International Urology and Nephrology (2019) 51:2027–2036
https://doi.org/10.1007/s11255-019-02271-6

NEPHROLOGY - ORIGINAL PAPER

Cinacalcet plus vitamin D versus vitamin D alone for the treatment of secondary hyperparathyroidism in patients undergoing dialysis: a meta-analysis of randomized controlled trials

Jun Xu[1,2] · Yan Yang[1] · Liang Ma[1] · Ping Fu[1] · Hongying Peng[2]

Received: 8 April 2019 / Accepted: 28 August 2019 / Published online: 17 September 2019

Abstract

Background Secondary hyperparathyroidism (SHPT) is a common and serious complication of chronic kidney disease, particularly in end-stage renal disease. Currently, both cinacalcet and vitamin D are used to treat SHPT via two different mechanisms, but it is still unclear whether the combination use of these two drugs can be a safe and effective alternative to vitamin D alone. Therefore, the aim of this meta-analysis was to assess the efficacy and safety of cinacalcet plus vitamin D in the treatment of SHPT.

Methods Four electronic databases, including PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science, were searched for eligible publications. All randomized-controlled trials comparing cinacalcet plus vitamin D with vitamin D alone in SHPT patients undergoing dialysis were included. Mean difference (MD) with 95% confidence intervals (CIs) and risk ratios (RRs) with 95% CIs were calculated using a random-effects model or fixed-effects model. Sensitivity analysis was conducted by removing any one study successively to estimate the stability of the pooled results, and subgroup analysis was carried out to explore potential sources of heterogeneity, and funnel plots were used to test publication bias.

Results A total of 8 randomized-controlled trials involving 1480 patients were included in the study. Compared with vitamin D treatment, the combination use of cinacalcet and vitamin D significantly lowered serum calcium (MD −0.82, 95% CI −1.02 to −0.61, $P<0.001$), phosphorus (MD −0.57, 95% CI −0.97 to −0.18, $P=0.005$), and calcium × phosphorus product (MD −9.41, 95% CI −10.00 to −8.82, $P<0.001$). However, there was no difference in serum parathyroid hormone (PTH, MD 43.99, 95% CI −49.22 to 137.20, $P=0.35$), ≥30% reduction in PTH (RR 1.02, 95% CI 0.69–1.52, $P=0.91$), and PTH achieve 150–300 pg/ml (RR 0.88, 95% CI 0.68–1.15, $P=0.35$). Moreover, the combination therapy did not increase the risk of all adverse events, all-cause mortality, diarrhea, muscle spasms, and headache (all $P>0.05$), but had a higher risk of hypocalcemia (RR 17.98, 95% CI 5.68–56.99, $P<0.001$), and nausea or vomiting (RR 3.47, 95% CI 2.25–5.35, $P<0.001$).

Conclusions In comparison with vitamin D alone, the combination use of cinacalcet and vitamin D significantly lowered serum calcium, phosphorus, and the calcium × phosphorus product, and did not increase the risk of all adverse events, all-cause mortality, diarrhea, muscle spasms, and headache, whereas had no effect on serum PTH and increased the risk of hypocalcemia and nausea or vomiting. Future studies are needed to assess the effects of cinacalcet plus vitamin D on PTH level, cardiovascular events, and other clinical outcomes in larger samples with longer durations.

Keywords Cinacalcet · Vitamin D · Secondary hyperparathyroidism · Dialysis · Meta-analysis

Introduction

Chronic kidney disease (CKD) is a global public health problem with an increasing incidence, poor outcomes, and high cost [1]. Decreased glomerular filtration rate (GFR) and increased urinary albumin excretion may progress to end-stage renal disease (ESRD) and require renal replacement therapy, including dialysis or transplantation. Secondary

Ping Fu and Hongying Peng have contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11255-019-02271-6) contains supplementary material, which is available to authorized users.

Extended author information available on the last page of the article

hyperparathyroidism (SHPT) is one of the most common and serious complications of ESRD, which is characterized by an elevation in parathyroid hormone (PTH) associated with inadequate levels of active vitamin D hormone. Many studies had demonstrated that SHPT was associated with an increased risk of mortality, cardiovascular disease, and bone fracture [2–4].

The traditional treatment for SHPT is oral or intravenous vitamin D analogs, which can inhibit PTH synthesis and secretion via binding to vitamin D receptor (VDR) in parathyroid gland. Although vitamin D have been shown to be effective in lowering serum PTH levels [5–7], the treatment also enhanced intestinal absorption of calcium and phosphorus, and led to hypercalcemia or hyperphosphatemia [8].

The calcimimetic cinacalcet was approved to treat SHPT patients by directly binding to and activating calcium-sensing receptor (CaR) in parathyroid gland. For this reason, cinacalcet could significantly increase sensitivity to extracellular calcium and suppress PTH secretion without increasing serum calcium and phosphate levels [9]. A growing number of randomized-controlled trials (RCTs) indicated that cinacalcet effectively improved biochemical parameters of SHPT patients, and had no negative impact on all-cause mortality and all adverse events [10–14].

Since vitamin D and cinacalcet exert therapeutic effect through two distinct mechanisms, whether the combination use of these two drugs can be a safe and effective alternative to vitamin D alone was still unknown. Therefore, this meta-analysis aimed to identify available RCTs, and evaluate the efficacy and safety of cinacalcet plus vitamin D in the treatment of SHPT.

Methods

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15].

Data sources and searches

Four electronic databases, including PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science, were searched from their inception to 18 July 2019. No language restrictions were applied. The following terms were used in the literature search: "kidney diseases or chronic kidney failure or dialysis or hemodialysis or haemodialysis", AND "secondary hyperparathyroidism or SHPT", AND "cinacalcet or calcimimetic or mimpara or sensipar or AMG 074 or AMG 073 or KRN 1493 or naphthalene" AND "vitamin D or cholecalciferol or calciferol or 25-hydroxyvitamin D". Moreover, reference lists of articles and all prior meta-analyses were searched manually to identify additional eligible studies.

Study selection

Eligible articles were selected based on the following inclusion criteria: (1) patients aged over 18 years and received dialysis more than 3 months; (2) patients were treated with calcimimetic agents plus vitamin D; (3) reported endpoint data of interest; (4) randomized-controlled trial. Citations were excluded for the following reasons: (1) duplicated studies; (2) lack of extractable data.

All studies were imported into Endnote X7 (Thomson Reuters, New York, USA) for the exclusion of duplicates, and two reviewers (Jun Xu and Yan Yang) independently screened the titles, abstracts, and full texts to identify potential eligible trials. Any disagreements were resolved through adjudication by the third researcher (Liang Ma).

