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REVIEW

Hypocalcemia and bone mineral density changes following denosumab treatment in end-stage renal disease patients: a meta-analysis of observational studies

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Abstract

The incidence of hypocalcemia and bone mineral density (BMD) changes in end-stage renal disease (ESRD) patients on denosumab remains unclear. We performed this meta-analysis to assess the incidence of denosumab-associated hypocalcemia and effects of denosumab on BMD in ESRD patients. A literature search was conducted using MEDLINE, EMBASE, and Cochrane Database from inception through November 2017 to identify studies evaluating incidence of denosumab-associated hypocalcemia and changes in serum calcium, phosphate, alkaline phosphatase (ALP), parathyroid hormone (PTH), and BMD from baseline to post-treatment course of denosumab in ESRD patients. Study results were pooled and analyzed using a random-effect model. The protocol for this meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42017081074). Six observational studies with a total of 84 ESRD patients were enrolled. The pooled estimated incidence of hypocalcemia during denosumab treatment was 42% (95% CI 29–55%, $I^2 = 0\%$). Hypocalcemia occurred approximately 7 to 20 days after the first dose and reached nadir of low calcium levels in the first 2 weeks up to 2 months. However, there were no significant changes in serum calcium or phosphate from baseline to post-treatment course (≥ 3 months after treatment) with mean differences [MDs] of 0.20 mg/dL (95% CI, − 0.30 to 0.69 mg/dL) and − 0.10 mg/dL (95% CI, − 0.70 to 0.49 mg/dL). There were significant reductions in ALP and PTH levels with standardized mean differences (SMDs) of − 0.65 (95% CI − 1.13 to − 0.16) and − 1.89 (95% CI − 3.44 to − 0.34), respectively. There were significant increases in T-scores with MDs of 0.39 (95% CI 0.10 to 0.69) and 0.79 (95% CI 0.60 to 0.98) for lumbar spine and femoral neck, respectively. Our study demonstrates the estimated incidence of denosumab-associated hypocalcemia in dialysis patients of 42%. From baseline to post-treatment course, although there are no differences in serum calcium and phosphate, our findings suggest significant reductions in ALP and PTH and a significant increase in BMD. Currently, denosumab should not be considered as the treatment of choice in ESRD patients until more safety and efficacy data are available.

Keywords Bone mineral density · Calcium · Denosumab · End-stage kidney disease · Hypocalcemia · Meta-analysis

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Introduction

Osteoporosis is one of the major and growing public health problems worldwide [1, 2]. Due to the global aging population, the prevalence of osteoporosis has been increasing [3, 4]. Worldwide, according to the National Osteoporosis Foundation, more than 200 million people have osteoporosis and it is estimated that its prevalence will continue to increase by almost 50% by 2020, when 61.4 million people in the USA are expected to be affected [5]. Approximately, 2.1 million osteoporosis-related bone fractures are reported each year in the USA, resulting in as much as US$20.3 billion annual direct health costs [6–8].

Reduced glomerular filtration rate (GFR) is a well-known risk factor for osteoporosis [9–14], which may lead to metabolic abnormalities that accelerate bone loss and metabolic bone diseases [15–20]. The incidence of osteoporotic fracture in patients with chronic kidney disease (CKD) is higher than age- and sex-matched population [20, 21]. In end-stage renal disease (ESRD) patients, the prevalence of osteoporosis ranges from 13 up to 80% [22] and hip fracture rates are 4-fold to 17-fold higher than in the general population [20, 21, 23, 24]. Despite recent advances in the treatment of osteoporosis, and hip fracture rates in ESRD patients which seem to have declined over time in the USA, in-hospital mortality after hip fracture surgery is 6.3% [21].

Denosumab is a fully human monoclonal antibody that specifically binds to the receptor activator of nuclear factor-κB ligand (RANKL) [25, 26], a key cytokine that is essential for osteoclast formation, function, and survival [27, 28]. Thus, treatment with denosumab can have an antiresorptive effect with a significant increase in BMD. In recent years, denosumab has been considered as effective as bisphosphonates for osteoporosis therapy, with similar effect on reducing fracture risk and greater effectiveness in increasing BMD [29, 30]. Despite the concern of severe hypocalcemia following denosumab in patients with CKD [19, 31–35], denosumab has been increasingly used not only in general population but also in those with CKD due to its effectiveness [14, 19, 36, 37]. However, in those patients with advanced renal insufficiency, especially patients with ESRD on dialysis, the incidence of denosumab-associated hypocalcemia and changes in BMD following denosumab use remain unclear, with conflicting findings from previous reports [18, 19, 36, 38–48].

