hormone (PTH) [17], upregulating osteoclastic bone resorption to liberate skeletal calcium and maintain normocalcemia. PTH also up-regulates renal expression of 1-α-hydroxylase to promote increased $1,25(OH)_2D_3$ synthesis. Eventually, skeletal resistance to PTH occurs [18], leading to further increases in PTH in attempts to maintain bone turnover and thereby sustain normocalcemia. Thus, at the potential cost of skeletal mineral, SHPT helps CKD patients maintain normocalcemia. The pathophysiology of SHPT, reviewed in greater detail elsewhere [19], suggests that its treatment would improve skeletal health.

METHODS

We searched PubMed and CINAHL Plus between January 1, 1974 and June 8, 2017 to identify randomized, placebo-controlled trials in which calcitriol, paricalcitol, alfacalcidol or doxercalciferol was used to treat SHPT in adults with CKD and any of the following clinical outcomes was measured: bone mineral density, fractures, falls, vascular events or lifespan. Key search terms were: calcitriol, paricalcitol, alfacalcidol, doxercalciferol, chronic kidney disease, secondary hyperparathyroidism, vitamin D and clinical trial. We excluded reviews and trials in children, dialysis and renal transplant patients. Studies in any language were considered. We also used references listed in review articles to supplement our own literature search.

Our literature search results are summarized in figure 1. We identified 102 potentially relevant articles including 82 articles in PubMed, 7 articles in CINAHL Plus and 13 articles through reference lists. We reviewed all titles and abstracts to determine whether each study qualified for inclusion. After applying all inclusion and exclusion criteria, we identified 16 publications for inclusion in the review.
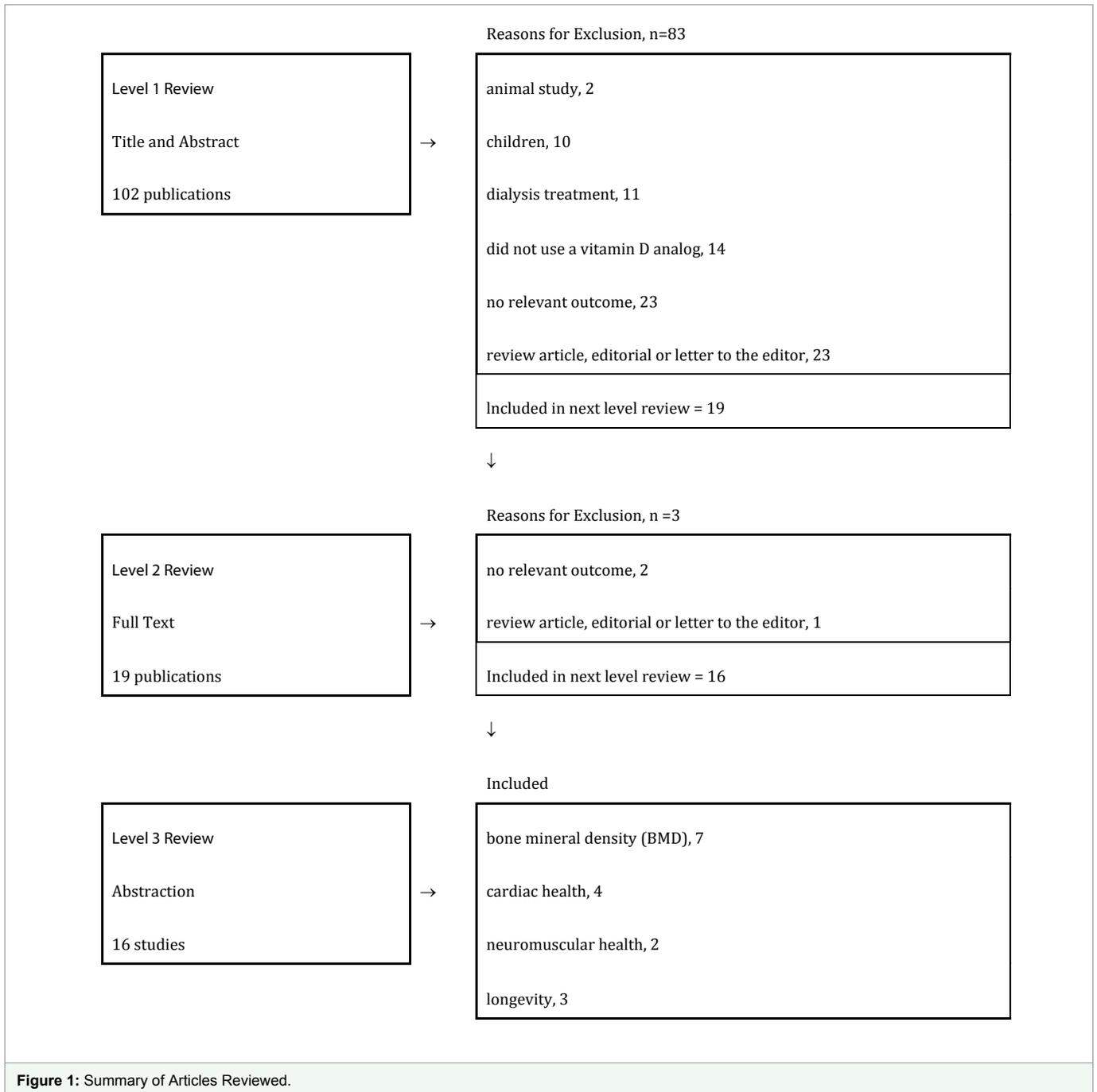
Level 1 Review Title and Abstract 102 publications	→	Reasons for Exclusion, n=83 animal study, 2 children, 10 dialysis treatment, 11 did not use a vitamin D analog, 14 no relevant outcome, 23 review article, editorial or letter to the editor, 23
		Included in next level review = 19

