

The effect of cinacalcet on hypercalcemia in kidney transplant patients with hyperparathyroidism: systematic review and meta-analysis

Hanie Fooladi¹, Fatemeh Vashahi Torfi², Ali Khodaparast³, Sara Abbasian⁴, Noorbakhsh Alivand⁵, Mohamad Khaledi¹, Soleyman Alivand⁶, Farshad Gharebakhshi⁷, Moein Shakerian^{8*}

¹Department of Nursing, Faculty of Nursing and Midwifery, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

²Student Research Committee, Faculty of Nursing and Midwifery, Shiraz University of Medical Sciences, Shiraz, Iran

³Department of Nephrology, Faculty of Medicine, Birjand University of Medical Sciences (BUMS), Birjand, Iran

⁴Department of Nursing, Faculty of Nursing and Midwifery, Tehran University of Medical Sciences, Tehran, Iran

⁵Department of Nutrition, School of Health, Shiraz University of Medical Sciences, Shiraz, Iran

⁶Department of Biostatistical and Epidemiology, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran

⁷Department of Radiology, Imam Hossein Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

⁸Department of Veterinary Medicine, Garmsar branch of Islamic Azad University, Garmsar, Iran

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ABSTRACT

Introduction: Following renal transplantation, patients with end-stage renal disease develop parathyroid dysfunction and electrolyte abnormalities, including calcium and phosphate levels. However, cinacalcet is one of the most used medications for hypercalcemia. Therefore, the present systematic review and meta-analysis aimed to investigate the effect of cinacalcet administration on hypercalcemia in patients with renal transplantation.

Materials and Methods: The online databases of Cochrane, Web of Science, Scopus, and PubMed were searched until April 2023 using validated keywords. Moreover, PRISMA was used for qualitatively evaluating the studies since the study protocol was registered on the PROSPERO website. In addition, data analysis was conducted using Stata version 14, and the significance level was set at 0.05.

Results: The present meta-analysis included 26 studies (24 cohort studies and two randomized clinical trials) investigating 602 patients with renal transplantation and hyperparathyroidism. According to our findings, cinacalcet reduced the serum calcium (MD: -2.24, 95% CI: -2.82, -1.67), parathormone (SMD: -0.85, 95% CI: -1.15, -0.54), and alkaline phosphatase levels (SMD: -0.45, 95% CI: -0.91, -0.01). Moreover, 30-60 mg of cinacalcet per day effectively treated hypercalcemia (SMD: -2.77, 95% CI: -3.57, -1.98), while other doses were not significantly effective. Furthermore, the effect of cinacalcet was investigated in patients using the medication for less than six months (SMD: -2.55, 95% CI: -4.25, -0.86), 12-18 months (SMD: -2.60, 95% CI: -3.53, -1.67), and more than 24 months (SMD: -1.71, 95% CI: -2.54, -0.88). Finally, the effect of cinacalcet was the highest in the patients who were 60-64 years old compared to other age groups (SMD: -3.59, 95% CI: -5.14, -2.04).

Conclusion: Cinacalcet could improve hypercalcemia and hyperparathyroidism in patients with renal transplantation. Moreover, the effect of cinacalcet had a direct and positive relationship with the patient's age.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42023428620) and Research Registry (UIN: reviewregistry1667) website.

Implication for health policy/practice/research/medical education:

This meta-analysis was conducted on 26 studies and according to our findings, cinacalcet could decrease the serum levels of calcium, parathormone, and alkaline phosphatase in patients with renal transplantation. Thus, this medication treated the hypercalcemia and hyperparathyroidism in these patients. However, it did not show any significant effect on estimated glomerular filtration rate, Ca_xP products and serum levels of creatinine, albumin, and 25-OH vitamin D. The effect of cinacalcet on calcium levels increased with the age of the patients.

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Introduction

Renal transplantation is the most effective therapeutic option for patients suffering from end-stage renal disease (1). However, several problems may develop following transplantation, including vitamin D deficiency, osteoporosis, secondary hyperparathyroidism (SHPT) and electrolyte abnormalities, such as disturbances in the levels of calcium (Ca) and phosphate (P) ions (2). According to previous studies, the prevalence of hypercalcemia is 5%-66% following renal transplantation (3-5), while the prevalence of post-transplantation SHPT is 10%-66% (6, 7). Moreover, SHPT may lead to vascular and soft tissue calcification and bone fractures (8-10).

