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The impact of cinacalcet on the serum phosphorus, calcium and PTH levels in dialysis patients; a systematic review and meta-analysis

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ABSTRACT

Introduction: Cinacalcet is a medication prescribed to manage hypercalcemia and hyperparathyroidism in patients with chronic kidney diseases. The present study aims to evaluate the impact of cinacalcet on serum levels of calcium, phosphorus, and parathyroid hormone (PTH) in patients undergoing dialysis using a systematic review and meta-analysis approach.

Materials and Methods: This study was conducted based on the PRISMA guidelines. A literature search without time restriction was performed on international databases, including Cochrane, Web of Science, Scopus, and PubMed. Data were analyzed using STATA 14 software at a significance level of $P<0.05$ for all tests.

Results: The present meta-analysis involved twelve studies with a sample size of 1131 patients. A reduction was noted in the serum levels of calcium [SMD: -1.32 (95% CI: -2.64, -0.01)], PTH [SMD: -3.95 (95% CI: -6.53, -1.37)], phosphorus [SMD: -1.61 (95% CI: -3.01, -0.20)] and Ca×P [SMD: -5.33 (95% CI: -10.16, -0.49)] after cinacalcet use in dialysis patients. However, the variations in serum levels of alkaline phosphatase were non-significant [SMD: -0.09 (95% CI: -0.94, 0.77)]. In addition, the effectiveness of cinacalcet use on calcium serum level reduction in dialysis patients was verified at a daily dose of 30-60 mg [SMD: -0.83 (95% CI: -1.25, -0.42)] and consumption duration of 24 months [SMD: -1.26 (95% CI: -1.66, -0.87)].

Conclusion: The administration of cinacalcet significantly decreased the serum calcium, phosphorous, PTH, and Ca×P product in dialysis patients. The lowest and highest effects of cinacalcet were found for calcium and Ca×P products, respectively. The prescription of this drug appears more effective in improving hypercalcemia in dialysis patients.

Registration: This investigation has been conducted in accordance with the PRISMA checklist, and its protocol was registered on the PROSPERO platform (ID: CRD42023428774).

Implication for health policy/practice/research/medical education:
Our meta-analysis was conducted on 1131 people and showed that administration of cinacalcet can lower serum calcium, phosphorus, Ca×P products, and PTH in dialysis patients. Hence, one can infer the effectiveness of cinacalcet in treating hypercalcemia and hyperparathyroidism in these patients. Considering the findings of the present meta-analysis, cinacalcet administration at a daily dose of 30-60 mg for two years seems beneficial for dialysis patients with hypercalcemia. However, further research is required to confirm its efficacy for hemodialysis patients.

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Meta-analysis

Introduction

Cinacalcet is a positive allosteric modulator of the calcium-sensing receptor (CaSR), which enhances the CaSR sensitivity in parathyroid glands, thereby diminishing the release of parathyroid hormone (PTH) and calcium serum level (1). This drug is frequently administered in dialysis patients to treat hyperparathyroidism-induced hypercalcemia and is consistently found to lower the risk of persistent hyperparathyroidism in hemodialysis patients (2). Cinacalcet use for 52 weeks is reported elsewhere to

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control the patients' hypercalcemia (3).

The cinacalcet prescription is approved for primary and secondary hyperparathyroidism (4). In 2014, cinacalcet received approval in Japan to treat hypercalcemia in cases of parathyroid carcinoma and patients with primary hyperparathyroidism (PHPT) who have a contraindication for parathyroidectomy or have experienced post-operative PHPT recurrence (5). The treatment in patients with PHPT is intended to normalize the serum calcium and PTH levels while ameliorating the clinical manifestations (6,7). Secondary hyperparathyroidism occurs due to reduced kidney function in chronic kidney disease and is characterized by elevated serum PTH levels (8). It is present at varying degrees during the dialysis treatment and may manifest as hypercalcemia in the post-kidney transplant period (9). The overproduction of PTH contributes to a systemic disorder characterized by high bone turnover and vascular calcification and elevates the risk of bone fractures and cardiovascular mortality (10,11). Controlling their serum levels of calcium, phosphorus, and PTH is of critical significance concerning the morbidity and risks of hypercalcemia and hyperparathyroidism in patients undergoing dialysis and hemodialysis. Given the inconsistencies in the previous studies regarding the effectiveness of cinacalcet use for dialysis and hemodialysis patients (2,12-14).