Our systematic review and meta-analysis aimed to assess the incidence of denosumab-associated hypocalcemia and effects of denosumab on BMD in ESRD patients.

Methods

Information sources and search strategy

The protocol for this meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42017081074). A systematic literature search was conducted utilizing Ovid Medline, EMBASE, and Cochrane Database from inception through November 2017 to identify all original studies that investigated the incidence of hypocalcemia during denosumab treatment and changes in serum calcium, phosphate, alkaline phosphatase (ALP), parathyroid hormone (PTH), and BMD from baseline to post-treatment course of denosumab in ESRD patients. The systematic literature review was individually conducted by two investigators (C.T and W.C.) using the search strategy as described in online supplementary data 1. A manual search for additional potentially relevant studies using references of the included articles was also performed. No language limitation was applied. Any differing decisions were resolved by mutual consensus. This study was conducted in agreement with the STROBE (reporting epidemiological studies) (16) and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Statement as described in online supplementary data 2.

Selection criteria

Eligible studies included (1) controlled clinical trials or observational studies such as case-control, cross-sectional, or cohort studies that evaluated the incidence of hypocalcemia during denosumab treatment and changes in serum calcium, phosphate, ALP, PTH, and BMD from baseline to post-treatment course of denosumab in ESRD patients; (2) studies that presented data to calculate mean differences (MDs), standardized mean differences (SMDs), relative risks, or hazard ratios with 95% confidence intervals (CIs); and/or (3) studies that evaluated changes in serum calcium, phosphate, ALP, PTH, and BMD with denosumab treatment when compared to control group composed of ESRD patients who did not receive denosumab. Inclusion was not restricted by study size. The quality of each study was evaluated by the investigators using the validated methodological index for non-randomized studies (minors) quality score [49].

Data abstraction

A structured data collection report was adopted to derive the following information from included studies: study

title, first author name, publication year, year of the study, demographic data, number of patients, data on PTH, calcium, phosphate, 25-OH vitamin D, 1,25 (OH)2 vitamin D levels, and dosing regimen of denosumab. To warrant the precision, this data extraction process was independently performed by three investigators (C.T., P.A., and W.C.).

Statistical analysis

Data analysis was performed using the Comprehensive Meta-analysis (version 3; Biostat Inc.). The incidence rate and 95% CIs of hypocalcemia were reported using a DerSimonian–Laird random-effect model, which allowed the weight of each study in the pooled analysis based on its variance [50]. The summary statistics for each outcome were the mean change from baseline and standard deviations (SD) of the mean change. The mean change in each group was obtained by subtracting the final mean from the baseline mean The MDs were preferred when all studies use the same continuous outcome and unit of measure. Otherwise, SMDs and 95% CIs were calculated for the summary effect of continuous data. The SD of mean change was computed assuming a conservative correlation coefficient of 0.5 [51]. An effect size of 0.2 was interpreted as small, those of 0.5 as moderate, and of 0.8 as large [52, 53]. Given a high likelihood of between-study variance, we used a random-effect model rather than a fixed-effect model. Cochran's Q test and I^2 statistic were used to determine the between-study heterogeneity. A value of I^2 of 0–25% represents insignificant heterogeneity, 26–50% represents low heterogeneity, 51–75% represents moderate heterogeneity, and more than 75% represents high heterogeneity [54]. Egger's regression symmetry test was used to assess for publication bias. The p value < 0.05 was considered statistically significant for all analysis.

Results

Our search strategy retrieved 283 potentially relevant articles. After the exclusion of 266 articles based on title and abstract not fulfilling inclusion criteria, 17 articles underwent full-length review [Fig. 1]. Additional 11 articles were excluded for failing to meet the criteria: 8 articles did not report the outcome of interest, and 3 articles were not observational studies.

