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Effect of sevelamer on serum phosphorus levels in chronic kidney disease and hemodialysis patients; a systematic review and meta-analysis

Farshad Gharebakhshi[1], Mohammad Hossein Taklif[2], Arash Izadpanah Ghahremani[3], Mohamad Khaledi[4], Sara Abbasian[5], Seyedeh Mahsa Shariati Sough[6], Fatemeh Vashahi Torfi[7], Hamidreza Khodabandeh[1], Elnaz Hajian[8*]

[1]Department of Radiology, Imam Hossein Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Nursing, Student Research Committee, Faculty of Nursing and Midwifery, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[3]Department of Emergency Medicine, School of Medicine, Arak University of Medical Sciences, Arak, Iran
[4]Department of Nursing, Faculty of Nursing and Midwifery, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[5]Department of Nursing, Faculty of Nursing and Midwifery, Tehran University of Medical Sciences, Tehran, Iran
[6]Department of Nursing, Faculty of Nursing and Midwifery, Rajaie Cardiovascular Medical and Research Center, Tehran, Iran
[7]Student Research Committee, Faculty of Nursing and Midwifery, Shiraz University of Medical Sciences, Shiraz, Iran
[8]Department of Nursing, Young and Elite Researchers Club, Bandar Abbas branch of Islamic Azad University, Bandar Abbas, Iran

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ABSTRACT

Introduction: Hyperphosphatemia is an independent risk factor for mortality in chronic kidney disease (CKD) patients.

Objectives: This systematic review and meta-analysis aimed to investigate the effect of Sevelamer on serum phosphorus levels in CKD and hemodialysis patients.

Materials and Methods: The data were obtained after searching the international databases of Cochrane, PubMed, Scopus, Web of Science, and the Google Scholar search engine until February 28, 2023. The heterogeneity of articles was assessed using the I2 index. The data were analyzed in STATA 14, and P values < 0.05 were considered significant.

Findings: A total of 22 articles were assessed with a total sample size of 3221. Sevelamer reduced calcium levels in CKD and hemodialysis patients compared with those in the comparison group (standardized mean difference [SMD]: -0.67; 95% CI: -1.23, -0.11); however, sevelamer had no significant effect on serum parathyroid hormone (PTH) levels (SMD: 0.07; 95% CI: -0.39, 0.54) and Ca × P product (SMD: -0.20; 95% CI: -0.41, 0). A significant decrease in serum phosphorus level was observed in patients who had taken sevelamer for a maximum of 12 weeks compared with the comparison group (SMD: -0.27; 95% CI: -0.54, -0.01); however, no significant decrease in serum phosphorus level was observed in patients who had taken sevelamer for more than 12 weeks. A significant decrease in serum phosphorus level was observed in sevelamer users compared to placebo group members (SMD: -0.36; 95% CI: -0.68, -0.05).

Conclusion: The administration of sevelamer reduced serum phosphorus levels in CKD and hemodialysis patients compared with those in the placebo group in the short term. Therefore, physicians are recommended to prescribe sevelamer for a maximum period of three months.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD42023406804).

Meta-analysis

Implication for health policy/practice/research/medical education:
In this systematic review and meta-analysis, on the effect of sevelamer on serum phosphorus levels in chronic kidney disease and hemodialysis patients; we found that the type of disease, type of sevelamer, and sevelamer dose did not significantly influence the effectiveness of sevelamer in reducing serum phosphorus levels.

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*Corresponding author: Elnaz Hajian, Email: Elnazhajian7999@gmail.com

Introduction

Chronic kidney disease (CKD) is considered a major public health problem worldwide. As the disease progresses, the filtering capacity of the kidney gradually decreases until renal replacement therapy (RRT) becomes necessary (1). In 2017, more than 700 million people worldwide were diagnosed with CKD, and the number of patients requiring RRT is predicted to exceed 5 million by 2030 (2). Failure to implement timely and effective measures has increased the prevalence of end-stage renal disease (ESRD) (3).

Hyperphosphatemia is a common complication in hemodialysis patients (4). Hyperphosphatemia is associated with increased cardiovascular complications and mortality in patients with stage 4 and 5 CKD (5). Removal of phosphate during dialysis and dietary phosphate restriction are clinical procedures to manage serum phosphate levels in CKD patients (6).