Objectives

This study aims to evaluate the impact of cinacalcet on calcium, phosphorus, and PTH serum levels in these patients using a systematic review and meta-analysis approach.

Materials and Methods

Study design

The current study comprised a systematic review and meta-analysis carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol was registered on the PROSPERO website (ID: CRD42023428774).

Search strategy

International databases such as Cochrane, Web of Science, Scopus, and PubMed were searched without any time restriction to identify pertinent articles. The search query was formulated using established keywords and the subsequent MeSH terms:

"Cinacalcet," "Sensipar," "AMG 073," "Dialysis," "Dialyses," "Hemodialysis," "Renal dialysis," "Calcium," "Parathyroid hormone," "PTH (1-84)," "Phosphorus".

An advanced search was executed by combining the keywords using Boolean operators (OR, AND). Moreover, the reference lists of the identified articles and the Google Scholar search engine were searched to retrieve additional articles. The literature search was updated until April 2023. The search strategy used in Web of Science was as follows: Cinacalcet OR Sensipar OR AMG 073 (Topic) AND Dialysis OR Dialyses OR Hemodialysis OR Renal dialysis (Topic) AND Calcium OR Hypercalcemia OR Parathyroid hormone OR PTH (1-84) OR Phosphorus (Topic).

PICO components

- Population: studies whose participants were dialysis patients.
- Intervention: cinacalcet use.
- Comparison: receiving placebo or other drugs such as vitamin D.
- Outcomes: serum levels of calcium, phosphorus, PTH, alkaline phosphatase, and Ca×P product.

Inclusion criteria

Cohort studies and clinical trials evaluating the efficacy of cinacalcet on serum levels of calcium, phosphorus, or PTH in dialysis patients entered the study.

Exclusion criteria

The following studies were excluded; duplicate studies, studies whose full texts were unavailable, case reports, descriptive studies, studies lacking the necessary information for data analysis, letters to editors, studies assessing the effect of the combination of cinacalcet with another drug, low-quality articles, studies reporting the results using odds ratio (OR) or relative risk (RR) indices, and studies that only reported the mean serum levels of the outcomes without providing their standard deviations.

Qualitative assessment

Two independent authors assessed the quality of the retrieved articles according to the type of the studies. The quality of cohort studies was evaluated using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (15). This checklist contains 22 items, yielding a total score ranging from 0 to 44. A cut-off score of 16 for the STROBE checklist was considered in this study. Likewise, the Cochrane Institute checklist was utilized for the quality assessment of clinical trials (16). The Cochrane checklist consists of seven items, each assessing a major dimension or type of bias in clinical trials. Each item consists of three choices: "Low risk," "High risk," and "Unclear risk." Finally, the inter-researcher inconsistencies regarding the quality of a study were resolved by consensus between the two authors on a single choice.

Data extraction

Two researchers extracted the required data to minimize data collection bias and error. The authors designed a checklist for data collection containing the name of the leading author, publication year, country, age of patients, sample size, the number of males and females, study

type, disease type, cinacalcet dose, duration of cinacalcet use, and the mean levels of outcomes pre-and post-intervention.

Statistical analysis

Given the quantitative nature of the outcomes, the effect size for intervention was measured. The standardized mean difference (SMD) index indicates the strength of the association between the intervention of interest and the studied outcome. The studies examined were pooled using sample sizes, means, and standard deviations. The I^2 index was employed to measure the heterogeneity of the studies. Considering the high heterogeneity among the studies, a random effect model was applied. Data analysis was conducted using STATA 14 software at a significance level of $P<0.05$ for all tests.