Data extraction

Two reviewers (Jun Xu and Yan Yang) individually extracted the following information from each study: author, publication year, title, eligibility criteria, baseline characteristics of the participants, sample size, and interventions. The following outcomes of interest were examined: serum PTH, calcium, phosphorous, calcium × phosphorus product, Kidney Disease Outcome Quality Initiative (KDOQI) target, all-cause mortality and all adverse events, hypocalcemia, nausea or vomiting, diarrhea, muscle spasms, and headache.

Quality assessment of the studies

The quality of the included RCTs was evaluated by the Cochrane Collaboration Risk of Bias tool [16], which was divided into three criteria, "low risk", "unclear", and "high risk", and contained seven items: random allocation, concealment, blinding of participants, outcome assessment, incomplete outcome, selective reporting, and other bias.

Statistical analysis

Data were analyzed using Review Manager (RevMan, Version 5.3, Cochrane Collaboration, Copenhagen, Denmark). For continuous and dichotomous variables, the pooled results were performed by mean differences (MDs) and risk ratios (RRs), respectively. All data were collected at the end of study. When standard deviation (SD) did not report, it was calculated using the values of the median and interquartile ranges (IQRs) [17]. Heterogeneity between studies was assessed with the Cochran's Q-statistic test and the I^2 statistics [18]. When heterogeneity was observed (Q-statistic: $P < 0.1$; $I^2 > 50\%$), the random-effects model (DerSimonian and Laird method) was adopted, or else a fixed-effects model was used [19]. In addition, sensitivity analysis was conducted by removing any one study successively to estimate the stability of the pooled results, subgroup analysis was carried out to explore potential sources of heterogeneity, and funnel plots were used to test publication bias. A p value <0.05 was considered statistically significant.

Results

Studies characteristics

With the applied search strategy, 613 potentially relevant studies were identified. After screening the title and abstract, 55 studies were relevant and obtained in full. Ultimately, 8 RCTs containing 1480 SHPT patients were included in the meta-analysis [20–27]. No additional studies were identified by manual retrieval. The PRISMA flowchart of literature review is shown in Fig. 1. See the Online Appendix for more details of retrieval process.

Characteristics of patients, interventions, treatment duration, and main outcome measures of all included studies are shown in Table 1. In brief, these trials were performed between 2008 and 2014, and varied in sample size (66–360 participants). In these RCTs, two studies originated from the ACHIEVE trial (study number: 20050102) [20, 21] and IMPACT-SHPT trial (trial registration: ClinicalTrials.gov NCT00977080) [23, 27], respectively. Notably, IMPACT-SHPT trial was a 28-week, multicentre, randomized, open-label phase 4 study, and randomization and analyses were stratified according to the mode of paricalcitol administration [intravenous (IV) at USA and Russian sites (IV stratum); oral at non-USA and non-Russian sites (oral stratum)]. Therefore, we split the trial into IV stratum and oral stratum for analysis [23]. In terms of dosage, five studies received an initial cinacalcet dosage of 30 mg/day orally, and raised to 180 mg/day to achieve a PTH level between 150 and 300 pg/ml [20–23, 27], and only one study reported the dosage of cinacalcet was between 25 and 50 mg/day [25]. On the other hand, vitamin D dosage of the eight RCTs was adjusted according to mineral metabolic parameter test.

Among these eight included studies, a high risk of bias was assigned to two for performance bias, one for detection bias and attrition bias. And also, an unclear risk of bias was assigned to one for selection bias, two for performance bias, four for detection bias, three for attrition bias, one for reporting bias, and three for other bias. The risk of bias within studies is shown in Supplementary Figure 1.

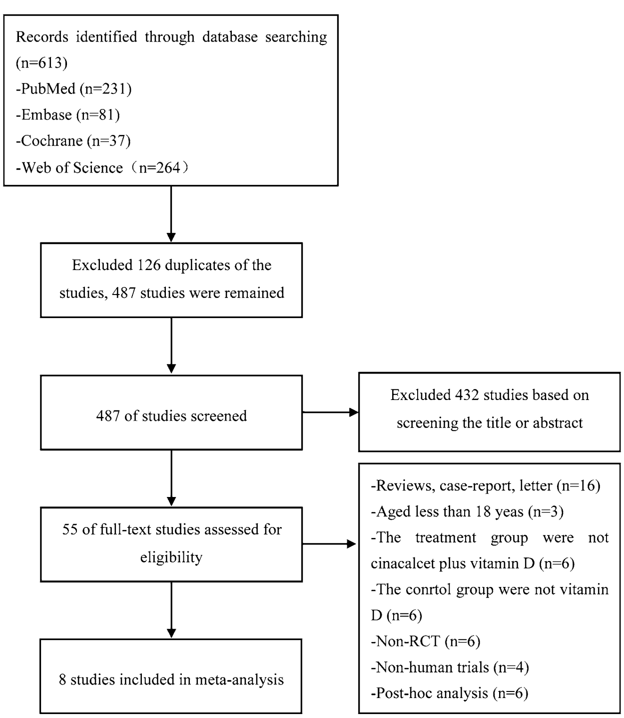


Fig. 1 Flowchart of identification of eligible studies in this study

Effects of cinacalcet plus vitamin D treatment on biochemical outcomes

Serum PTH

Serum PTH, ≥30% reduction in PTH, and PTH achieve 150–300 pg/ml were main outcome measures of cinacalcet treatment, and four trials that reported these indicators were included in our meta-analysis. There was no significant difference between cinacalcet plus vitamin D group and vitamin D group in serum PTH (MD 43.99, 95% CI −49.22 to 137.20, $P=0.35$; Fig. 2a), ≥30% reduction in PTH (RR 1.02, 95% CI 0.69–1.52, $P=0.91$; Fig. 2b), and PTH achieve 150–300 pg/ml (RR 0.88, 95% CI 0.68–1.15, $P=0.35$; Fig. 2c). Subjectively, the funnel plot for ≥30% reduction in PTH and PTH achieve 150–300 pg/ml are symmetric, as shown in Supplementary Figure 2.

Serum calcium, phosphorus, and calcium × phosphorus product

As shown in Fig. 3, the combination use of cinacalcet and vitamin D significantly lowered serum calcium (MD −0.82, 95% CI −1.02 to −0.61, $P<0.001$; Fig. 3a), phosphorus (MD −0.57, 95% CI −0.97 to −0.18, $P=0.005$; Fig. 3b), and calcium × phosphorus product (MD −9.41 to 95% CI −10.00, −8.82, $P<0.001$; Fig. 3c).