The four main phosphate binders, including calcium-based binders (calcium acetate and calcium carbonate), non-calcium-based binders (sevelamer and lanthanum), aluminum-based binders, and iron-based binders, lower serum phosphate levels (7). In addition to decreasing phosphorus absorption, sevelamer (carbonate/hydrochloride) can also modify adaptive mechanisms (e.g., reduce fibroblast growth factor 23 (FGF23) or parathyroid hormone (PTH)) due to its potential to absorb phosphorus in the intestine without added calcium (8). Some studies suggest that sevelamer reduces mortality in hemodialysis patients (9,10). However, the effect of sevelamer on phosphorus levels in hemodialysis patients remains controversial. Given the conflicting results of previous studies, this systematic review and meta-analysis investigated the effect of sevelamer on serum phosphorus levels in CKD and hemodialysis patients.

Materials and Methods

Study design

This systematic review and meta-analysis were conducted based on the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guideline, and the study protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website (ID: CRD42023406804).

Search strategy

Reputable international databases of Cochrane, Web of Science, Scopus, and PubMed, and the Google Scholar search engine were searched without a time limit using the following MeSH (Medical Subject Headings) search terms: "Sevelamer; sevelamer hydrochloride; sevelamer carbonate; phosphorus; chronic kidney disease; renal insufficiency, chronic; hemodialysis; renal dialysis; extracorporeal dialysis".

Various combinations of keywords were searched using the operators "AND" and "OR", and the search was updated until February 28, 2023. All relevant studies and references were also searched. The following search strategy was used to find relevant articles in PubMed:

((Sevelamer[Title/Abstract] OR Sevelamer Hydrochloride[Title/Abstract] OR Sevelamer Carbonate[Title/Abstract]) AND (Phosphorus[Title/Abstract] OR Phosphorus 31[Title/Abstract])) AND (Chronic Kidney Disease[Title/Abstract] OR Renal Insufficiency, Chronic[Title/Abstract] OR Hemodialysis[Title/Abstract] OR Renal Dialysis[Title/Abstract] OR Extracorporeal Dialysis[Title/Abstract])

Components of the Population, Intervention, Comparison, and Outcome (PICO) framework include Population: CKD and hemodialysis patients, Intervention: the use of sevelamer, Comparison: the placebo group or patients who had used other phosphate binders, and Outcome: assessing serum phosphate levels.

Inclusion criteria

All randomized clinical trials, observational, and quasi-experimental that investigated the effect of sevelamer on serum phosphate levels in CKD and hemodialysis patients were assessed.

Exclusion criteria

Articles that had investigated the effect of a combination of multiple drugs on serum phosphate levels in CKD and hemodialysis patients, repeated articles, low-quality articles (based on the Cochrane Risk-of-bias tool for randomized trials), articles that had investigated the effect of sevelamer on the lipid profile of CKD and hemodialysis patients, articles that had reported only qualitative results, articles that did not contain sufficient data for data analysis, and those without full text were removed.

Quality evaluation

fter the initial article list was generated, two researchers independently evaluated the quality of the articles using the Cochrane risk-of-bias tool for randomized trials (11). This checklist assesses potential sources of bias in clinical trials in 7 steps. The risk of bias in each step is interpreted as "low," "high," or "unclear." Reviewers examined and solved cases of discrepancy using the inter-reviewer agreement method. In addition, observational studies were evaluated using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (12).

Data extraction

To avoid bias and errors in data collection, two members of the research team extracted the following data from the

relevant articles: first author's name, year of publication, duration of sevelamer use, sample size, mean age of patients, type of disease, type of sevelamer, type of study, sevelamer dose, and comparison group, as well as the mean and standard deviation (SD) of serum phosphate, calcium, PTH, and (Ca×P product) levels before and after the interventions.

Data analysis

Because of the quantitative nature of the initial outcome, the standardized mean difference (SMD) was used to calculate the effect size of the intervention. SMD is a classic effect size statistic that shows the strength of the relationship between a desired intervention and the respective outcome. The closer the SMD value is to 0, the weaker the relationship would be; however, values close to 1 indicate stronger relationships. The selected articles were combined based on the frequency, mean, and SD of different variables. The heterogeneity of the selected articles was assessed using the I2 index and a random effects model. The data were analyzed in STATA 14, and *P* values < 0.05 were considered significant.

Results

A total of 532 articles were screened, of which 145, 32, and 9 articles were excluded after title screening, abstract screening, and full text screening, respectively. Another 324 articles that did not meet other exclusion criteria were also removed. Finally, 22 high-quality articles were included in the systematic review and meta-analysis process (Figure 1).