Results

A total of 1430 articles were retrieved during the search process. After checking the titles, 774 duplicates were eliminated. The abstracts of the remaining 656 articles were screened, and 175 irrelevant articles were omitted. Of the remaining 481 articles, the full texts of twelve were unavailable, and another 457 were discarded due to meeting other exclusion criteria. Eventually, twelve high-quality articles entered the meta-analysis process (Figure 1).

Three of the twelve reviewed studies were conducted in the US, three in Spain, and one each in Brazil, Japan, Russia, Italy, Portugal, and the Netherlands. Among them, seven were cohort studies, and five were randomized controlled trials (RCTs) (Table 1).

The serum calcium level showed a significant reduction in patients on dialysis after cinacalcet treatment [SMD: -1.32 (95% CI: -2.64, -0.01)] (Figure 2).

Cinacalcet had a statistically significant effect on reducing the serum levels of PTH [SMD: -3.95 (95% CI: -6.53, -1.37)] (Figure 3) and phosphorus [SMD: -1.61 (95% CI: -3.01, -0.20)] in dialysis patients (Figure 4).

Ca×P product dropped in dialysis patients after cinacalcet use [SMD: -5.33 (95% CI: -10.16, -0.49)] (Figure 5). However, serum level variations of alkaline phosphatase were statistically non-significant [SMD: -0.09 (95% CI: -0.94, 0.77)] (Figure 6).

In sub-group analysis, the effectiveness of cinacalcet in lowering the serum calcium level in dialysis patients was verified at a daily dose of 30 to 60 mg [SMD: -0.83 (95% CI: -1.25, -0.42)]. In addition, the patients who were administered cinacalcet for a duration of 24 months had a significantly reduced calcium level [SMD: -1.26 (95% CI: -1.66, -0.87)]. In an analysis by disease type, cinacalcet use in dialysis patients noticeably affected their calcium levels [SMD: -0.83 (95% CI: -1.19, -0.47)]. However, this was not the case in hemodialysis patients. Significant changes were not reported in other subgroups analyzed (Table 2).

As presented in Figure 7, the publication bias plot

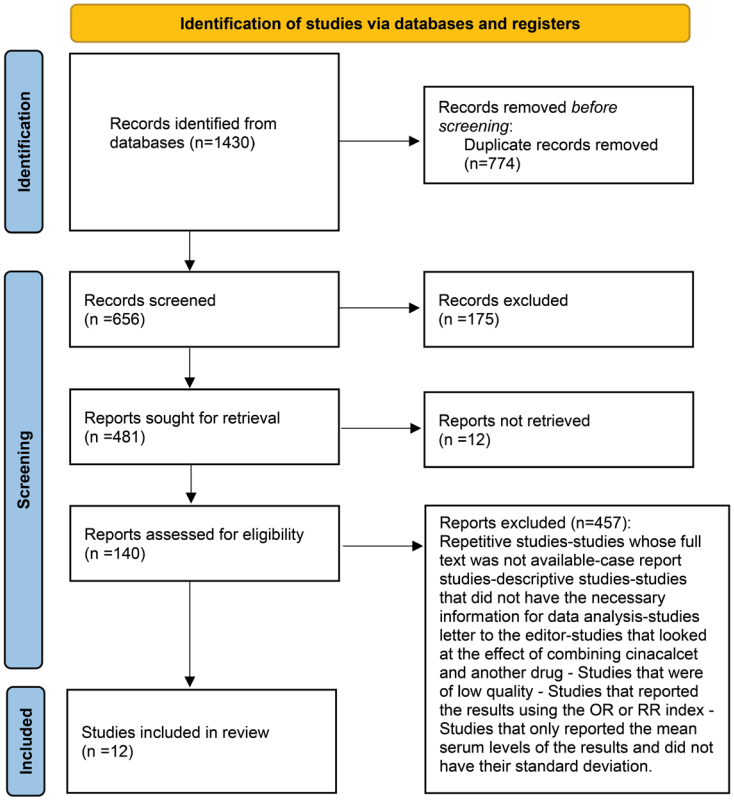

Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Table 1. Summary of article information