↓

Level 2 Review Full Text 19 publications	→	Reasons for Exclusion, n =3 no relevant outcome, 2 review article, editorial or letter to the editor, 1
		Included in next level review = 16

↓

Level 3 Review Abstraction 16 studies	→	Included bone mineral density (BMD), 7 cardiac health, 4 neuromuscular health, 2 longevity, 3

Figure 1: Summary of Articles Reviewed.

RESULTS

Evidence that treating SHPT improves skeletal health

Low BMD is associated with increased fractures in pre-dialysis CKD patients [11, 20-24]. As a result, BMD tests can be used clinically to assess fracture risk in these patients. Indeed, in a meta-analysis [25] of 384 pre-dialysis CKD patients from three cross-sectional studies, 129 subjects experienced fractures, and their femoral neck BMD was 0.11 gm/cm² lower than those who did not fracture (95% CI: -0.15 to -0.07, $p < 0.001$, $I^2 = 30\%$).

In a Tufts evidence review performed for the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, 14 of 20 observational studies in 2,371 subjects with CKD found an inverse correlation between PTH and BMD [19], while the remaining studies found no relationship. However, only 2 studies recruited patients with pre-dialysis CKD. We found two additional studies; all four are summarized below and in table 1.

Using peripheral quantitative computed tomography, Tsuchida, et al. [26] found no correlation between cortical, trabecular and total ultra-distal radius BMD in 85 pre-dialysis CKD patients (Table 2). In a subset of 53 subjects returning one year later [27], the annual change in cortical, trabecular and total ultra-distal radius BMD was likewise not associated with PTH. In a cross-sectional study [28] of 113 patients with pre-dialysis CKD, subjects were divided into three groups: PTH< 60 pg/mL (normal range), PTH 60-120 pg/mL and PTH >120 pg/mL. Subjects with PTH ≥ 60 pg/mL had significantly lower spine and femoral neck, but not forearm, Z-scores than those with PTH <60 pg/mL ($p < 0.05$); a correlation coefficient was not

Table 1: Studies of the Relationship between Bone Mineral Density (BMD) and Parathyroid Hormone (PTH) Levels in Pre-Dialysis Chronic Kidney Disease.