A total of 22 articles published between 1999 and 2023 were assessed with a total sample size of 3221 (1604 people in the sevelamer group and 1617 people in the comparison group). Moreover, 11 articles had examined the effect of sevelamer on CKD patients, whereas the remaining 11 articles investigated hemodialysis patients (Table 1).

The administration of sevelamer had no significant effect on serum phosphorus levels in CKD and hemodialysis patients compared with those in the comparison group (SMD: 0.01; 95% confidence interval [CI]: -0.32, 0.35) (Figure 2).

The use of sevelamer hydrochloride (SMD: 0.02; 95% CI: -0.23, 0.27) and sevelamer carbonate (SMD: 0.48; 95% CI: -0.88, 1.83) had no significant impact on serum phosphorus levels in CKD and hemodialysis patients compared with those in the comparison group (Figure 3).

There was a statistically non-significant relationship between sevelamer dose and serum phosphorus levels in

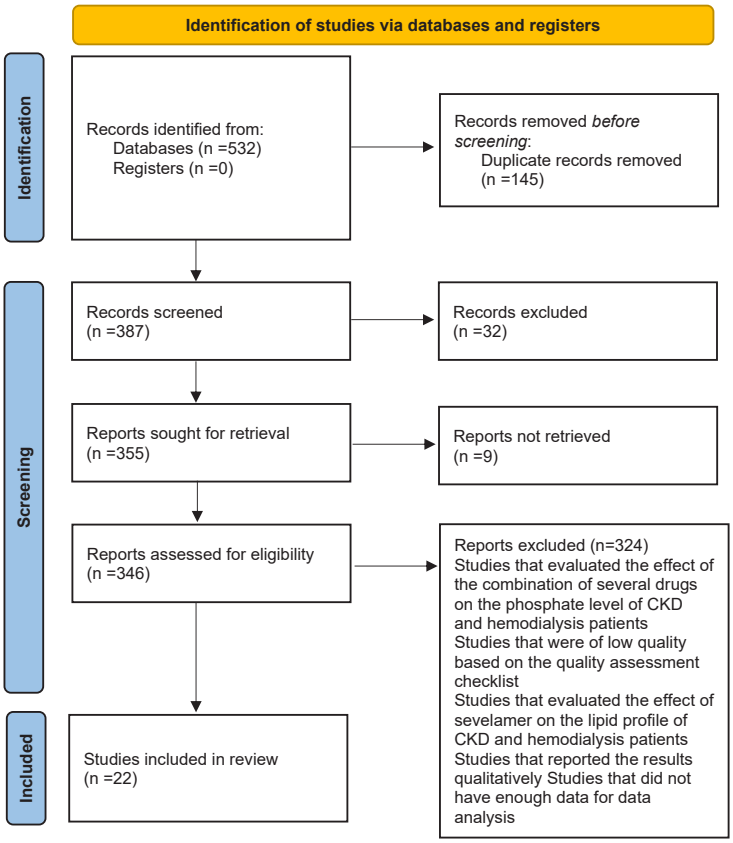

Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Table 1. Summary of the information available in the reviewed articles