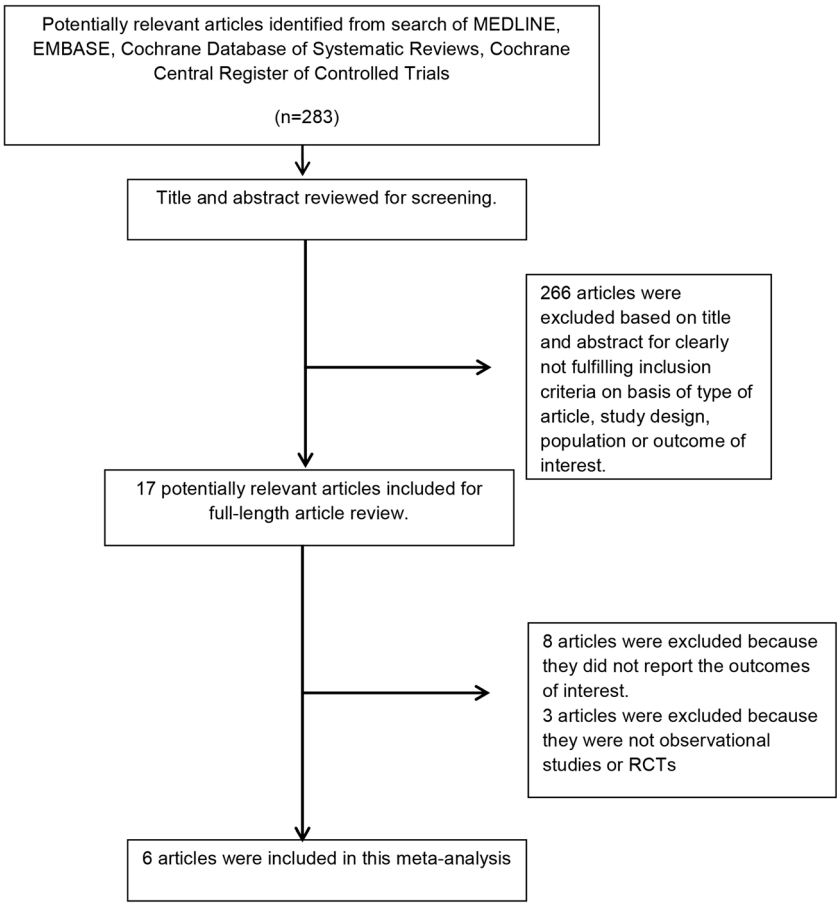

Fig. 1 Literature review process

Table 1 Characteristics of included studies [36, 38–42]

Study	Block [36]	Chen et al. [38]	Hiramatsu et al. [39]
Year	2012	2014	2015
Study sample	HD patients	HD/PD patients with severe hyperparathyroidism (iPTH > 1000 pg/mL), low BMD (femoral neck, lumbar spine T-score < − 1.0 SD)	HD patients with low BMD (lumbar spine, femoral neck, or distal radius T-score ≤ − 2.5. Well-controlled mineral and iPTH level (iPTH < 300 pg/mL)
Aims	To evaluate pharmacokinetics, pharmaco dynamics, and safety of Denosumab	To evaluate the efficacy and safety of denosumab	To evaluate the effects of Denosumab on BMD
Outcomes	Ca	Ca, PTH, BMD	BMD, Ca, Phos, PTH, ALP
Number	8	12	11
Male	6 (75%)	7 (58%)	1 (9%)
Age	67 ± 15	53.5 ± 3.8	66 (60–71)
iPTH (pg/mL)	158.2 ± 125.1	1702.1 ± 181.9	142.0 (125–211)
Ca (mg/dL)	9.1 ± 0.4	10.1 ± 0.4	9.7 (9.4–10.5)
Phosphate (mg/dL)	N/A	5.3 ± 0.3	4.4 (3.5–5.3)
25-OH vitamin D	39.2 ± 40.4	N/A	15.0 (11.6–19.3)
1,25 (OH)2 vitamin D	46.7 ± 23.5	N/A	11.6 (7.3–32.5)
ALP (IU/L)	N/A	449.8 ± 94.2	295 (255–412)
Frequency of Ca measurement	Day 2, 3, 6, 8, 11, 15, 22, 29, 43, 57, 85, and 113	Day 7, 14, 21, and every month thereafter	Day 7, 30, 90, and 180
Control	No	8 controls	No
Denosumab	A single 60 mg subcutaneous of denosumab	A single 60 mg subcutaneous of denosumab	A single 60 mg subcutaneous of denosumab
Follow-up	16 weeks	24 weeks	24 weeks
Supplement	Calcium (up to 1000 mg/day) and vitamin D (up to 800 IU/day)	Calcium (calcium carbonate 3 g/day) and vitamin D (calcitriol 1 μg/day)	Calcium (calcium carbonate mean 1.42 ± 1.8 g/day), vitamin D (alfacalcidol mean 0.25 ± 0.4 μg/day), cinacalcet (0–75 mg/day)
Dialysate Ca	N/A	3 mEq/L at the start of the study and were titrated according to the serum Ca levels and phosphate	2.5–3 mEq/L
MINORs quality score	14/16	21/24	14/16
Study	Chen et al. [40]	Takami et al. [41]	Festuccia et al. [42]
Year	2015	2017	2017
Study sample	HD/PD patients with severe hyperparathyroidism (iPTH > 800 pg/mL) and low BMD (forearm, femoral neck, lumbar spine T-score < − 2.5 SD)	HD patients with low BMD (< 70% of the young adult mean)	HD patients with severe osteoporosis or prior history or high risk of femoral and vertebral fractures
Aims	To evaluate the effect of co-administration of calcitriol and denosumab on PTH secretion and parathyroid structure and the incidence of adverse effects	To evaluate the effects of denosumab on BMD	To evaluate the efficacy and tolerability of denosumab in HD patients with osteoporosis
Outcomes	Ca, PTH, BMD	Ca, phosphate, ALP, PTH, BMD	Ca, phosphate, PTH, ALP
Number	24	17	12
Male	5 (21%)	17 (100%)	1/12 (8%)
Age	58.4 ± 2.8	72.8 ± 9.5	66.4 ± 9.4
iPTH (pg/mL)	1464.8 ± 93.2	164 (58.5–228)	655.9 ± 658.5
Ca (mg/dL)	10.1 ± 0.2	9.2 ± 0.5	9.1 ± 0.5
Phosphate (mg/dL)	5.7 ± 0.3	5.0 ± 1.3	5.9 ± 1.5
25-OH vitamin D	30.0 ± 3.1	N/A	N/A
1,25 (OH)2 vitamin D	N/A	N/A	N/A
Alkaline phosphatase (IU/L)	331.7 ± 48.9	276 ± 129	Bone alkaline phosphatase 33.5 ± 28.8