Author, Year and Study Design	Number of Subjects	Inclusion Criteria	Exclusion Criteria	Pre-specified Outcomes	Relationship between PTH and BMD
Bianchi, 1992, Cross-sectional	69 subjects and 69 controls matched for age, sex and menopausal status	Chronic kidney disease	Controls took no bone active medication and had no prior fragility fractures or metabolic bone diseases	Relationship between spine and 33% radius BMD and a) renal function, b) gender and c) menopause	PTH inversely associated with 33% radius BMD (r = -0.7, p < 0.01) but not associated with spine BMD.
Rix, 1999, Cross-sectional	113 subjects and 89 healthy controls	Creatinine >1.5 mg/dL	Dialysis, renal transplant, acute renal failure, use of glucocorticoid, immunosuppressant, estrogen, vitamin D, lithium, anticoagulant	Relationship between BMD, bone turnover and calcitropic hormone levels in subjects with and without chronic kidney disease	CKD patients had lower BMD than healthy controls. CKD patients with PTH >2 times upper normal limit had lower spine, hip and total body BMD, but not lower radius BMD when compared to CKD patients with normal PTH.
Tsuchida, 2005, Cross-sectional	85 subjects	Creatinine >1.5 mg/dL	Creatinine >1.5 mg/dL Use of glucocorticoid, estrogen, thyroid hormone or vitamin D	Relationship between ultradistal radius BMD by pQCT, bone turnover markers and calcitropic hormone levels	No correlation between PTH and cortical, trabecular or total ultradistal radius BMD in all 85 subjects. No correlation between PTH and 1-year change in radius BMD in subset of 53 patients.
Stavroulopoulos, 2008, Cross-sectional	89 subjects	18-65 years old, Stage 3-4 chronic kidney disease	Parathyroidectomy, use of medication affecting 25(OH)D, PTH or BMD	Relationship between hip and total radius BMD and calcitropic hormone levels	Log PTH inversely associated with log total hip BMD (r= -0.3, p = 0.003) but not radius BMD. In a multiple linear regression model , body mass index and log PTH (r= -0.3, p < 0.001) independently predicted log hip BMD.

reported. In a cross-sectional study of 89 patients with stage 3-4 CKD, log PTH was inversely associated with log total hip BMD (r = -0.313, p = 0.003) [3]. In 69 patients with pre-dialysis CKD, PTH was inversely correlated with 33% radius (r = -0.701, p < 0.01) but not spine BMD [29].

In summary, three of four studies in 356 patients found that hyperparathyroidism was associated with lower BMD. However, the studies did not find a preferential effect of SHPT on cortical bone. Additionally, the single prospective study [27] detected no relationship between SHPT and changes in radius BMD.

Observational data describe an inverse relationship between PTH and BMD in CKD patients, suggesting that treatment of SHPT with bioactive vitamin D might increase BMD and reduce fractures. Unfortunately, few clinical trials have tested this hypothesis. Przedlacki, et al. [30] randomized 26 subjects to one year of daily placebo. GFR was 31 (SEM, 4) mL/minute in the placebo and 22 (SEM, 3) mL/minute in the calcitriol arms, respectively. While SHPT was not an inclusion criterion, baseline PTH levels were 150 (SEM, 26) ng/L and 123 (SEM, 26) ng/L in the calcitriol and placebo arms, respectively (Table 2). Femoral neck and spine BMD increased by 3.4% and 3.9% in the calcitriol arm, but decreased by 2.2% and 0.6% in the placebo arm (p <0.01, all between-arm comparisons). In a second study, Rix, et al. [31] randomized 36 subjects with GFR between 10 to 60 mL/min to placebo or alfacalcidol for 18 months. Again, SHPT was not an inclusion criterion, but PTH levels were 183 pg/mL and 121 pg/mL in alfacalcidol and placebo arms, respectively (Table 2). Subjects randomized to alfacalcidol experienced a 4.2% gain in spine and 3.0% gain in total hip BMD, relative to placebo-treated subjects (p < 0.05, all between-arm comparisons). While both studies suggest that treating SPHT increases BMD, neither study required SHPT for study inclusion nor followed the K/DOQI treatment algorithms.