First author, year of publication	Country	Type of study	No. of people in the sevelamer group	No. of people in the comparison group	Type of disease	Duration of treatment	Type of Sevelamer	Sevelamer dose per day	Compared with
Chertow, 2002(13)	USA	RCT	99	101	Hemodialysis	52 Weeks	Hydrochloride	800 mg	Calcium asetate
Block, 2005 (14)	USA	RCT	54	55	Hemodialysis	18 Months	Hydrochloride	Not report	Calcium asetate
Kakuta, 2011 (15)	Japan	RCT	79	84	Hemodialysis	12 Months	Hydrochloride	9 g	Calcium asetate
Di Iorio, 2013 (9)	Italy	RCT	232	234	Hemodialysis	36 Months	Hydrochloride	4800 mg	Calcium asetate
Ruggiero, 2019 (16)	Italy	RCT	26	27	CKD	3 Months	Carbonate	4800 mg	Placebo
Bleyer, 1999 (17)	USA	RCT	42	42	Hemodialysis	8 Weeks	Hydrochloride	465 mg 1 to 3 tablets	Calcium asetate
Lin, 2010(18)	Taiwan	RCT	26	26	Hemodialysis	8 Weeks	Hydrochloride	One, two, or three capsules of sevelamer (800 mg)	Calcium asetate
Katopodis, 2006 (19)	Greece	RCT	15	15	Hemodialysis	20 Weeks	Hydrochloride	2-4 capsule 403 mg	Aluminum hydroxide
Liabeuf, 2017(20)	France	RCT	39	39	CKD	12 Weeks	Carbonate	4.5 g	Placebo
Bleskestad, 2012 (21)	Norway	RCT	10	11	CKD	6 Weeks	Carbonate	800 mg	Alphacalcidol
Caglar, 2008 (22)	Sweden	RCT	25	25	CKD	8 Weeks	Not report	4800 mg	Calcium asetate
Mason, 2022 (23)	USA	RCT	15	15	CKD	12 Weeks	Carbonate	4800 mg	Calcium asetate
Chertow, 2003 (24)	USA	RCT	54	54	Hemodialysis	52 Weeks	Not report	800 mg	Calcium asetate
Iimori, 2012 (25)	Japan	Observational	156	156	Hemodialysis	37 Months	Hydrochloride	Not report	Calcium carbonate
Lin, 2014 (26)	Taiwan	RCT	23	23	Hemodialysis	48 Weeks	Not report	2400 mg	Calcium carbonate
Nain, 2023 (27)	India	RCT	75	75	CKD	6 Months	Carbonate	2400 mg	Lanthanum Carbonate
Gulati, 2010 (28)	India	RCT	11	11	CKD	12 Weeks	Hydrochloride	1200 mg	Calcium carbonate
Akizawa, 2014 (29)	Japan	RCT	50	54	Hemodialysis	12 Weeks	Hydrochloride	3.0 or 6.0 g	Bixalomer
Takkavatakarn, 2021(30)	Thailand	RCT	20	20	CKD	24 Weeks	Not report	2400 mg	Calcium carbonate
Tahir, 2022 (31)	Pakistan	Quasi-experimental	47	44	CKD	12 Weeks	Carbonate	1200 mg	Calcium asetate
Gupta, 2020 (32)	India	Observational	405	405	CKD	9 Months	Not report	800 mg	Calcium asetate
Chen, 2022 (33)	China	RCT	101	101	CKD	8 Weeks	Carbonate	2.4–12 g	Placebo

CKD, chronic kidney disease; RCT: randomized clinical trial

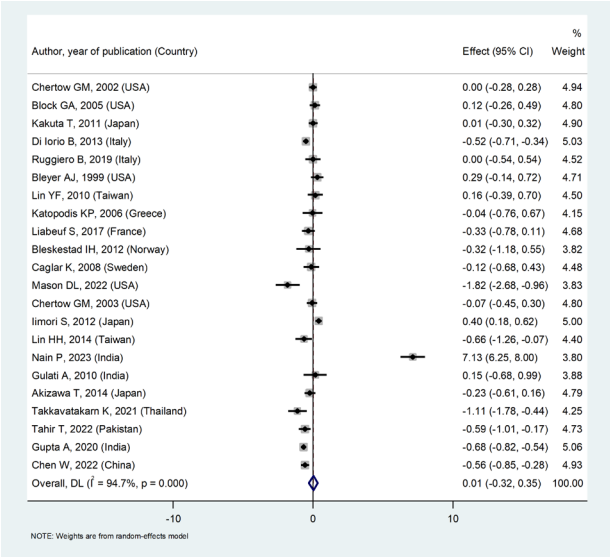

Figure 2. Forest plot showing effect of sevelamer on the phosphorus level of CKD and hemodialysis patients compared to the comparison group.

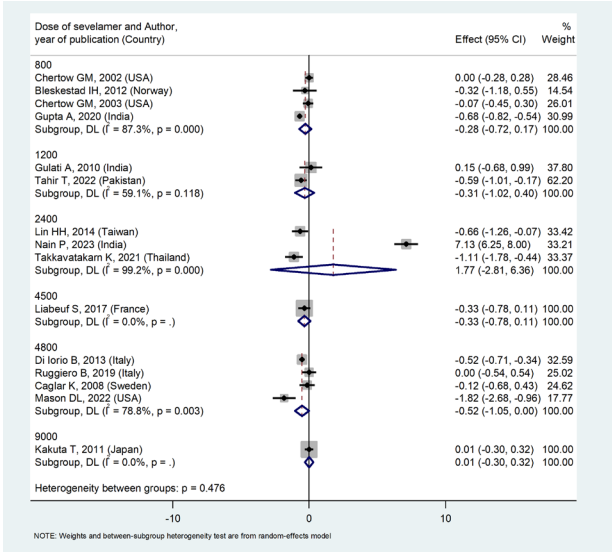

Figure 4. The effect of sevelamer on the phosphorus level of CKD and hemodialysis patients compared to the comparison group by dose of sevelamer.