Based on I^2 index, each of the biochemical parameters demonstrated high heterogeneity across the studies. General

Table 1 Characteristics of included studies

Study name/first author, year	Trial registration	Country	Patients number (T/C)	Age (SD)	Female (%)	Treatment group (cinacalcet plus vitamin D)	Control group (vitamin D)	Treatment duration	Main outcome measures
Fishbane et al., 2008 (ACHIEVE)	Study number: 20050102	USA	173 (87/86)	T: 57.7 (14.9) C: 59.0 (12.4)	T: 40 C: 48	Cinacalcet (30–180 mg/day) plus low dose of paricalcitol (2 µg thrice weekly) or doxercalciferol (1 µg thrice weekly)	Flexible doses of paricalcitol or doxercalciferol	33 weeks: screening 6 weeks; titration 16 weeks; assessment 11 weeks	Primary endpoint: PTH achieve 150–300 pg/ml; Ca × P achieve < 55 mg^2/dl^2 Secondary endpoint: KDOQI targets; ≥ 30% reduction in PTH
Wetmore et al., 2010 (ACHIEVE)	Study number: 20050102	USA	91 (48/43)	T: 57.9(15.7) C: 59.5(13.1)	T: 40 C: 44	Cinacalcet (30–180 mg/day) plus low dose of paricalcitol (2 µg thrice weekly) or doxercalciferol (1 µg thrice weekly)	Flexible doses of paricalcitol or doxercalciferol	33 weeks: screening 6 weeks; titration 16 weeks; assessment 11 weeks	Percent relative change in Ca, P, PTH, and log-transformed FGF23
Raggi et al., 2011 (ADVANCE)	ClinicalTrials.gov NCT00379899	USA	360 (180/180)	T: 61.2 (12.6) C: 61.8 (12.8)	T: 38 C: 47	Cinacalcet (30–180 mg/day) plus low dose of vitamin D sterols equivalent to ≤ 2 µg paricalcitol with each dialysis	Flexible doses of vitamin D sterols.	52 weeks: titration 20 weeks; follow-up 32 weeks	Primary endpoint: percentage change in CAC score Secondary endpoint: change in PTH, calcium, phosphorus and Ca × P; safety
Ketteler et al., 2012 (IMPACT-SHPT)	ClinicalTrials.gov NCT00977080	IV stratum: USA Oral stratum: non-USA	IV stratum: 126 (64/62) Oral stratum: 142 (70/72)	IV stratum: T: 61.2(12.7) C: 59.9(12.0) Oral stratum: T: 65.7(13.5) C:65.1(12.5)	IV: T: 38.7 C: 40.6 Oral: T: 31.9 C: 38.6	Cinacalcet (30–180 mg/day) plus IV doxercalciferol (1 µg thrice weekly) Cinacalcet (30–180 mg/day) plus oral alfacalcidol (0.25 µg/day)	Received IV or oral paricalcitol according to stratum	28 weeks: treatment 28 weeks; assessment 21–28 weeks	Primary endpoint: iPTH achieve 150–300 pg/ml Secondary endpoint: iPTH and calcium achieve 30 or 50% KDOQI reduction; FGF23, BSAP, phosphate and PTH; safety

Table 1 (continued)

Study name/first author, year	Trial registration	Country	Patients number (T/C)	Age (SD)	Female (%)	Treatment group (cinacalcet plus vitamin D)	Control group (vitamin D)	Treatment duration	Main outcome measures
Rodriguez et al., 2013	ClinicalTrials.gov NCT00803712; Eudract 2008-004558-34	Switzerland	304 (153/151)	T: 57.9 (13.6) C: 57.0 (14.6)	T: 45.8 C: 37.1	Cinacalcet plus amounts equivalent to 2 μg paricalcitol thrice weekly	Flexible doses of calcitriol	56 weeks: treatment 52 weeks; assessment 52/56 week	Calcium-regulated PTH release.
Kim et al., 2013 (CUPID)	ClinicalTrials.gov NCT01101113	Korea	66 (33/33)	T: 48.8 (11.5) C: 47.2 (8.4)	T: 39.4 C: 54.5	Cinacalcet (25–50 mg/day) plus vitamin D	Flexible doses of oral calcitriol	20 weeks: screening 4 weeks; titration 12 weeks; assessment 22–26/48–52 weeks	Primary endpoint: > 30% reduction of PTH Secondary endpoint: absolute or percent change of FGF23; KDOQI targets
Urena-Torres et al., 2013	Eudract 2008-004558-34	France	309 (154/155)	T: 57.9 (13.6) C: 57.0 (14.6)	T: 45.8 C: 37.1	Cinacalcet(30 mg/day and adjusted) plus low doses of vitamin D (IV: ≤ calcitriol 0.5 μg, doxercalciferol 1 μg or paricalcitol 2 μg per dialysis) or oral (calcitriol 0.25 μg/day, paricalcitol 1 μg/day, alfacalcidol 0.25 μg/day)	Flexible dose of active vitamin D	56 weeks: washout 4 weeks; titration 22 weeks; efficacy assessment 22–26/48–52 weeks.	Primary endpoint: > 30% reduction of PTH at 6 months Secondary endpoint: > 30% reduction of PTH at 12 months; targets for PTH, calcium, and phosphorus at 6 and 12 months; safety
Cozzolino et al., 2014 (IMPACT-SHPT)	ClinicalTrials.gov NCT00977080	IV stratum: USA Oral stratum: non-USA	IV stratum: 126 (64/62) Oral stratum: 142 (70/72)	IV stratum: T: 61.2 (12.7) C: 59.9 (12.0) Oral stratum: T: 65.7 (13.5) C:65.1 (12.5)	IV: T: 38.7 C: 40.6 Oral: T: 31.9 C: 38.6	Cinacalcet (30–180 mg/day) plus IV doxercalciferol 1 μg thrice weekly Cinacalcet (30–180 mg/day) plus oral alfacalcidol (0.25 μg/day)	Received IV or oral paricalcitol according to stratum	28 weeks: treatment 28 weeks; efficacy assessment 21–28 weeks	Changes in AP, BSAP and FGF-23 and the proportion of patients who achieved an iPTH level of 150–300 pg/ml during weeks 8, 16, and 21–28

CKD chronic kidney disease, *PTH* parathyroid hormone, *iPTH* intact PTH, *KDOQI* Kidney Disease Outcome Quality Initiative, *Ca* calcium, *P* phosphorus, *Ca* × *P* calcium × phosphorus product, *FGF23* fibroblast growth factor-23, *BSAP* bone-specific alkaline phosphatase, *IV* intravenous