Author, year of publication	Country	Type of study	Sample size	Number of females	Number of males	Mean age (year)	Type of disease	Time of treatment	Dose of cinacalcet
Moe SM, 2005 (14)	USA	RCT	59	26	33	51	Dialysis	24 Months	30 mg/d
Fukagawa M, 2008 (17)	Japan	RCT	72	32	40	54.7	Dialysis	14 Weeks	25 mg/d
Valle C, 2008 (18)	Spain	Cohort	9	4	5	49	Hemodialysis	2 Months	30 mg/d
Block GA, 2004 (2)	Spain	RCT	371	145	226	54	Hemodialysis	13-26 Weeks	From 30 mg to 180 mg
Bucharles SG, 2019 (19)	Brazil	Cohort	26	14	12	52	Dialysis	12 Months	30 mg/d
Wetmore JB, 2015 (20)	Russia	Cohort	155	62	93	53	Hemodialysis	12 Months	30 mg/d
Zawierucha J, 2019 (12)	Poland	Cohort	50	19	31	63	Hemodialysis	12 Months	NR
Lindberg JS, 2005 (13)	USA	RCT	294	113	181	51.8	Hemodialysis	26 Weeks	From 30 to 180 mg
Silverstein DM, 2008 (21)	USA	RCT	9	NR	NR	14.5	Both	3 Months	30 to 120 mg
Conde SQ, 2017 (22)	Portugal	Cohort	27	12	15	46.3	Dialysis	6 Months	45 mg/d
Fusaro M, 2011 (23)	Italy	Cohort	5	NR	NR	65.9	Dialysis	12 Months	212.6 mg/wk
Portolés J, 2012 (24)	Spain	Cohort	54	21	33	51.3	Dialysis	12 Months	30 mg/d

NR: Not report.

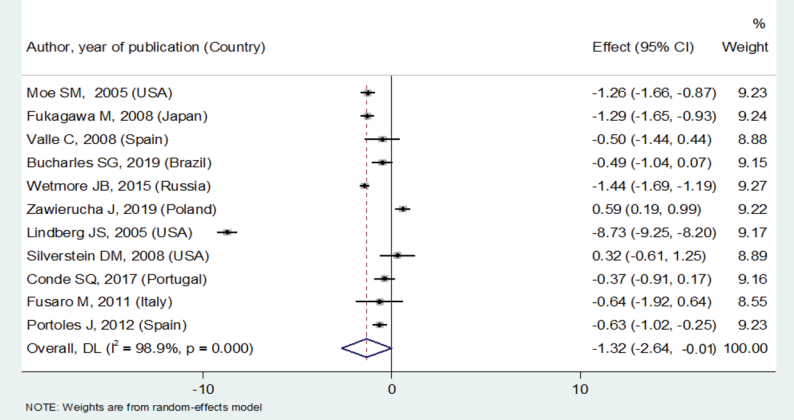

Figure 2. Forest plot showing calcium level changes after the administration of cinacalcet.