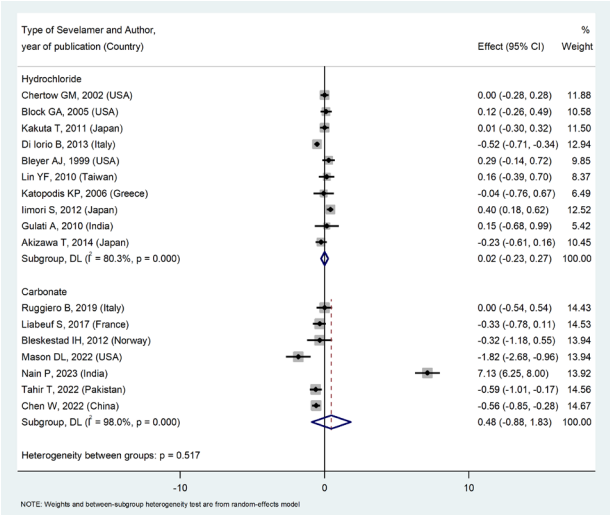

Figure 3. The effect of sevelamer on the phosphorus level of CKD and hemodialysis patients compared to the comparison group by type of sevelamer.

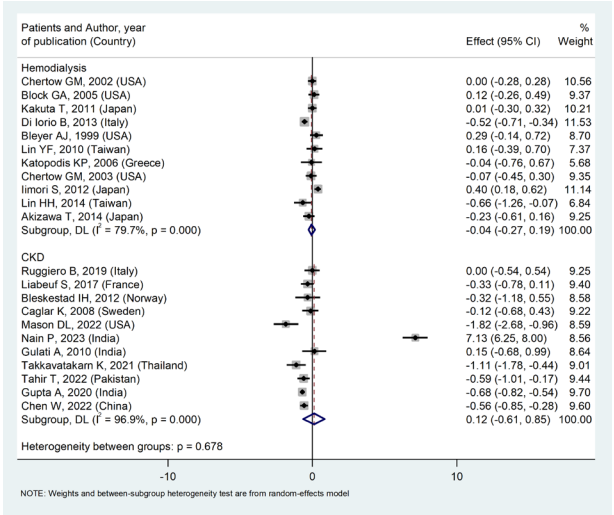

Figure 5. The effect of sevelamer on the phosphorus level of CKD and hemodialysis patients compared to the comparison group by type of disease.

CKD and hemodialysis patients compared with those in the comparison group—800 mg sevelamer per day: (SMD: -0.27; 95% CI: -0.72, 0.17), 1200 mg sevelamer per day: (SMD: -0.31; 95% CI: -1.02, 0.40), 2400 mg sevelamer per day: (SMD: 1.77; 95% CI: -2.81, 6.36), 4500 mg sevelamer per day: (SMD: -0.33; 95% CI: -0.78, 0.11), 4800 mg sevelamer per day: (SMD: -0.52; 95% CI: -1.05, 0), and 9000 mg sevelamer per day: (SMD: 0.01; 95% CI: -0.30, 0.32) (Figure 4).

No significant relationship was observed between the type of disease and the effect of sevelamer on serum phosphorus levels—CKD patients: (SMD: -0.04; 95% CI: -0.27, 0.19), hemodialysis patients: (SMD: 0.12; 95% CI: -0.61, 0.85) (Figure 5).

A significant decrease in serum phosphorus level was observed in patients who had taken sevelamer for a maximum of 12 weeks compared to those in the comparison group (SMD: -0.27; 95% CI: -0.54, -0.01); however, no significant decrease in serum phosphorus level was observed in those who had taken sevelamer for longer than 12 weeks (Figure 6).

A significant decrease was observed in serum phosphorus levels in sevelamer users compared to placebo group members (SMD: -0.36; 95% CI: -0.68, -0.05).