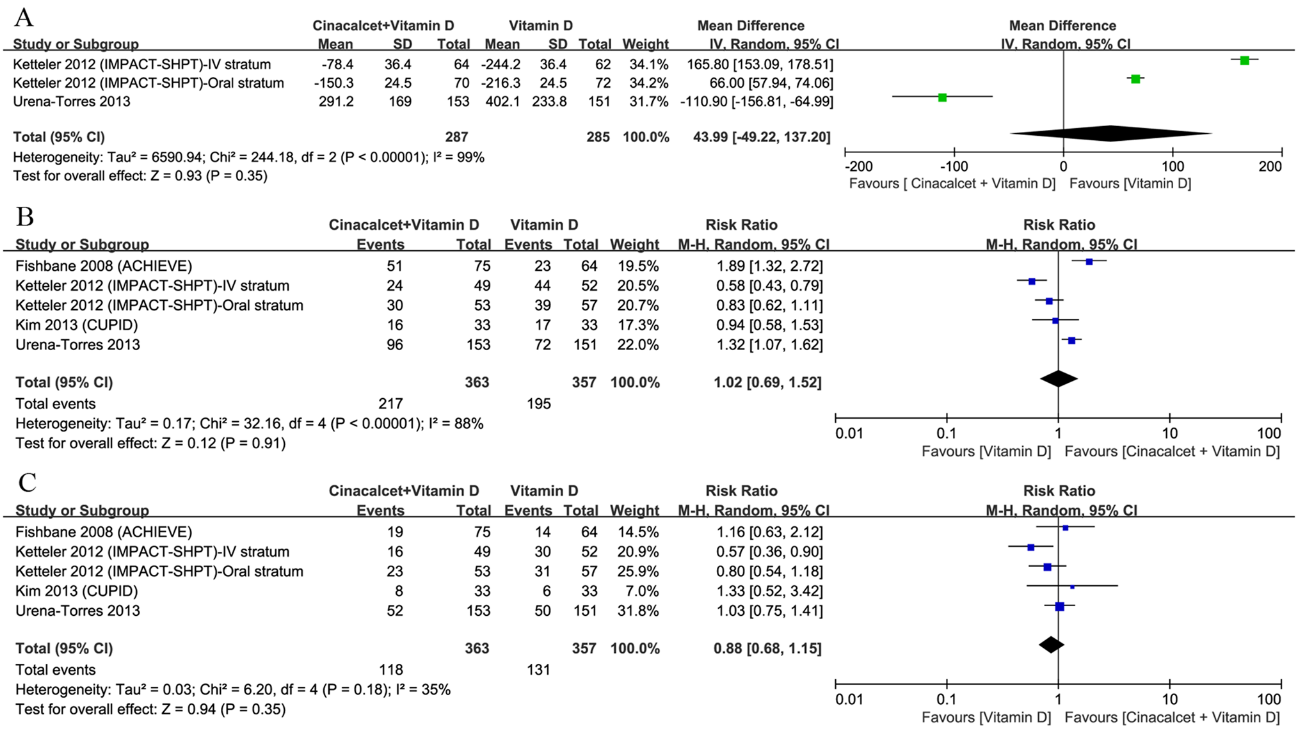


Fig. 2 Forest plots of patients treated with calcimimetic plus vitamin D versus vitamin D for serum PTH (**a**), ≥ 30% reduction in PTH (**b**), and PTH achieve 150–300 pg/ml (**c**)

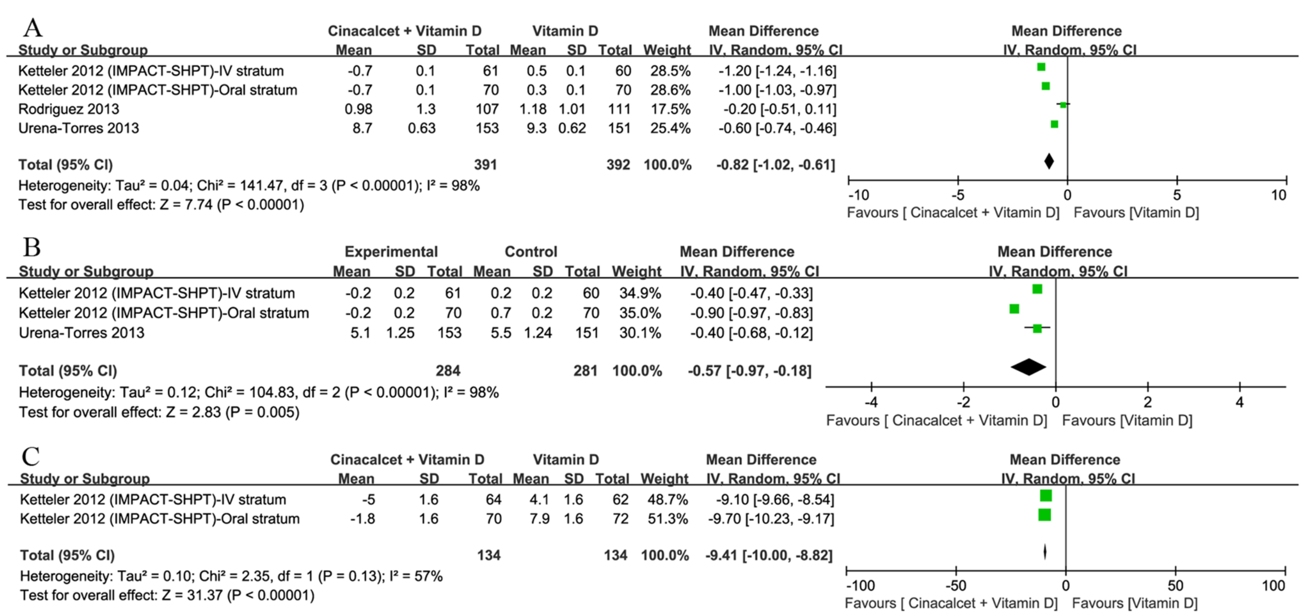


Fig. 3 Forest plots of patients treated with calcimimetic plus vitamin D versus vitamin D for serum calcium (**a**), phosphorus (**b**), and calcium × phosphorus product (**c**)

speaking, meta-regression analysis was usually performed to explore the heterogeneity between studies and at least ten studies were required. Whereas only a limited number of studies included, sensitivity analysis was conducted to check the stability of summary estimates and explore the potential sources of heterogeneity between studies. The pooled results showed that the removal of each study one by one in sensitivity analysis did not change the outcome of serum calcium, phosphorus, and calcium × phosphorus product.