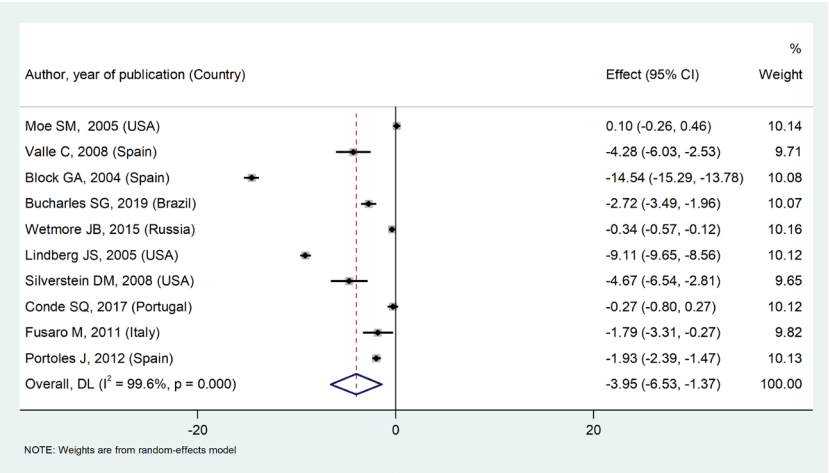

Figure 3. Forest plot showing parathyroid hormone level changes after the administration of cinacalcet.

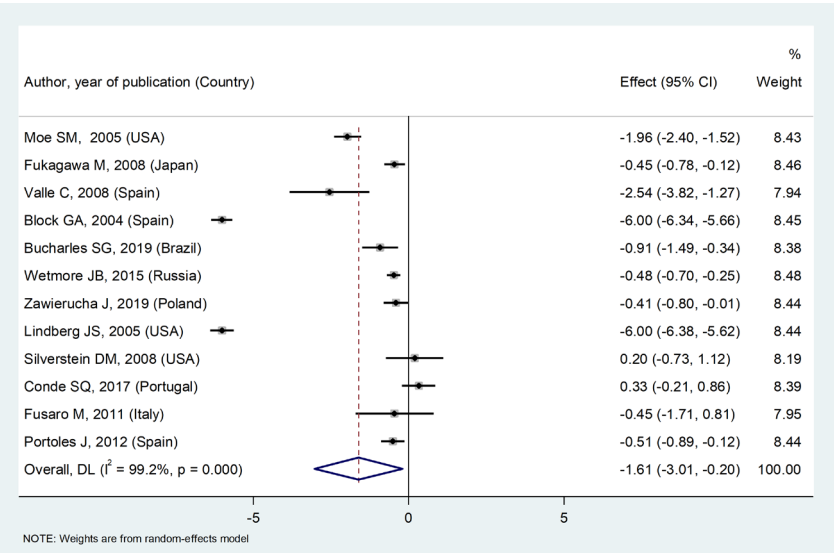

Figure 4. Forest plot showing phosphorus level changes after the administration of cinacalcet.

Table 2. The effect of cinacalcet on serum calcium level, based on different subgroups

Subgroups		SMD	Low limit	Up limit	*P* value	I^2 (%)
Type of study	RCT	-2.75	-6.33	0.83	<0.001	99.5
	Cohort	-0.49	-1.14	0.15	<0.001	92.1
Time of treatment (month)	≤6	-2.12	-5.54	1.29	<0.001	99.4
	12	-0.52	-1.36	0.32	<0.001	94.5
	24	-1.26	-1.66	-0.87	-	0
Type of disease	Dialysis	-0.83	-1.19	-0.47	0.008	67.9
	Hemodialysis	-2.52	-6.16	1.12	<0.001	99.6
Dose of cinacalcet (mg/d)	30-60	-0.83	-1.25	-0.42	<0.001	80.9
	Other	-2.60	-7.11	1.92	<0.001	99.5

was statistically non-significant, and no bias occurred during the literature search (*P* =0.954). Consequently, the literature search process was carried out thoroughly and successfully.

Discussion

Overall, the study results suggest that cinacalcet use causes a reduction in serum calcium, phosphorus, Ca×P product, and PTH levels in dialysis patients. A sub-group analysis also confirmed the cinacalcet efficacy in lowering the calcium levels of patients at a dose of 30-60 mg/day and a duration of 24 months.