As an inevitable complication of renal replacement therapy, hyperparathyroidism can be classified into several types (11). Primary hyperparathyroidism (PHPT), which is more prevalent in women and the elderly. This disease is a common endocrine disorder resulting from parathormone (PTH) hypersecretion and is characterized by simultaneous disorders of the calcium and phosphor metabolisms (12). However, SHPT, which is also associated with elevated serum PTH levels, is caused by decreased renal function due to chronic kidney disease (CKD) (13). The most important factors predicting the chance of post-transplantation SHPT include the serum levels of calcium, alkaline phosphatase (ALP) and PTH at the time of transplantation, dialysis type and the function of the transplanted kidney (14,15).

The therapeutic options that slow the SHPT progress include parathyroidectomy, limited dietary phosphorus intake, and the administration of cinacalcet, vitamin D, vitamin D analogs, and phosphate binders (13, 16-18). However, some studies have reported that parathyroidectomy disturbs the function of the transplanted kidney (19, 20). Thus, studies have focused on the medical treatment of this disorder. Cinacalcet is one of the most used medications for SHPT. According to some studies, the administration of cinacalcet can decrease serum calcium and PTH levels following renal transplantation (21-23). However, some studies have not reported its significant effect on the serum calcium levels of these patients (24, 25). Therefore, the present systematic review and meta-analysis aimed to make a comprehensive conclusion on the effect of cinacalcet on calcium levels in patients with SHPT following renal transplantation. We investigated the results of previous studies in this field.

Materials and Methods

Study design

The present systematic review and meta-analysis utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol was registered on both PROSPERO (CRD42023428620) and Research Registry (UIN: reviewregistry1667) websites.

Search strategy

To collect data, we searched the international online databases of Cochrane, Web of Science, Scopus, and PubMed up to April 2023. An advanced search was conducted using standard MeSH keywords, including "Cinacalcet," "AMG 073," "Kidney Transplantation," "Renal Transplantation," "Hyperparathyroidism," "Hypercalcemia," and "Milk-Alkali Syndrome," along with the AND and OR operators. We also performed a manual search using the references of the studies found in the aforementioned databases. Additionally, we utilized Google Scholar as an additional search database. For example, the search strategy for the PubMed database was as follows: (((Hypercalcemia[Title/Abstract]) AND (Hyperparathyroidism[Title/Abstract])) AND (Kidney Transplantation[Title/Abstract] OR Renal Transplantation[Title/Abstract])) AND (Cinacalcet[Title/Abstract] OR Sensipar[Title/Abstract] OR AMG 073[Title/Abstract]).

PICO components

- Population: Patients who underwent renal transplantation
- Intervention: Administration of cinacalcet
- Comparison: Patients who did not receive cinacalcet or received a placebo
- Outcomes: Serum levels of calcium, creatinine (Cr), phosphorus (P), albumin, parathyroid hormone (PTH), estimated glomerular filtration rate (eGFR), alkaline phosphatase (ALP), 25-OH vitamin D, and Ca×P products.

Inclusion criteria

The present systematic review included cohort studies and clinical trials investigating the effect of cinacalcet on hypercalcemia in patients with renal transplantation.

Exclusion criteria

The case reports, descriptive studies, repeated studies, studies without access to full text, low-quality studies, studies with data incomplete for analysis, and studies reporting results using other indicators rather than the mean and standard deviation (SD) were excluded from the analysis.

Qualitative evaluation

The studies were qualitatively evaluated by two independent authors using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort studies (26). This checklist includes 22 items and is scored from 0-44, while we used the cut-off score of 16 in the present systematic review. Moreover, the checklist by the Cochrane Institute was used for clinical trials (27). This checklist includes seven items, each evaluating one of the important dimensions or

errors in clinical trials. Likewise, each item has a 3-point score: “low risk”, high risk”, and “unclear risk”. Finally, disagreements between the authors were evaluated and resolved.

Data extraction

Data extraction was performed by two of the authors to minimize bias and data collection errors. The authors used a checklist for data collection that included the name of the first author, publication year, country, age of the participants, type of the study, cinacalcet dosage, duration of cinacalcet use, sample size, type of hyperparathyroidism, number of male and female participants, and the mean values of outcomes before and after the intervention.