Safety analyses

In terms of safety, five studies reported the adverse events [20, 22, 23, 25, 26]. Compared with vitamin D alone, cinacalcet plus vitamin D treatment had no significant difference in all adverse events (RR 1.02, 95% CI 0.97–1.08, $P=0.38$; Fig. 4a), all-cause mortality (RR 0.80, 95% CI 0.42–1.52, $P=0.49$; Fig. 4b), diarrhea (RR 1.16, 95% CI 0.73–1.85, $P=0.52$; Fig. 4e), muscle spasms (RR 1.12, 95% CI 0.66–1.92, $P=0.68$; Fig. 4f), and headache (RR 0.82, 95% CI 0.41–1.62, $P=0.56$; Fig. 4g), but increased the risk of hypocalcemia (RR 17.98, 95% CI 5.68–56.99, $P<0.001$; Fig. 4c) and nausea or vomiting (RR 3.47, 95% CI 2.25–5.35, $P<0.001$; Fig. 4d). Subjectively, the funnel plot for safety analyses was symmetric, as shown in the Supplementary Figure 3.

Due to the large heterogeneity between studies, we also performed subgroup analyses based on study design and clinical characteristics, including study sample size, duration of treatment, country, and mean age of patients. For the specific outcomes (≥ 30% reduction in PTH, PTH achieve 150–300 pg/ml, serum calcium, and phosphorus), sample size less than 150, the duration of treatment less than 30 weeks, the studies from Europe, and patients aged over 60 years might source the high heterogeneity between studies, as shown in Supplementary Table 1.

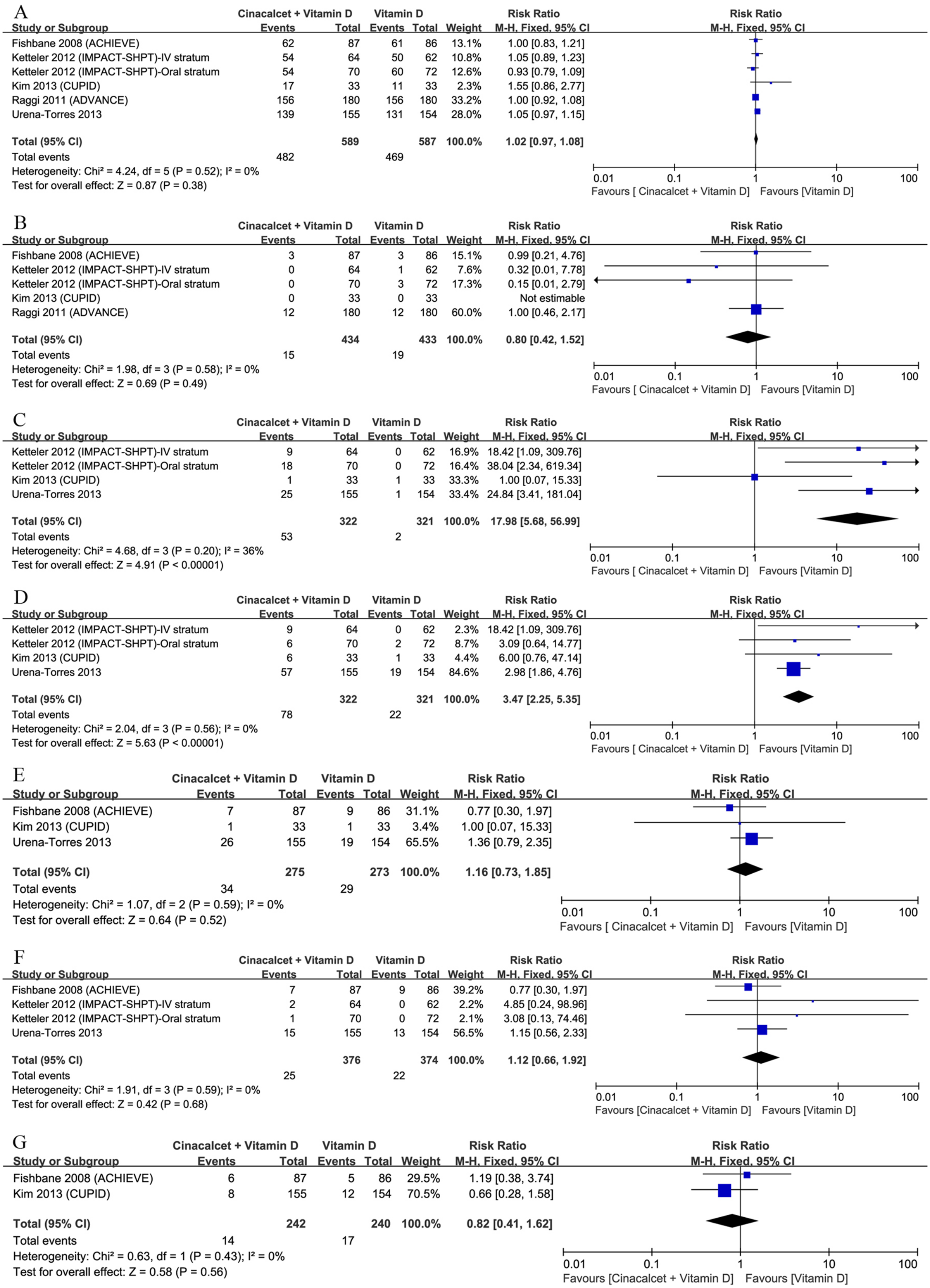
Discussion

Several published meta-analyses have explored the therapeutic effects of cinacalcet in the treatment of SHPT [10–14]. To our knowledge, this is the first meta-analysis evaluating the efficacy and safety of cinacalcet plus vitamin D therapy. The results indicated that relative to vitamin D alone, the combination use of cinacalcet and vitamin D had no difference in serum PTH, but significantly lowered serum calcium, phosphorus, and calcium × phosphorus product. Despite the risk of hypocalcemia and nausea or vomiting, cinacalcet plus vitamin D treatment did not increase the occurrence of all adverse events, all-cause mortality, diarrhea, muscle spasms, and headache. In agreement with our meta-analysis, Lee et al. [28] conducted a retrospective study to evaluate treatment with either low-dose calcitriol and cinacalcet or calcitriol alone in dialysis patients, and observed a significant decrease of serum calcium, phosphorus, and calcium phosphate product in the combination use of cinacalcet and calcitriol. Chertow et al. [29] also reported that treatment with cinacalcet and low-dose vitamin D sterols led to significant improvement of clinical symptoms in SHPT patients, including pain in the muscles, joints and bones, joint stiffness, dry and itchy skin, excessive thirst, and trouble with memory.