Table 1 (continued)

Frequency of Ca measurement	Day 7, 14, 21, and every month thereafter	Every month	Every month
Control	8 controls	20 controls	No
Denosumab	A single 60 mg subcutaneous of denosumab	A single 60 mg subcutaneous of denosumab every 6 months	A single 60 mg subcutaneous of denosumab every 6 months
Follow-up	24 weeks	1 year	24 months
Supplement	Calcium (calcium carbonate3 g/day) and vitamin D (calcitriol 2 μg/day)	Calcium carbonate mean 1.47 g/day, alfacalcidol mean 0.31 μg/day, calcitriol mean 0.01 μg/day, max acalcitol mean 5 μg/week, cinacalcet mean 2.94 mg/day, phosphate binder	Calcium, vitamin D, cinacalcet, phosphate binder
Dialysate Ca	3.5 mEq/L at the start of the study and were titrated according to the serum Ca levels and phosphate	2.5 mEq/L	Adjusted according to the biochemistry data
MINORs quality score	21/24	21/24	14/16

ALP alkaline phosphatase, *BMD* bone mineral density, *ESRD* end-stage renal disease, *HD* hemodialysis, *N/A* not available, *PD* peritoneal dialysis, *PTH* parathyroid hormone

Six observational studies [36, 38–42] with a total of 84 ESRD patients met the eligible criteria and were enrolled in our meta-analysis. The literature retrieval, review, and selection process are shown in Fig. 1. The characteristics of included studies [36, 38–42] and quality assessment of the studies included in this meta-analysis are shown in Table 1.

Incidence of hypocalcemia in ESRD patients during denosumab treatment

Four cohort studies [36, 38–40] were included in the meta-analysis to assess the incidence of hypocalcemia in ESRD patients during denosumab treatment. The pooled estimated incidence of hypocalcemia during denosumab treatment was 42% (95% CI 29–55%, $I^2 = 0\%$), Fig. 2a.

Data on the incidence of symptomatic hypocalcemia with the use of denosumab were limited. Festuccia et al. [42] reported 25% (3/12) of ESRD patients treated with denosumab developed symptomatic hypocalcemia, including paresthesias and myalgias. However, those patients did not require hospitalization. Block et al. [36] reported that 25% (2/8) of the patients were hospitalized for intravenous calcium gluconate. A patient (12.5%) had symptomatic hypocalcemia (perioral numbness with numbness of both feet). On the contrary, Chen et al. [38] and Hiramatsu et al. [39] reported that none of ESRD patients treated with denosumab developed symptomatic hypocalcemia when treated with adequate calcium and active vitamin D supplementation (Table 1).