Chandran et al conducted a meta-analysis of RCTs, including 940 patients with PHPT. They found that cinacalcet administration for up to 28 weeks decreases serum calcium levels compared to placebo [RR: 20 (95% CI: 6.04-68.52)]. Additionally, serum PTH levels declined following two weeks and up to 28 weeks of cinacalcet treatment. Similarly, the cohort studies revealed the normalization of the serum calcium levels in 76% of patients regardless of treatment length (25). In a meta-analysis by Greeviroj et al with 10031 dialysis patients, cinacalcet treatment reduced serum calcium, phosphate, and PTH levels. However, the osteogenesis biomarkers (bone alkaline phosphatase and osteocalcin) remained unchanged (26). The results of the above studies corroborate those of the present meta-analysis.

According to a meta-analysis by Ng et al involving 28

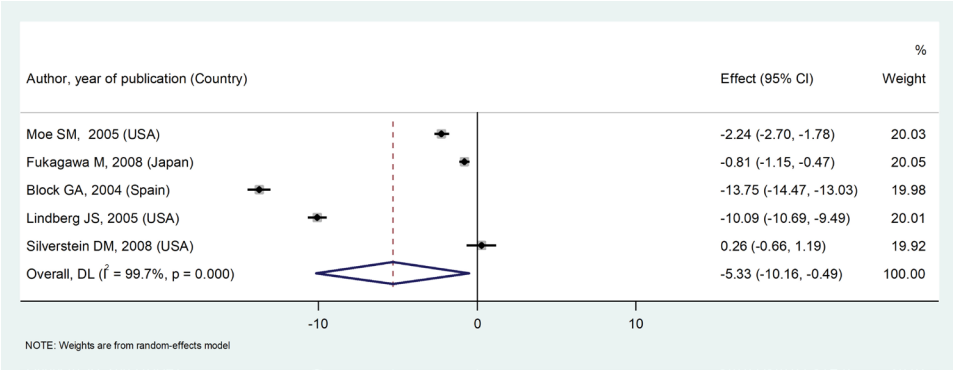

Figure 5. Forest plot showing Ca×P product changes after the administration of cinacalcet.

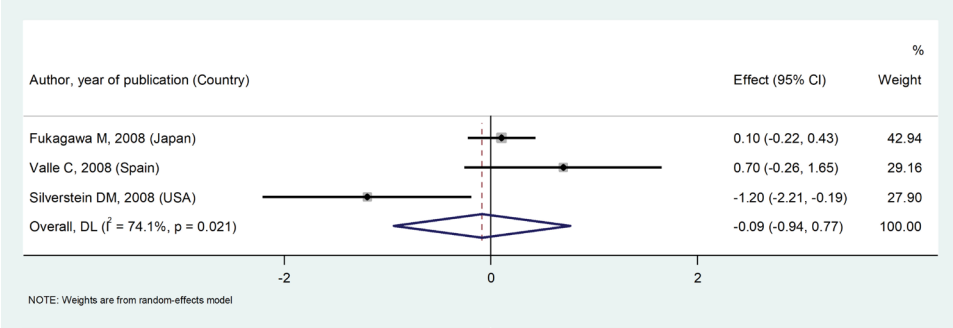

Figure 6. Forest plot showing alkaline phosphatase level changes after the administration of cinacalcet.

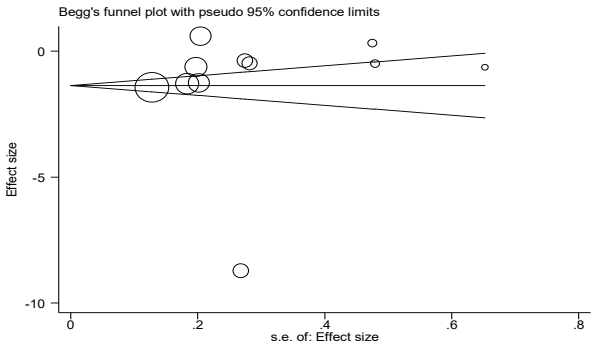

Figure 7. Publication bias.

studies on patients with PHPT, the serum calcium and PTH levels decreased significantly (calcium, weight mean difference (WMD): 1.64, 95% CI: −1.92, −1.37; PTH, WMD: −31.21, 95% CI: −41.67, −20.76). In contrast, phosphate levels significantly increased after cinacalcet treatment (WMD: 0.49, 95% CI: 0.40, 0.596) (27). Consistent with the meta-analysis by Ng et al, the present meta-analysis also reported reduced levels of calcium and PTH. However, the phosphate levels showed a reduction which contradicted their findings. The observed inconsistency can be due to the difference in type and sample size of studied patients, the dose, and the duration of cinacalcet use.