However, we did not observe a decrease in serum PTH, and percentage of ≥ 30% reduction in PTH and PTH achieve 150–300 pg/ml in patients treated with cinacalcet and vitamin D. Ketteler et al. [23] found that the proportion of subjects who had PTH values between 150 and 300 pg/ml was significantly greater, and mean PTH was lower in the paricalcitol group than cinacalcet plus vitamin D group in intravenous stratum, but had no significance difference in oral stratum. Conversely, Urena-Torres et al. [26] reported that PTH levels decreased obviously in patients treated with cinacalcet plus low-dose vitamin D treatment at both 6 months and 12 months. In direct comparison of cinacalcet and vitamin D as mono-therapy, Wetmore et al. [8] found similar modest reductions in PTH with either cinacalcet or vitamin D alone over 52 weeks of treatment. A recent RCT also evaluated the improvement of PTH levels and bone parameters by supplementing nutritional vitamin D (cholecalciferol) together with cinacalcet and active vitamin D analog (calcitriol) among severe SHPT patients, and reported that cholecalciferol additively reduced serum PTH levels more than cinacalcet plus calcitriol use [30]. Recently, a Bayesian network meta-analysis by Ye et al. [31] showed that paricalcitol therapy might be the most optimal regimen in controlling PTH levels for dialysis patients with SHPT, which was similar to our conclusion. Interestingly, a meta-analysis implied that higher initial level of creatinine was correlated to more pronounced reduction in PTH level [32].

The most common adverse events associated with cinacalcet were gastrointestinal symptoms, including nausea, vomiting, and diarrhea after taking cinacalcet. In this meta-analysis, cinacalcet plus vitamin D treatment had no significant difference in all adverse events, all-cause mortality, diarrhea, muscle spasms, and headache, but significantly increased the risk of hypocalcemia and nausea or vomiting. Cardiovascular disease is the main cause of death in patients with SHPT, and many studies had observed that supraphysiological dose of PTH increased endothelial expression of the inflammatory cytokine, and subsequently promoted to arterial plaque formation and vascular calcification [33]. Only the ADVANCE trial reported the cardiovascular events, and found that cinacalcet plus low-dose vitamin D may attenuate vascular and cardiac valve calcification in moderate-to-severe secondary hyperparathyroidism [22]. Recently, Wang et al. [10] performed a meta-analysis to assess the efficacy and safety of cinacalcet in patients with SHPT, and also demonstrated that cinacalcet increased the risk of hypocalcemia, nausea, vomiting, and diarrhea, whereas it did not increase all-cause and cardiovascular mortality.

The limitation of our meta-analysis still existed. First, the number of included studies was small. Due to the limited


A
Cinacalcet + Vitamin D
Vitamin D
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Fishbane 2008 (ACHIEVE) 62 87 61 86 13.1% 1.00 [0.83, 1.21]
Ketteler 2012 (IMPACT-SHPT)-IV stratum 54 64 50 62 10.8% 1.05 [0.89, 1.23]
Ketteler 2012 (IMPACT-SHPT)-Oral stratum 54 70 60 72 12.6% 0.93 [0.79, 1.09]
Kim 2013 (CUPID) 17 33 11 33 2.3% 1.55 [0.86, 2.77]
Raggi 2011 (ADVANCE) 156 180 156 180 33.2% 1.00 [0.92, 1.08]
Urena-Torres 2013 139 155 131 154 28.0% 1.05 [0.97, 1.15]
Total (95% CI) 589 587 100.0% 1.02 [0.97, 1.08]
Total events 482 469
Heterogeneity: Chi² = 4.24, df = 5 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.87 (P = 0.38)
0.01 0.1 1 10 100
Favours [Cinacalcet + Vitamin D] Favours [Vitamin D]
B
Cinacalcet + Vitamin D
Vitamin D
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Fishbane 2008 (ACHIEVE) 3 87 3 86 15.1% 0.99 [0.21, 4.76]
Ketteler 2012 (IMPACT-SHPT)-IV stratum 0 64 1 62 7.6% 0.32 [0.01, 7.78]
Ketteler 2012 (IMPACT-SHPT)-Oral stratum 0 70 3 72 17.3% 0.15 [0.01, 2.79]
Kim 2013 (CUPID) 0 33 0 33 Not estimable
Raggi 2011 (ADVANCE) 12 180 12 180 60.0% 1.00 [0.46, 2.17]
Total (95% CI) 434 433 100.0% 0.80 [0.42, 1.52]
Total events 15 19
Heterogeneity: Chi² = 1.98, df = 3 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)
0.01 0.1 1 10 100
Favours [Cinacalcet + Vitamin D] Favours [Vitamin D]
C
Cinacalcet + Vitamin D
Vitamin D
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Ketteler 2012 (IMPACT-SHPT)-IV stratum 9 64 0 62 16.9% 18.42 [1.09, 309.76]
Ketteler 2012 (IMPACT-SHPT)-Oral stratum 18 70 0 72 16.4% 38.04 [2.34, 619.34]
Kim 2013 (CUPID) 1 33 1 33 33.3% 1.00 [0.07, 15.33]
Urena-Torres 2013 25 155 1 154 33.4% 24.84 [3.41, 181.04]
Total (95% CI) 322 321 100.0% 17.98 [5.68, 56.99]
Total events 53 2
Heterogeneity: Chi² = 4.68, df = 3 (P = 0.20); I² = 36%
Test for overall effect: Z = 4.91 (P < 0.00001)
0.01 0.1 1 10 100
Favours [Cinacalcet + Vitamin D] Favours [Vitamin D]
D
Cinacalcet + Vitamin D
Vitamin D
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Ketteler 2012 (IMPACT-SHPT)-IV stratum 9 64 0 62 2.3% 18.42 [1.09, 309.76]
Ketteler 2012 (IMPACT-SHPT)-Oral stratum 6 70 2 72 8.7% 3.09 [0.64, 14.77]
Kim 2013 (CUPID) 6 33 1 33 4.4% 6.00 [0.76, 47.14]
Urena-Torres 2013 57 155 19 154 84.6% 2.98 [1.86, 4.76]
Total (95% CI) 322 321 100.0% 3.47 [2.25, 5.35]
Total events 78 22
Heterogeneity: Chi² = 2.04, df = 3 (P = 0.56); I² = 0%
Test for overall effect: Z = 5.63 (P < 0.00001)
0.01 0.1 1 10 100
Favours [Cinacalcet + Vitamin D] Favours [Vitamin D]
E
Cinacalcet + Vitamin D
Vitamin D
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Fishbane 2008 (ACHIEVE) 7 87 9 86 31.1% 0.77 [0.30, 1.97]
Kim 2013 (CUPID) 1 33 1 33 3.4% 1.00 [0.07, 15.33]
Urena-Torres 2013 26 155 19 154 65.5% 1.36 [0.79, 2.35]
Total (95% CI) 275 273 100.0% 1.16 [0.73, 1.85]
Total events 34 29
Heterogeneity: Chi² = 1.07, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.64 (P = 0.52)
0.01 0.1 1 10 100
Favours [Cinacalcet + Vitamin D] Favours [Vitamin D]
F
Cinacalcet + Vitamin D
Vitamin D
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Fishbane 2008 (ACHIEVE) 7 87 9 86 39.2% 0.77 [0.30, 1.97]
Ketteler 2012 (IMPACT-SHPT)-IV stratum 2 64 0 62 2.2% 4.85 [0.24, 98.96]
Ketteler 2012 (IMPACT-SHPT)-Oral stratum 1 70 0 72 2.1% 3.08 [0.13, 74.46]
Urena-Torres 2013 15 155 13 154 56.5% 1.15 [0.56, 2.33]
Total (95% CI) 376 374 100.0% 1.12 [0.66, 1.92]
Total events 25 22
Heterogeneity: Chi² = 1.91, df = 3 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.42 (P = 0.68)
0.01 0.1 1 10 100
Favours [Cinacalcet + Vitamin D] Favours [Vitamin D]
G
Cinacalcet + Vitamin D
Vitamin D
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Fishbane 2008 (ACHIEVE) 6 87 5 86 29.5% 1.19 [0.38, 3.74]
Kim 2013 (CUPID) 8 155 12 154 70.5% 0.66 [0.28, 1.58]
Total (95% CI) 242 240 100.0% 0.82 [0.41, 1.62]
Total events 14 17
Heterogeneity: Chi² = 0.63, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)
0.01 0.1 1 10 100
Favours [Cinacalcet + Vitamin D] Favours [Vitamin D]