We found only one randomized trial mentioning fracture as a function of calcitriol vs. placebo therapy in pre-dialysis CKD patients [32]. However, only 7 of the 17 subjects had SHPT. During the one-year trial, one participant per arm sustained a fracture, as reported to authors of a subsequent meta-analysis [6].

A 2009 Cochrane meta-analysis [6] summarizing the efficacy of bioactive vitamin D compounds in pre-dialysis CKD criticized all three studies, citing uncertain blinding procedures, unclear randomization methods and lack of intent-to-treat analysis. Using data from 7 studies in 612 participants, the meta-analysis also concluded that bioactive vitamin D therapy for SHPT was associated with increased risk of hypercalcemia (RR 3.04, 95% CI 1.17 to 7.90; I^2=0%).

In conclusion, three of four observational studies in 356 patients suggest that PTH is inversely correlated with BMD in CKD patients. Additionally, BMD predicts fracture risk in pre-dialysis CKD. However, we found limited clinical trials data confirming that treatment of SHPT with bioactive vitamin D increases BMD, and no evidence that treatment reduces fractures.

Evidence that treating SHPT improves cardiovascular health

Cardiovascular events are the primary cause of death in patients with CKD [33]. Vascular calcification and Left Ventricular Hypertrophy (LVH) are more prevalent among patients with CKD, and both conditions are independent risk factors for cardiovascular disease [34-36]. Additionally, hyperparathyroidism [4] and hypovitaminosis D [37] are independent predictors of vascular calcification. Therefore, treating SPHT might reduce vascular calcification, subsequently lowering rates of cardiovascular events and prolonging life. On the other hand, hypercalcemia or hyperphosphatemia resulting from bioactive vitamin D therapy might promote vascular calcification, thereby increasing the risk of vascular events and shortening life span.

To date, there are no randomized, placebo-controlled trials evaluating whether treatment of SHPT reduces cardiovascular events in pre-dialysis CKD patients. However, we found four studies evaluating the efficacy of vitamin D therapy on cardiac function. Singh, et al. [38] randomized 30 pre-dialysis CKD patients with GFR <30 mL/min and PTH >180pg/mL to daily calcitriol 0.5µg or placebo for 12 weeks (Table 2). Calcitriol users experienced decreased early atrial filling velocities (0.696 ± 0.089 m/s to 0.680 ± 0.084 m/s, p <

0.001), in contrast to the placebo group. There were no significant between-arm changes in left ventricular dimensions or left ventricular ejection fraction. No cardiovascular events were reported.

In another trial, Ivarsen, et al. [39] randomized 13 patients with stage 4 CKD, SHPT (PTH > 3 times upper limit of normal) and LVH to alfacalcidol 0.5μg or placebo daily for 6 months (Table 2). Fractional shortening (a two-dimensional estimate of left ventricular function) increased by 20% in the alfacalcidol group, but remained stable among placebo users ($p < 0.05$). Investigators found no between-arm changes in left ventricular mass, blood pressure, 25(OH)D or phosphate levels.

In a third study called Paricalcitol Capsule Benefits in Renal Failure-Induced Cardiac Morbidity or "PRIMO" [40], 227 patients with stage 3-5 CKD, PTH 50-300 pg/mL and LVH were randomized to 48 weeks of placebo or paricalcitol 2 μg/d (Tables 2,3). Paricalcitol normalized PTH within one month yet had no effect on the primary outcome of left ventricular mass index, nor measures of diastolic dysfunction. Hypercalcemia occurred in almost one in four individuals randomized to paricalcitrol, but in only 1% of individuals in the placebo arm ($p < 0.001$, Table 3) indicating potential excess

harm of paricalcitol. Interestingly, fewer in the paricalcitol arm experienced cardiovascular events subjects (1 versus 7 subjects, $p = 0.03$).