Statistical analysis

Since our outcome variables were quantitative, the present study used the standard mean difference (SMD), an indicative of the strength of the intervention-outcome relationship. At first, the studies were combined using the sample size, mean and SD. Moreover, the I^2 index was used for investigating the heterogeneity between the studies, which was revealed to be high. Therefore, the random model was used. Moreover, data analysis was performed using Stata version 14, and the significance level was set

at 0.05.

Results

A total of 391 studies were found by searching the online databases. However, 103 studies were excluded because of repetition. Afterward, the abstracts for the 288 remaining studies were checked and 24 studies were excluded due to incomplete data. Additionally, of the 264 remaining studies, the full texts of 14 studies were not available, while 224 studies were excluded due to other reasons. Finally, 26 high-quality studies remained, including two clinical trials and 24 cohort studies (Figure 1, Table 1).

According to our analyses, the serum calcium level significantly decreased in the participants after the administration of cinacalcet (MD: -2.24, 95% CI: -2.82, -1.67), showing the efficacy of cinacalcet in treating the hypercalcemia in patients with renal transplantation (Figure 2). Moreover, the serum levels of PTH (SMD: -0.85, 95% CI: -1.15, -0.54) and ALP (SMD: -0.45, 95% CI: -0.91, -0.01) decreased as well (Figures 3 and 4).

On the other hand, cinacalcet did not cause a significant effect on the serum levels of creatinine (SMD: -0.03, 95% CI: -0.19, 0.13), albumin (SMD: 0.06, 95% CI: -0.48, 0.59), 25-OH vitamin D (SMD: 0.08, 95% CI: -0.85, 1), eGFR (SMD: -0.21, 95% CI: -0.47, 0.05), and $\text{Ca} \times \text{P}$ products

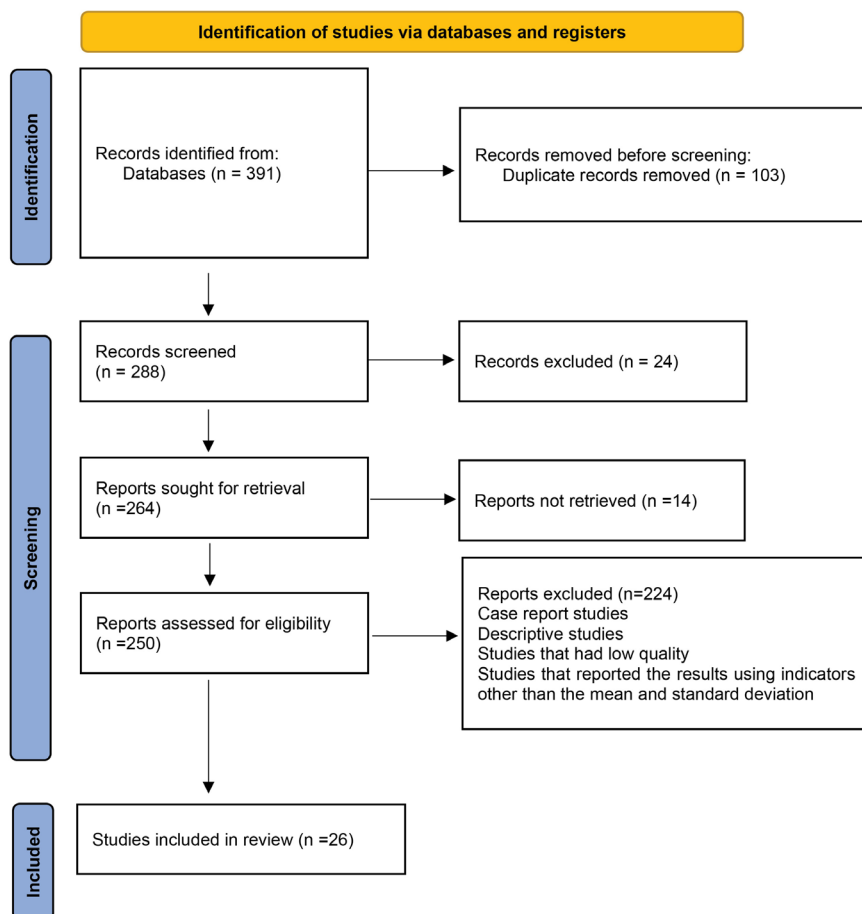


Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Table 1. Part of the background information of the reviewed articles