◂**Fig. 4** Forest plot of patients treated with calcimimetic plus vitamin D versus vitamin D for all adverse events (**a**), all-cause mortality (**b**), hypocalcemia (**c**), nausea/vomiting (**d**), diarrhea (**e**), muscle spasms (**f**), and headache (**g**)

number of current studies, the high heterogeneity between studies did not explain well according to sensitivity and subgroup analyses. Second, all these trials were short-term (28–56 weeks), and thus, the long-term effects of cinacalcet plus vitamin D were not yet clear. Third, several studies had not clearly reported the data about cinacalcet dose and PTH change level, and thus, dose–response could not be carried out at present.

In conclusion, the results of this meta-analysis indicated that relative to vitamin D alone, the combination use of cinacalcet and vitamin D significantly lowered serum calcium, phosphorus, and the calcium × phosphorus product, and did not increase the risk of all adverse events, all-cause mortality, diarrhea, muscle spasms, and headache, whereas had no effect on serum PTH and increased the risk of hypocalcemia and nausea or vomiting. Future studies are needed to assess the effects of cinacalcet plus vitamin D on PTH level, cardiovascular events, and other clinical outcomes in larger samples with longer durations.

Financial support and sponsorship None.

Compliance with ethical standards

Conflict of interest There are no conflicts of interest.

References

1. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G (2003) National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 139(2):137–147
2. Fukagawa M, Kido R, Komaba H, Onishi Y, Yamaguchi T, Hasegawa T, Kurita N, Fukuma S, Akizawa T, Fukuhara S (2014) Abnormal mineral metabolism and mortality in hemodialysis patients with secondary hyperparathyroidism: evidence from marginal structural models used to adjust for time-dependent confounding. Am J Kidney Dis 63(6):979–987
3. Wheeler DC, London GM, Parfrey PS, Block GA, Correa-Rotter R, Dehmel B, Drueke TB, Floege J, Kubo Y, Mahaffey KW et al (2014) Effects of cinacalcet on atherosclerotic and nonatherosclerotic cardiovascular events in patients receiving hemodialysis: the EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events (EVOLVE) trial. J Am Heart Assoc 3(6):e001363
4. Dhanwal DK, Sahoo S, Gautam VK, Saha R (2013) Hip fracture patients in India have vitamin D deficiency and secondary hyperparathyroidism. Osteoporos Int 24(2):553–557
5. Sprague SM, Silva AL, Al-Saghir F, Damle R, Tabash SP, Petkovich M, Messner EJ, White JA, Melnick JZ, Bishop CW (2014) Modified-release calcifediol effectively controls secondary hyperparathyroidism associated with vitamin D insufficiency in chronic kidney disease. Am J Nephrol 40(6):535–545
6. Zheng JQ, Hou YC, Zheng CM, Lu CL, Liu WC, Wu CC, Huang MT, Lin YF, Lu KC (2016) Cholecalciferol additively reduces serum parathyroid hormone and increases vitamin D and cathelicidin levels in paricalcitol-treated secondary hyperparathyroid hemodialysis patients. Nutrients 8(11):E708
7. Thadhani R, Zella JB, Knutson DC, Blaser WJ, Plum LA, Clagett-Dame M, Buck RD, DeLuca HF (2017) 2MD (DP001), a single agent in the management of hemodialysis patients: a randomized trial. Am J Nephrol 45(1):40–48
8. Wetmore JB, Gurevich K, Sprague S, Da Roza G, Buerkert J, Reiner M, Goodman W, Cooper K (2015) A randomized trial of cinacalcet versus vitamin d analogs as monotherapy in secondary hyperparathyroidism (PARADIGM). Clin J Am Soc Nephrol 10(6):1031–1040
9. Sumida K, Nakamura M, Ubara Y, Marui Y, Tanaka K, Takaichi K, Tomikawa S, Inoshita N, Ohashi K (2013) Cinacalcet upregulates calcium-sensing receptors of parathyroid glands in hemodialysis patients. Am J Nephrol 37(5):405–412
10. Wang GQ, Liu HY, Wang CZ, Ji XJ, Gu WJ, Mu YM (2018) Cinacalcet versus Placebo for secondary hyperparathyroidism in chronic kidney disease patients: a meta-analysis of randomized controlled trials and trial sequential analysis. Sci Rep 8:3111
11. Ballinger Angela E, Palmer Suetonia C, Nistor I, Craig Jonathan C, Strippoli Giovanni FM (2014) Calcimimetics for secondary hyperparathyroidism in chronic kidney disease patients. Cochrane Database of Systematic Reviews. Wiley, New York
12. Zhang Q, Li M, You L, Li H, Ni L, Gu Y, Hao C, Chen J (2012) Effects and safety of calcimimetics in end stage renal disease patients with secondary hyperparathyroidism: a meta-analysis. PLoS One 7(10):e48070
13. Greeviroj P, Kitrungphaiboon T, Katavetin P, Praditpornsilpa K, Eiam-Ong S, Jaber B, Susantitaphong P (2018) Cinacalcet for treatment of chronic kidney disease-mineral and bone disorder: a meta-analysis of randomized controlled trials. Nephron 139(3):197–210
14. Sekercioglu N, Busse J, Sekercioglu M, Agarwal A, Shaikh S, Lopes L, Mustafa R, Guyatt G, Thabane L (2016) Cinacalcet versus standard treatment for chronic kidney disease: a systematic review and meta-analysis. Ren Fail 38(6):857–874
15. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6(7):e1000097
16. Robertson C, Ramsay C, Gurung T, Mowatt G, Pickard R, Sharma P (2014) Practicalities of using a modified version of the Cochrane Collaboration risk of bias tool for randomised and non-randomised study designs applied in a health technology assessment setting. Res Synth Methods 5(3):200–211
17. Wan X, Wang W, Liu J, Tong T (2014) Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 14:135
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ (Clin Res Ed) 327(7414):557–560
19. Thorlund K, Wetterslev J, Awad T, Thabane L, Gluud C (2011) Comparison of statistical inferences from the DerSimonian–Laird and alternative random-effects model meta-analyses—an empirical assessment of 920 Cochrane primary outcome meta-analyses. Res Synth Methods 2(4):238–253
20. Fishbane S, Shapiro WB, Corry DB, Vicks SL, Roppolo M, Rappaport K, Ling X, Goodman WG, Turner S, Charytan C (2008) Cinacalcet HCl and concurrent low-dose vitamin D improves treatment of secondary hyperparathyroidism in dialysis patients