However, there was no significant difference between the use of sevelamer and aluminum hydroxide (SMD: -0.04; 95% CI: -0.76, 0.67), sevelamer and alfacalcidol (SMD: -0.31; 95% CI: -1.18, 0.55), sevelamer and calcium acetate (SMD: -0.25; 95% CI: -0.50, 0.01), sevelamer and calcium carbonate (SMD: -0.29; 95% CI: -1.07, 0.50), and sevelamer and bixalomer (SMD: -0.23; 95% CI: -0.61, 0.1) in terms of lowering serum phosphorus levels. On the other hand, a significant increase in serum phosphorus level was found in sevelamer users compared to those using lanthanum carbonate (LC) (SMD: 7.13; 95% CI: 6.25, 8) (Figure 7).

In a quasi-experimental study, sevelamer decreased patients' serum phosphorus levels (SMD: -0.59; 95% CI: -1.01, -0.17); however, in randomized controlled trials (RCTs) (SMD: 0.07; 95% CI: -0.34, 0.48) and observational studies (SMD: -0.14; 95% CI: -1.20, 0.91), sevelamer did not significantly affect participants' phosphorus levels (Figure 8).

Sevelamer decreased calcium levels in CKD and hemodialysis patients compared to those in the comparison group (SMD: -0.67; 95% CI: -1.23, -0.11); however, Sevelamer did not significantly influence levels of serum PTH and Ca × P product (Table 2).

Discussion

Sevelamer significantly reduced serum phosphorus levels in CKD and hemodialysis patients compared to those in the comparison group. Serum phosphorus levels of patients who had taken sevelamer for a maximum of 12 weeks decreased significantly compared to members of the comparison group. In addition, a significant decrease was observed in serum phosphorus levels of sevelamer users compared to members of the placebo group. The type of disease (hemodialysis or CKD), type of sevelamer (carbonate or hydrochloride), and the sevelamer dose did not significantly influence the effectiveness of sevelamer in reducing serum phosphorus levels. The discrepancy between the present results and the findings of some previous meta-analyses regarding the effectiveness of

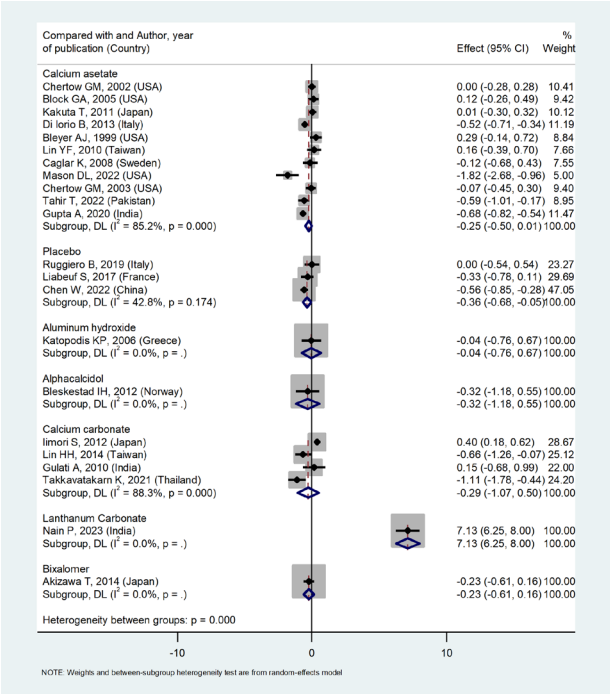

Figure 7. The effect of sevelamer on the phosphorus level of CKD and hemodialysis patients by comparison group..

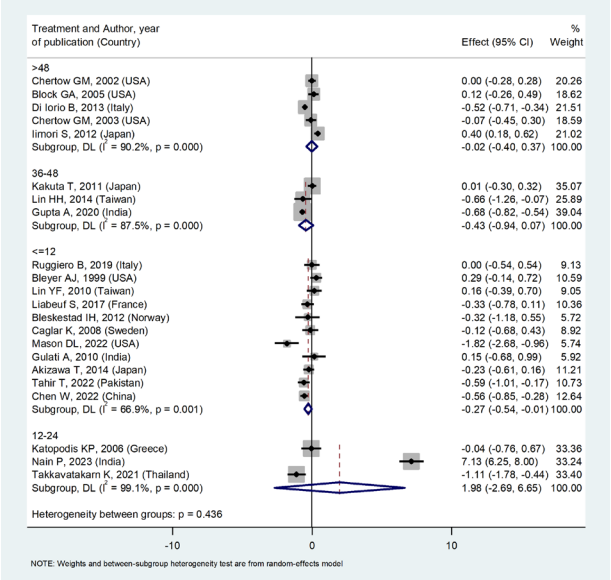

Figure 6. The effect of sevelamer on the phosphorus level of CKD and hemodialysis patients compared to the comparison group by duration of treatment.