Changes in calcium and bone metabolism from baseline to post-treatment course

We included six studies, enrolling 84 ESRD patients that evaluated changes in calcium and bone metabolism from baseline to post-treatment course (16 weeks up to 1 year). There were no significant changes in serum calcium or phosphate from baseline to post-treatment course (≥ 3 months after treatment) with MDs of 0.20 mg/dL (three studies; 95% CI, − 0.30 to 0.69 mg/dL, $I^2 = 58\%$, Supplementary Figure1) and − 0.10 mg/dL (three studies; 95% CI, − 0.70 to 0.49 mg/dL, $I^2 = 0\%$, Supplementary Figure 2). There were significant reductions in ALP and PTH levels with SMDs of − 0.65 (three studies; 95% CI − 1.13 to − 0.16, $I^2 = 0\%$, Fig. 2b) and − 1.89 (five studies; 95% CI − 3.44 to − 0.34, $I^2 = 88\%$, Supplementary Figure 3), respectively. There were significant increases in T-scores with MDs of 0.39 (95% CI 0.10 to 0.69, $I^2 = 0\%$, Fig. 2c) and 0.79 (95% CI 0.60 to 0.98, $I^2 = 61\%$) for lumbar spine and femoral neck, respectively.

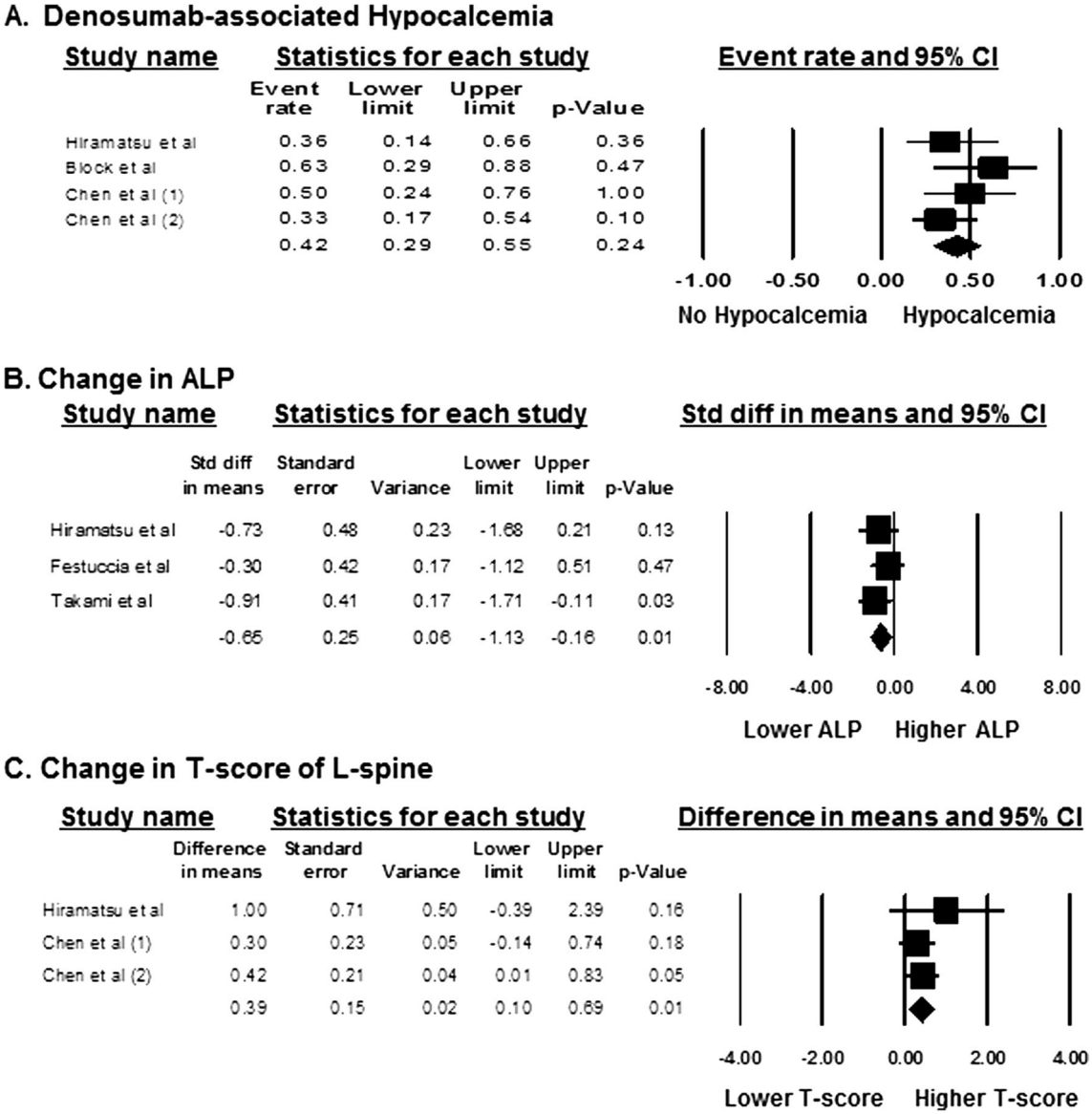

Fig. 2 Forest plot of all included studies evaluating **a** incidence of hypocalcemia during denosumab treatment, **b** changes in ALP, and **c** changes in T-scores for lumbar spine

Sensitivity analysis

Of the six studies [36, 38–42], three studies [38, 40, 42] included ESRD patients with significant secondary hyperparathyroidism. In the analysis that limited only patients with significant secondary hyperparathyroidism, there was a significant reduction in the PTH level with SMD of − 8.44 (95% CI − 11.25 to − 5.64, $I^2 = 0\%$). In addition, there were significant increases in T-scores with MDs of 0.36 (95% CI 0.06 to 0.67, $I^2 = 0\%$) and 0.79 (95% CI 0.60 to 0.98, $I^2 = 61\%$) for lumbar spine and femoral neck, respectively. Among those without significant or severe secondary hyperparathyroidism, there was no significant change in PTH level with SMD of − 0.26 (95% CI − 0.71 to 0.19, $I^2 = 0\%$). The data on the changes in BMD in ESRD patients without significant secondary hyperparathyroidism were limited. A study by Hiramatsu et al. [39] demonstrated insignificant change in T-scores for lumbar spine with MD of 1.00 (95% CI − 0.39 to 2.39).

Evaluation for publication bias