First author, year of publication	Country	Type of Study	Sample size	Number of women	Number of men	Mean Age (y)	Type of hyperparathyroidism	Time of treatment	Dosage
Bergua, 2007 (28)	Spain	Cohort	13	3	10	57	SHPT	6 Months	30 mg/d (5 patients received 60 mg/d)
Lopez, 2009 (29)	Spain	Cohort	29	15	14	55.5	SHPT	12 Months	60 mg
Paschoalin, 2012 (30)	Spain	Cohort	23	17	6	54	SHPT	12 to 172 Months	40.4 mg/d
Wazna-Jablonska, 2016 (31)	Poland	Cohort	30	14	16	NR	Hyperparathyroidism	17 Months	30 mg/d
Jo, 2019(22)	Korea	Cohort	9	2	7	53.2	Hyperparathyroidism	12 Months	NR
Leca, 2006 (32)	USA	RCT	10	NR	NR	NR	Hyperparathyroidism	6 Months	30 mg/d
Cho, 2010 (25)	USA	Cohort	8	2	6	44.9	Hyperparathyroidism	4 Months	56 mg/d
Evenepoel, 2014(33)	Belgium	RCT	57	26	31	53	Persistent Hyperparathyroidism	12 Months	NR
Alpay, 2023(1)	Turkey	Cohort	23	7	16	52.7	Hyperparathyroidism	33 Months	30-60 mg/d
Bergua, 2008(34)	Spain	Cohort	9	8	1	61.8	SHPT	12 Months	30 mg/d
Szwarc, 2006(23)	France	Cohort	9	NR	9	52	Hyperparathyroidism	6 Months	30 mg/d
Rivelli, 2020 (35)	Brasil	Cohort	46	19	27	50	Hyperparathyroidism	12 Months	30 mg p.o. and was adjusted to 60 mg/day
Serra, 2005 (36)	Switzerland	Cohort	11	6	5	59.1	Persistent Hyperparathyroidism	10 Weeks	30 mg/d
Guerra, 2011 (37)	Spain	Cohort	17	6	11	49	SHPT	12 Months	30 mg/d
Oruc, 2020 (38)	Turkey	Cohort	14	7	7	47.1	Hyperparathyroidism	12 Months	30 mg/d
Srinivas, 2006 (39)	USA	Cohort	11	5	6	48.5	Hyperparathyroidism	18 Months	30 mg/d
Cruzado, 2016 (40)	Spain	Cohort	15	8	7	55	Hyperparathyroidism	12 Months	NR
Zavvos, 2018 (41)	Greece	Cohort	47	19	28	49.9	SHPT	60 Months	NR
El-Amm, 2007 (42)	USA	Cohort	18	10	8	45	SHPT	6 Months	from 30 mg to 180 mg
Schwarz, 2011 (43)	Germany	Cohort	58	33	25	NR	Persistent Hyperparathyroidism	12 Months	30 to 90 mg
Borstnar, 2010 (24)	Slovenia	Cohort	11	7	4	39-64	Hyperparathyroidism	12 Months	30 mg/d
Rivelli GG, 2020 (44)	Brasil	Cohort	46	19	27	50	Persistent Hyperparathyroidism	36 Months	NR
Moreno, 2020 (45)	Spain	Cohort	13	NR	NR	NR	SHPT	60 Months	NR
Soliman, 2016 (46)	Egypt	Cohort	45	21	24	41.1	SHPT	8 Weeks	30 mg/d
Kamar, 2008 (47)	France	Cohort	11	5	6	50.5	Hyperparathyroidism	12 Months	60 mg/d
Jung, 2022 (48)	Korea	Cohort	19	7	12	45.7	SHPT	36 Months	25 mg/d

NR: Not report, SHPT: Secondary hyperparathyroidism,

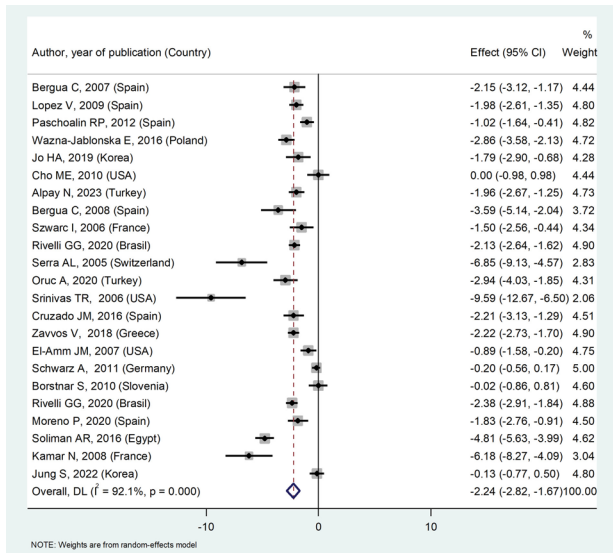


Figure 2. Forest plot showing the effect of cinacalcet on serum calcium level.