A final study evaluated the efficacy of oral paricalcitol on retarding cardiac hypertrophy, reducing inflammation and atherosclerosis in patients with stage 3-5 CKD. The "OPERA" study [41] randomized 60 patients with stage 3-5 CKD, PTH ≥55 pg/mL and LVH to paricalcitol 1 μg/d or placebo for one year (Tables 2, 3). Although paricalcitol reduced PTH by a median of 86 pg/mL, researchers detected no between arm differences in the primary outcome of left ventricular mass index. Even though the dose of paricalcitol was lower in OPERA than in the PRIMO trial, hypercalcemia affected almost half of subjects randomized to paricalcitol but only 3% of subjects assigned to placebo ($p < 0.001$). Fewer paricalcitol treated subjects had cardiovascular events requiring hospitalization (0 versus 5 subjects, p-value not reported). Interestingly, a post-hoc analysis [42] of the trial found that paricalcitol reduced left atrial enlargement index, a marker of cardiovascular events.

In summary, while hyperparathyroidism and CKD are strong predictors of cardiovascular disease, we found scant evidence that

Table 2: Summary of Clinical Trials Included in Review.

	Author	Subjects	GFR[1]	PTH
Bone Mineral Density (BMD)	Bianchi, 1992	Group 1, n = 25	CrCl: 58 – 36 mL/minute	79 ± 18 pg/mL
		Group 2, n = 25	CrCl: 30 – 18 mL/minute	123 ± 21 pg/mL
		Group 3, n = 19	CrCl: 15 – 9 mL/minute	312 ± 39 pg/mL
	Przedlacki, 1995	Calcitriol, n = 13	21.5 (SEM, 3.2) mL/minute	150.3 (SEM, 26.2) ng/L
		Placebo, n = 12	31.3 (SEM, 4.0) mL/minute	122.6 (SEM, 26.1) ng/L
	Rix, 1999	n = 113	37 mL/minute[2]	Not Given (only divided into three groups of ranges)
	Rix, 2004	Alfacalcidol, n = 18	CrCl: 49 ± 20 mL/minute	183 ± 350 pg/mL
		Placebo, n = 18	CrCl: 36 ± 13 mL/minute	121 ± 111 pg/mL
	Tsuchida, 2005	n = 85	23 ± 12 mL/minute	127 ± 113 pg/mL
	Obatake, 2007	n = 53	Estimated CrCl: 26.8 ± 14.5 mL/minute	100 ± 55 pg/mL
	Stavroulopoulos, 2008	Vitamin D deficient, n = 34	33 ± 11 mL/minute	85 (IQR, 23-283) ng/L
		Vitamin D insufficient, n = 35	38 ± 12 mL/minute	76 (IQR, 9-192) ng/L
		Vitamin D replete, n = 20	40 ± 11 mL/minute	40 (IQR, 17-175) ng/L
Cardiac Health	Singh, 2007	Calcitriol, n = 20	13.84 ± 4.16 mL/minute	549.0 ± 378.66 pg/mL
		Placebo, n = 10	13.10 ± 3.57 mL/minute	496.4 ± 351.71 pg/mL
	Ivarsen, 2012	Alfacalcidol, n = 6	CrCl 23.3 ± 3.0	PTH > 3 times upper limit of normal
		No therapy, n = 7	CrCl 22.4 ± 1.7	
	PRIMO Study, Thadhani, 2012,	Paricalcitol, n = 115	31 (IQR, 24-43) mL/minute	100 (IQR, 66-174) pg/mL
		Placebo, n = 112	36 (IQR, 26-42) mL/minute	106 (IQR, 71-153.5) pg/mL
	OPERA Study, Wang, 2014,	Paricalcitol, n = 30	20 (IQR, 16-431) mL/minute	156 (IQR, 108-235) pg/mL
		Placebo, n = 30	24 (IQR, 21-31) mL/minute	129 (IQR, 121-176) pg/mL
Neuromuscular Health	Dukas, 2005	n = 142	CrCl < 65 mL/minute	40.6 ± 27.5 pg/mL
		n = 236	CrCl ≥ 65 mL/minute	36.4 ± 15.4 pg/mL
	Gallagher, 2007	n = 489	Mean measured 24 hour urine CrCl for women with CrCl < 60 mL/minute = 50.3 ± 0.69 mL/minute	36.6 pg/mL[2]
			Mean measured 24 hour urine CrCl for women with CrCl > 60 mL/minute = 80.4 ± 0.83 mL/minute	
Longevity	Kovesdy, 2008	Calcitriol, n = 258	30.8 ± 11.3 mL/minute	152 (IQR, 143-163) ng/mL
		No therapy, n = 262		75 (IQR, 68-83) ng/mL
	Shoben, 2008	Calcitriol, n = 258	31 ± 9 mL/minute	231 ± 127 pg/dL
		No therapy, n = 262	33 ± 10 mL/minute	145 ± 92 pg/dL
	Sugiura, 2010	Alfacalcidol, n = 107	15 ± 7 mL/minute	214 ± 194 pg/mL
		No therapy, n = 558	17 ± 10 mL/minute	152 ± 159 pg/mL