compared with vitamin D alone: the ACHIEVE study results. Clin J Am Soc Nephrol 3(6):1718–1725
21. Wetmore JB, Liu S, Krebill R, Menard R, Quarles LD (2010) Effects of cinacalcet and concurrent low-dose vitamin D on FGF23 levels in ESRD. Clin J Am Soc Nephrol 5(1):110–116
22. Raggi P, Chertow GM, Torres PU, Csiky B, Naso A, Nossuli K, Moustafa M, Goodman WG, Lopez N, Downey G et al (2011) The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. Nephrol Dial Transplant 26(4):1327–1339
23. Ketteler M, Martin KJ, Cozzolino M, Goldsmith D, Sharma A, Khan S, Dumas E, Amdahl M, Marx S, Audhya P (2012) Paricalcitol versus cinacalcet plus low-dose vitamin D for the treatment of secondary hyperparathyroidism in patients receiving haemodialysis: study design and baseline characteristics of the IMPACT SHPT study. Nephrol Dial Transplant 27(5):1942–1949
24. Rodriguez M, Urena-Torres P, Petavy F, Cooper K, Farouk M, Goodman WG (2013) Calcium-mediated parathyroid hormone suppression to assess progression of secondary hyperparathyroidism during treatment among incident dialysis patients. J Clin Endocrinol Metab 98(2):618–625
25. Kim HJ, Kim H, Shin N, Na KY, Kim YL, Kim D, Chang JH, Song YR, Hwang YH, Kim YS et al (2013) Cinacalcet lowering of serum fibroblast growth factor-23 concentration may be independent from serum Ca, P, PTH and dose of active vitamin D in peritoneal dialysis patients: a randomized controlled study. BMC Nephrol 14:112
26. Urena-Torres P, Bridges I, Christiano C, Cournoyer SH, Cooper K, Farouk M, Kopyt NP, Rodriguez M, Zehnder D, Covic A (2013) Efficacy of cinacalcet with low-dose vitamin D in incident haemodialysis subjects with secondary hyperparathyroidism. Nephrol Dial Transplant 28(5):1241–1254
27. Cozzolino M, Ketteler M, Martin KJ, Sharma A, Goldsmith D, Khan S (2014) Paricalcitol- or cinacalcet-centred therapy affects markers of bone mineral disease in patients with secondary hyperparathyroidism receiving haemodialysis: results of the IMPACT-SHPT study. Nephrol Dial Transplant 29(4):899–905
28. Lee YT, Ng HY, Kuo CC, Chen TC, Wu CS, Chiu TT, Lee WC, Lee CT (2013) Comparison between calcitriol and calcitriol plus low-dose cinacalcet for the treatment of moderate to severe secondary hyperparathyroidism in chronic dialysis patients. Nutrients 5(4):1336–1348
29. Chertow GM, Lu ZJ, Xu X, Knight TG, Goodman WG, Bushinsky DA, Block GA (2012) Self-reported symptoms in patients on hemodialysis with moderate to severe secondary hyperparathyroidism receiving combined therapy with cinacalcet and low-dose vitamin D sterols. Hemodial Int Symp Home Hemodial 16(2):188–197
30. Zheng CM, Wu CC (2018) Cholecalciferol additively reduces serum parathyroid hormone levels in severe secondary hyperparathyroidism treated with calcitriol and cinacalcet among hemodialysis patients. Nutrients 10(2):E196
31. Ye H, Ye P, Zhang Z, Hou A, Liang Z, Kong Y (2019) A Bayesian network analysis on comparative efficacy of treatment strategies for dialysis patients with secondary hyperparathyroidism. Exp Ther Med 17(1):531–540
32. Cohen JB, Gordon CE, Balk EM, Francis JM (2012) Cinacalcet for the treatment of hyperparathyroidism in kidney transplant recipients: a systematic review and meta-analysis. Transplantation 94(10):1041–1048
33. Rashid G, Bernheim J, Green J, Benchetrit S (2007) Parathyroid hormone stimulates endothelial expression of atherosclerotic parameters through protein kinase pathways. Am J Physiol Ren Physiol 292(4):F1215–F1218

Affiliations

Jun Xu[1,2] · Yan Yang[1] · Liang Ma[1] · Ping Fu[1] · Hongying Peng[2]

✉ Ping Fu
fupinghx@scu.edu.cn

✉ Hongying Peng
penghongying168@126.com

1 Division of Nephrology and National Clinical Research Center for Geriatrics, Kidney Research Institute, West China Hospital of Sichuan University, Chengdu 610041, Sichuan, China

2 Department of Nephrotic Rheumatism, The Affiliated Baiyun Hospital of Guizhou Medical University, Guiyang 550014, China