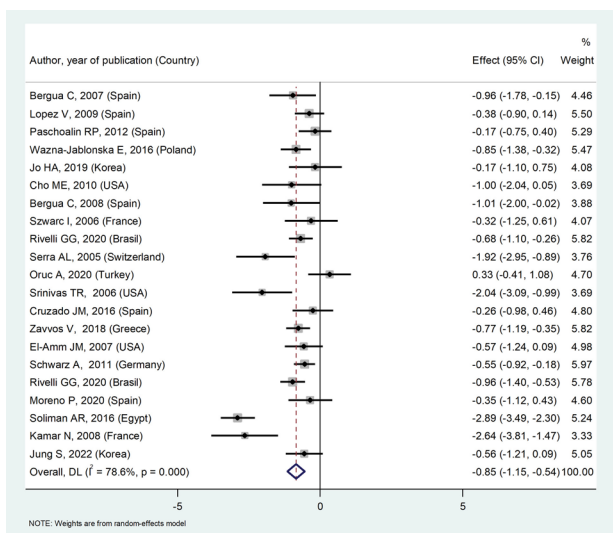


Figure 3. Forest plot showing the effect of cinacalcet on serum PTH level.

(SMD: -0.85, 95% CI: -2.14, 0.44) of the patients receiving renal transplantation (Figures 5-9).

According to our results, the effect of cinacalcet on hypercalcemia in patients with renal transplantation increased with age, showing the highest effect in the age group of 60-64 years (SMD: -3.59, 95% CI: -5.14, -2.04). Moreover, the effective dose of cinacalcet for hypercalcemia treatment was 30-60 mg/d (SMD: -2.77, 95% CI: -3.57, -1.98), while other doses were not effective. Besides, the patients taking cinacalcet for 12-18 months showed the highest efficacy compared to those using the medication for different durations (SMD: -2.60, 95% CI: -3.53, -1.67, Table 2).

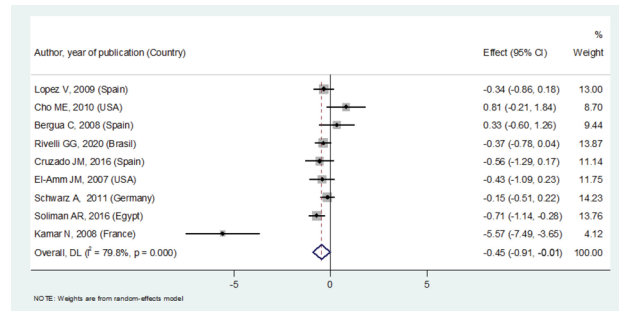


Figure 4. Forest plot showing the effect of cinacalcet on serum ALP level.

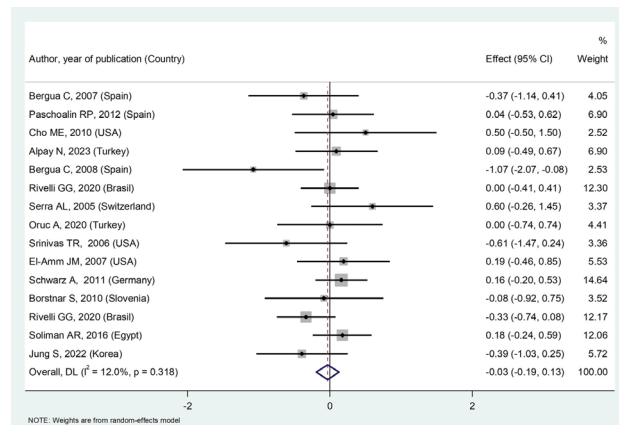


Figure 5. Forest plot showing the effect of cinacalcet on serum creatinine level.