[1]The following are terms and abbreviations used within the table: Creatinine Clearance (CrCl); Glomerular Filtration Rate (GFR); Interquartile Range (IQR); Liter (L); Parathroid Hormone (PTH); Picogram (pg); Milliliter (mL); Nanogram (ng); and Standard Error of the Mean (SEM).
[2]No measure of error given for GFR (Rix, 1999) or PTH (Gallagher, 2007).

Table 3: Randomized Placebo-Controlled Trials of Paricalcitol to Improve Cardiac Function.

Author Year	Paricalcitol Dose & Duration	Primary Study Outcome	Results	Hypercalcemia
Thadhani, 2012, PRIMO Study	2 µg/day or matching placebo x 48 weeks	Change in left ventricular mass index by MRI	No difference in primary outcome between paricalcitol and placebo arms	23% in paricalcitol and 1% in placebo arms, p<0.001
Wang, 2014, OPERA Study	1 µg/day or matching placebo x 52 weeks	Change in left ventricular mass index by MRI	No difference in primary outcome between paricalcitol and placebo arms	43% in paricalcitol and 3% of placebo arms, p<0.001

treatment of SHPT in pre-dialysis CKD patients directly reduces vascular events or mortality. The surrogate marker of left ventricular mass was not affected in four studies of vitamin D analogs versus placebo. Two recent trials, PRIMO and OPERA, highlighted the high incidence of hypercalcemia with the use of bioactive vitamin D. It is possible that lower doses of paricalcitol, or treatment of only patients with severe SHPT, would reduce the incidence of hypercalcemia. However, the risks of bioactive vitamin D prompted the KDIGO work group to recommend against routine treatment of SHPT in the 2017 KDIGO Clinical Practice Guidelines for the Diagnosis, Prevention and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder. It should be noted the work group did not achieve universal agreement against routine treatment of SHPT. The reason for lack of consensus was not explained, but might be due to the milder degree of SHPT in the PRIMO and OPERA studies, or the lower rate of cardiovascular events in subjects randomized to paricalcitol.

Evidence that treating SHPT improves neuromuscular health

Cholecalciferol or ergocalciferol is often recommended to improve muscle strength and decrease falls in older adults [43,44]. CKD is an independent risk factor for falling [12,45-48], and nearly all osteoporotic fractures occur after a fall [49]. Regrettably, few studies have addressed whether vitamin D reduces falls in pre-dialysis CKD patients with SHPT.