Wang et al presented a meta-analysis of 8481 chronic kidney disease patients and concluded that when compared to the control group, cinacalcet administration reduced the incidence of parathyroidectomy (RR: 0.48, 95% CI: 0.40, 0.50) while elevating the hypocalcemia risk (RR: 8.48, 95% CI: 6.37, 11.29) (28). Another meta-analysis by Garside et al, including 846 patients on dialysis, evaluated the effect of cinacalcet in treating secondary hyperparathyroidism. The results indicated the higher effectiveness of cinacalcet in achieving the PTH target level (40% versus 5% in the placebo group; $P<0.001$). Moreover, the cinacalcet group experienced a 90% drop in Ca×P product compared to the 1% reduction in the placebo group (29). In a meta-analysis by Palmer et al on dialysis patients, cinacalcet had a minor effect on all-cause mortality (0.97 [95% CI: 0.89, 1.05]) and prevented the incidence of parathyroidectomy (0.49 [95% CI: 0.40-0.59]) and hypercalcemia (0.23 [95% CI: 0.05-0.97]) (30). The findings of these three studies agree with those of the present meta-analysis and thus can verify the efficacy of cinacalcet in dialysis patients.

Conclusion

Cinacalcet administration can lower serum calcium, phosphorus, Ca×P product, and PTH in dialysis patients. Hence, one can infer the effectiveness of cinacalcet in treating hypercalcemia and hyperparathyroidism in these patients. Considering the findings of the present meta-analysis, cinacalcet administration at a daily dose of 30-60 mg for two years seems beneficial for dialysis patients with hypercalcemia. However, further research is required to confirm its efficacy for patients undergoing hemodialysis. Given the limitation of the reviewed studies, future researchers are encouraged to conduct further research on this topic to evaluate the relationship between age and gender with cinacalcet use, thereby overcoming the restrictions of this study.

Limitations

This meta-analysis faces some limitations. 1) The lack of reporting of hyperparathyroidism type in some reviewed studies hindered further sub-group analysis of the cinacalcet impact on primary and secondary hyperparathyroidism. 2) Due to the limited number of articles and the similarity of the age range in reviewed studies, we could neither classify the studies based on the age range of patients nor assess the association between age variable and cinacalcet effectiveness in patients. 3) The reviewed articles did not address the gender-specific impact of cinacalcet use on variables such as calcium, phosphorus, and PTH among men and women and only reported the overall results. For this reason, the association between gender and cinacalcet efficacy in patients remains unknown, resulting in considerable heterogeneity among the studies.

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Authors' contribution

Conceptualization: Mohammad Reza Moonesan.
Data curation: Mehdi Yarahmadi.
Formal analysis: Mehdi Yarahmadi.
Funding Acquisition: Mohammad Reza Moonesan, Mehdi Yarahmadi.
Investigation: Mohammad Reza Moonesan, Mehdi Yarahmadi.
Methodology: Mehdi Yarahmadi.
Project administration: Mehdi Yarahmadi.
Resources: Mohammad Reza Moonesan.
Supervision: Mohammad Reza Moonesan.
Validation: Mohammad Reza Moonesan.
Visualization: Mohammad Reza Moonesan.
Writing–original draft: Mohammad Reza Moonesan.
Writing–review & editing: Mohammad Reza Moonesan, Mehdi Yarahmadi.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study has been compiled based on the PRISMA

checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website with (ID: CRD42023428774). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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