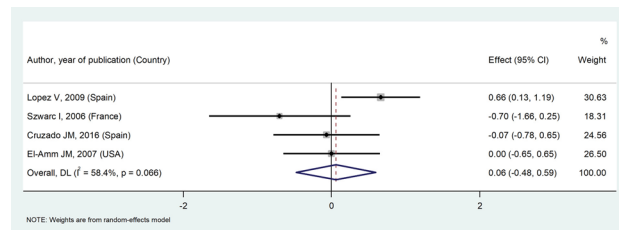


Figure 6. Forest plot showing the effect of cinacalcet on serum albumin level.

Discussion

The present systematic review showed the decreasing effect of cinacalcet on serum levels of calcium, PTH, and ALP in patients with renal transplantation. Moreover, a daily dose of 30-60 mg of cinacalcet and the use of the medication for 12-18 months caused the highest effectiveness. Furthermore, the age group of 60-64 years of age had the best response to treatment.

A meta-analysis by Greeviroj et al on patients undergoing dialysis showed the effectiveness of cinacalcet in reducing the serum levels of calcium, P, and PTH. However, it did not show any significant difference in ALP levels (49). The results of this study were compatible

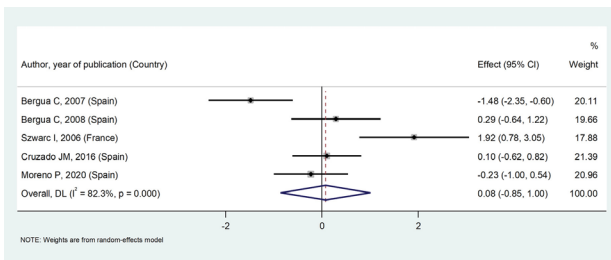


Figure 7. Forest plot showing the effect of cinacalcet on serum 25-OH vitamin D level.

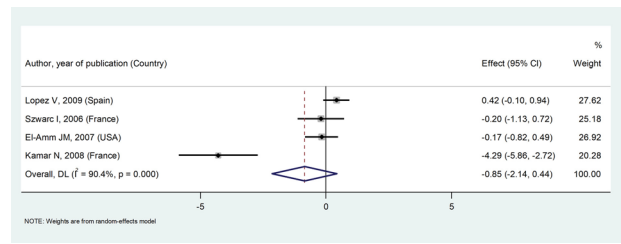


Figure 9. Forest plot showing the effect of cinacalcet on serum Ca x P products.

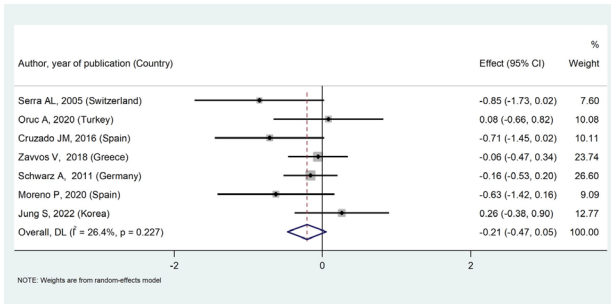


Figure 8. Forest plot showing the effect of cinacalcet on serum eGFR level.

with our results in calcium and PTH levels, while they were incompatible in ALP levels. These differences can be explained by different study populations and sample sizes. The study by Greeviroj et al included patients undergoing dialysis, while our study investigated patients with renal transplantation.

Another meta-analysis by Frey et al (2021) did not show any significant changes in creatinine levels and eGFR in patients with hyperparathyroidism following cinacalcet administration (50), which was compatible with our results. The present study did not report any significant effect on Cr, albumin, 25-OH vitamin D, and Ca x P products following the administration of cinacalcet.

On the other hand, another meta-analysis by Cohen et

al (2012) on 411 patients with renal transplantation and hyperparathyroidism reported that cinacalcet reduced the calcium and PTH serum levels by 1.14 mg/dL (95% CI: -1.00, -1.28) and 102 pg/mL (95% CI: -69, -134), respectively, while increasing the phosphor levels by 0.46 mg/dL (95% CI: 0.28, 0.64). Moreover, no significant change was observed in creatinine levels (a reduction of 0.02 mg/dL; 95% CI: -0.09, 0.06) (21). The mentioned study was completely compatible with our meta-analysis and confirmed our findings.