Dukas, et al. [47] performed a post-hoc analysis of subjects with CrCl <65 mL/min enrolled in a 36-week double-blind placebo-controlled trial to assess efficacy of alfcalcidol on falls. However, the study did not specifically recruit patients with SHPT, and basal PTH levels were largely normal (40 ± 17 and 29 ± 25 pg/mL in the alfacalcidol and placebo arms, respectively) (Table 2).

In a randomized double-blind, placebo-controlled trial that included 106 subjects with CrCl <60 mL/minute [48], Gallagher, et al. evaluated the effect of 3 years of conjugated equine estrogens and calcitriol on BMD and falls. However, subjects' baseline serum PTH levels were 37 pg/mL, suggesting that few subjects had SHPT (Table 2).

In summary, post-hoc analyses of two trials suggest that calcitriol and alfacalcidol reduce falling in pre-dialysis CKD patients. However, we found no randomized, placebo-controlled trials that specifically recruited subjects with SHPT, or tested the effect of the K/DOQI treatment algorithms on risk of falling.

Evidence that treating SHPT prolongs life

SHPT is associated with increased mortality in hemodialysis patients [50], and bioactive vitamin D therapy is associated with improved survival in this population [51-54]. However, such therapy might simply be a marker of greater access to health care, including better management of cardiovascular risk factors. It is therefore critical to evaluate whether treating SHPT improves survival among patients with pre-dialysis CKD.

In a retrospective single-center observational study of 520 men with stage 3-5 CKD not on dialysis [54], calcitriol therapy was associated with decreased mortality (incidence rate ratio 0.35, 95% CI 0.23 to 0.54) compared with no therapy (Table 2). Shoben, et al. [53] compared mortality rates in calcitriol users and nonusers in a retrospective study of 1418 Veterans Affairs patients with stage 3-4 CKD and PTH >70 pg/mL (Table 2). The mortality risk, after adjustment for age, gender and race, was 26% lower (95% CI, 5% to 40%) among calcitriol users, compared to nonusers. In a third retrospective study [55] of 665 patients with pre-dialysis CKD, hazards of cardiovascular events, cardiovascular death and death from any cause was compared between patients treated with alfacalcidol or no therapy (Table 2). Alfacalcidol was associated with lower all-cause mortality in unadjusted models (hazard ratio 0.47, 95% CI 0.27 to 0.81) but not in multivariate models controlling for age, gender and co-morbidities (hazard ratio 0.80, 95% CI 0.44 to 1.46).

Two meta-analyses of these three retrospective studies concluded that bioactive vitamin D reduced mortality. The hazard ratio for death was 0.59 (95% CI 0.35 to 0.99, I^2=79%) in one meta-analysis [56] and the risk ratio for death was 0.73 (95% CI 0.55 to 0.98, I^2=0%) in the other meta-analysis [57].

In summary, retrospective studies suggest that bioactive vitamin D therapy prolongs life in pre-dialysis CKD. However, we found no prospective, randomized clinical trials to confirm these retrospective study findings.

DISCUSSION

In conclusion, observational data suggest that SHPT is associated with low BMD and excess vascular calcification, presumably contributing to fractures, cardiovascular events and shortened lifespan. Retrospective studies suggest that bioactive vitamin D might prolong life. However, we found very few prospective, randomized, double-blind placebo-controlled clinical trials confirming that treatment of SHPT affects patient-centered health outcomes such as BMD, fractures, falls, cardiovascular events or lifespan. Furthermore, over-suppression of PTH with vitamin D analogs could promote hypercalcemia and vascular calcification, and/or reduce bone turnover leading to adynamic bone disease [58]. Well-designed placebo-controlled clinical trials with relevant clinical outcomes are needed, to clarify the benefits and harms of treating SHPT in CKD patients. Given the lack of evidence that treating SHPT improves patient-centered outcomes, the 2017 National Kidney Foundation guidelines recommend against routine treatment of all CKD patients with SHPT [15].

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