Funnel plots (Supplementary Figure 4–6) and Egger's regression asymmetry tests were performed to evaluate for publication bias in the incidence of hypocalcemia during denosumab treatment and changes in serum calcium and phosphate from baseline to post-treatment course in ESRD patients. There was no significant publication bias, $p = 0.20$, 0.60, and 0.55, respectively.

Discussion

In this meta-analysis, we demonstrated that the overall incidence of denosumab-associated hypocalcemia in the dialysis-dependent ESRD population is 42%. However, with calcium and vitamin D supplementation, from baseline to post-treatment course, our meta-analysis showed no differences in serum calcium and phosphate. In addition, there were significant reductions in ALP and PTH levels and increase in BMD after following denosumab treatment.

Following the approval by the US Food and Drug Administration (FDA) in 2010 as a treatment for postmenopausal osteoporosis in women who are at high risk of fractures [25], denosumab has been increasingly used for the treatment of many conditions including osteoporosis, bone metastases, bone destruction in rheumatoid arthritis, multiple myeloma, and giant cell tumor of bone in recent years [25, 26, 55–57]. Among ESRD patients, following denosumab treatment, we demonstrated that de novo hypocalcemia can occur commonly approximately in 42%. Studies demonstrated that ESRD patients developed hypocalcemia within the first month after therapy, approximately 7 to 20 days [38, 40–42] after the first dose and reached nadir of low calcium levels in the first 2 weeks up to 2 months [38, 40, 42]. Hypocalcemia subsequently improved with up-titration of active vitamin D dosage [38, 40, 42]. Thus, from baseline to post-treatment course with denosumab, based on the findings from our meta-analysis, there was no difference in serum calcium level. Although there have been several reported cases of severe symptomatic hypocalcemia following denosumab treatment in ESRD patients [48, 58], the data on the incidence of symptomatic hypocalcemia are limited [36, 38, 39, 42], ranging from 0 to 25% [36, 38, 39, 42]. With appropriately high calcium dialysate, adequate calcium, and active vitamin supplementation [38], none of the ESRD patients treated with denosumab developed symptomatic hypocalcemia in several reports [38, 39].