Another meta-analysis by Xu et al investigated 456 patients using paricalcitol and 412 patients using cinacalcet, reporting no significant differences in the serum levels of PTH (mean difference: 71.82, 95% CI: -185.20, -328.85) and phosphor (SMD: 0.59, 95% CI: -0.82, -2.001). However, serum calcium level were significantly higher in the paricalcitol group compared to the cinacalcet group (MD: 1.10, 95% CI: 0.92-1.28) (51). The comparison group was the main difference between the mentioned study and our study. As mentioned, the study by Xu et al, used the patients receiving paricalcitol as the comparison group, while our study, the patients received a placebo or other medications rather than cinacalcet as the comparison group.

Accordingly, the study by Henschkowski et al investigated the relationship between the administration of cinacalcet and reduced renal function in 118 patients

Table 2. The effect of cinacalcet on hypercalcemia in kidney transplant patients based on the investigated subgroups

Subgroups	SMD (95% CI)	P value	I ² (%)	Is this relationship statistically significant?
Duration (month)	≤6	<0.001	94.4	Yes
	12-18	<0.001	93.1	Yes
	≥24	<0.001	88	Yes
Dosage of cinacalcet	30-60 mg/d	<0.001	91.3	Yes
	Others	0.184	40.9	No
Age group (year)	45-49	<0.001	92.4	Yes
	50-54	<0.001	75.7	Yes
	55-59	0.001	81.7	Yes
	60-64	-	0	Yes

with renal transplantation and hyperparathyroidism, reporting a significant decrease in renal function following cinacalcet receiving (52). Incompatible with their findings, the present study reported several desirable effects from cinacalcet, including decreased levels of calcium and PTH. Considering the significant number of studies published from 2011 until now, our meta-analysis is much more comprehensive compared to that of Henschkowski et al, which includes more studies and larger sample size. Therefore, our results are more updated and reliable.

Conclusion

According to our findings, cinacalcet could decrease the serum levels of calcium, PTH, and ALP in patients with renal transplantation. Thus, this medication treated the hypercalcemia and hyperparathyroidism in these patients. However, it did not show any significant effect on eGFR, Ca \times P products, and serum levels of Cr, albumin, and 25-OH vitamin D. The effect of cinacalcet on calcium levels increased with the age of the patients, showing the highest effect in the age group of 60-64 years old. Furthermore, we recommend physicians use the daily dose of 30-60 mg for prescribing cinacalcet in patients with renal transplantation because this dose showed the highest effect in our meta-analysis. Finally, the administration of cinacalcet for 12-18 months showed the highest effect compared to other durations.

Considering the limited number of clinical trials on this topic, we recommend performing further randomized clinical trials to investigate the effect of cinacalcet on hypercalcemia and hyperparathyroidism in patients with renal transplantation.

Limitations of the study

In the present meta-analysis, we did not investigate the effect of cinacalcet on the hypercalcemia of the patients considering the type of hyperparathyroidism (primary or secondary) because some included studies had not mentioned the type of hyperparathyroidism in their patients. Moreover, there were no studies on this topic in several countries and regions of the world. In addition, most studies had used the dose of 30-60 mg daily for cinacalcet. Thus, the studies that did not mention the dosage or the dosage of the cinacalcet was outside the range of 30 to 60 mg were included in one group. We did not investigate the effect of cinacalcet considering the gender of the patients because some studies had not considered this variable. As mentioned before, the full texts of several studies were not available.

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Authors' contribution

Conceptualization: Mohamad Khaledi and Farshad Gharebakhshi.

Data curation: Hanie Fooladi and Farshad Gharebakhshi.

Formal analysis: Noorbakhsh Alivand and Soleyman Alivand.

Investigation: Ali Khodaparast and Fatemeh Vashahi Torfi.

Methodology: Soleyman Alivand.

Project management: Moein Shakerian.

Resources: Soleyman Alivand and Noorbakhsh Alivand.

Supervision: Hanie Fooladi.

Validation: Soleyman Alivand and Mohamad Khaledi.

Visualization: Noorbakhsh Alivand and Mohamad Khaledi.

Writing—original draft: Hanie Fooladi, Fatemeh Vashahi Torfi, Ali Khodaparast, Soleyman Alivand, and Noorbakhsh Alivand.

Writing—reviewing and editing: Mohamad Khaledi, Sara Abbasian, Farshad Gharebakhshi, and Moein Shakerian.

Conflicts of interest

There are 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: CRD42023428620; <https://www.crd.york.ac.uk/prospERO/#recordDetails>) and Research Registry website with (UIN: reviewregistry1667) (<https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmeta-analyses/>). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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