In recent years, denosumab has been used for the treatment of osteoporosis in patients at high risk of fracture, especially in those with severe osteoporosis with very low BMD, multiple fractures, steroid use, younger age group, and those who cannot tolerate bisphosphonate, such as patients with reduced kidney function [25, 26, 29, 30, 35, 45, 46, 55, 56]. A recent meta-analysis of nine studies including a total of 4890 postmenopausal women demonstrated potential greater effectiveness in increasing BMD among patients treated with denosumab, when compared to bisphosphonates [29]. Among CKD patients, bisphosphonates are not recommended in those with creatinine clearance < 35 mL/min since they are eliminated by the kidneys [22]. Although bisphosphonates are removed by dialysis and several reports have supported the use of bisphosphonates in dialysis patients [59, 60], FDA recommendations have not been revised, thus limiting the use of bisphosphonates in this population. In this meta-analysis, we demonstrated that denosumab could effectively increase BMD among ESRD patients on dialysis. In addition, following treatment with denosumab, up to 1 year, we found significant reductions in ALP and PTH. Previous studies for treatment of osteoporosis with denosumab (in patients without advanced CKD) have demonstrated a significant increase in PTH levels, especially following the first administration of denosumab, conceivable due to the effects following inhibition of bone resorption [61, 62]. Among dialysis patients treated with denosumab, most patients had increased PTH levels within the first month. However, after adequate calcium and active vitamin supplementation, PTH levels subsequently reduced and were significantly lower than those prior to denosumab treatment [38, 40].

To our knowledge, this is the first meta-analysis performed on the use of denosumab in dialysis population; however, this study faced several limitations. First, there was a high statistical heterogeneity present in the final analysis of the effects of denosumab on changes in calcium, phosphate, and BMD in ESRD patients. The possible source of this heterogeneity includes the differences in laboratories, testing methodology, and unit of measure in each study. Thus, we used a random-effect model and summarized statistics for these outcomes with SMDs and 95% CIs. Second, there were limited numbers of patients included in the meta-analysis as well as limited numbers of studies with control groups [38, 40, 41] and pooled analysis could not be performed due to the limited number of studies and lack of power. On those studies that included a control group, a significant difference in BMD was found in those ESRD patients using denosumab when compared to their controls. In a recent study by Takami et al. [41], which included 17 ESRD patients treated denosumab and 20 ESRD patients without treatment with denosumab as a control group, the investigators found a statistically significant difference in BMD among the two groups at 1 year follow-up (an increase by 2.6 ± 4.4% in the denosumab group vs. a decrease by 4.5 ± 7.7%, in the control group, $p < 0.01$). In addition, the significant improvement in BMD in ESRD patients treated with denosumab, compared to control, was also demonstrated in another two studies [38, 40]. Third, the use of BMD may be affected by several factors in dialysis patients [63, 64]. There are very limited data that low BMD can predict fractures in dialysis patients, especially by using lumbar BMD, which the findings may be falsely increased due to aortic calcifications [12]. Moreover, there is currently a lack of evidence in ESRD patients demonstrating improvement of fracture rates or mortality with interventions to improve BMD. A bone biopsy still remains the gold standard analysis for assessing the exact type of renal osteodystrophy if a more targeted treatment is considered [65]. For example, using antiresorptive agents may exacerbate low bone turnover, which can be deleterious in ESRD patients with a dynamic bone disease [65]. Lastly, this is a

meta-analysis of observational studies, not randomized controlled trials. The improvement in BMD after denosumab treatment could have potentially been affected by additional treatment with calcium and D-analogs. Thus, future large randomized controlled trials are needed to confirm these findings from our meta-analysis.

In summary, our systematic review and meta-analysis suggest an efficacy of denosumab in the improvement in BMD among ESRD patients on dialysis. However, randomized controlled trials are needed to further investigate the role of denosumab in the ESRD population, as our current conclusions are based mainly on the analysis of observational studies reported in the literature and several of them did not include a control group. The estimated incidence of denosumab-associated hypocalcemia in dialysis patients is as high as 42%. With careful monitoring and appropriate adjustment in calcium dialysate, adequate calcium, and active vitamin supplementation, symptomatic hypocalcemia is potentially preventable in ESRD patients treated with denosumab.

Compliance with ethical standards

Conflicts of interest None.

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