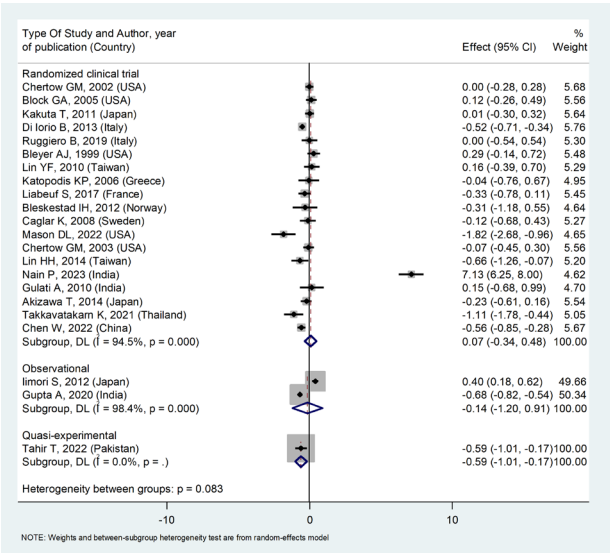

Figure 8. The effect of sevelamer on the phosphorus level of CKD and hemodialysis patients compared to the comparison group by type of study..

Table 2. The effect of sevelamer on the Calcium, Parathyroid hormone, Ca × phosphorus product of CKD and hemodialysis patients compared to the comparison group

Variables	SMD	Low limit	Up limit	*P* value	I^2 (%)
Calcium	-0.67	-1.23	-0.11	0.000	97.9
Parathyroid hormone	0.07	-0.39	0.54	0.000	95.1
Ca × P product	-0.20	-0.41	0	0.002	64.2

sevelamer in lowering serum phosphorus levels can be due to the fact that the type of disease, type of sevelamer, the drug dose, duration of use, age group of patients, and the comparison group in this meta-analysis differed from other studies.

In a meta-analysis, Wang et al investigated the effects of calcium carbonate and calcium acetate in the treatment of hyperphosphatemia in hemodialysis patients. They found a significant decrease in serum phosphorus levels in the calcium acetate group compared with the calcium carbonate group at both 4 weeks (mean difference [MD]: -0.15 mmol/L, 95% CI: -0.28 to -0.01) and 8 weeks (MD: -0.25 mmol/L, 95% CI: -0.40 to -0.11) after administration. However, there was no difference between the two groups in serum calcium, PTH, and Ca × P levels (34). The findings on the changes in PTH and Ca × P levels are consistent with the results of the present study.

Huang et al conducted a meta-analysis with 950 patients and found that LC effectively controls hyperphosphatemia in dialysis patients compared to those in the placebo group (SMD: -0.06; 95% CI: -0.27 to -0.86). In addition, fewer changes were observed in serum PTH and Ca × P product levels of patients who used LC compared with those in the placebo group (SMD: -0.21; 95% CI: -0.48 to 0.06 and SMD: -0.90; 95% CI: -1.13 to -0.66) (35).

In a meta-analysis with 1754 participants, Li et al concluded that ferric citrate significantly reduces serum phosphorus levels in CKD patients compared to those in the placebo group (MD: -1.76 mg/dL, 95% CI: -2.78 to -0.75) (36). This is consistent with the result of the present research.

Guo et al observed no significant difference between ESRD patients taking LC and those in the placebo group in terms of serum phosphate levels (weighted mean difference [WMD]: 0.26, 95% CI: -0.06 to 0.58) and serum calcium levels (WMD: -0.24, 95% CI: -0.77 to 0.29) (37). However, in contrast to the findings of Guo et al, in the present study, sevelamer lowered serum calcium and serum phosphorus levels in hemodialysis patients compared to those in the placebo group.

Zhao et al performed a meta-analysis in 2021 to examine the effects of LC and other phosphate binders on CKD patients. They found that LC can effectively reduce phosphorus levels, Ca × P product, and intact PTH in CKD patients (38). Given the conflicting results of previous meta-analyses on the effect of LC on hyperphosphatemia, researchers are suggested to compare the effects of sevelamer and LC in future clinical trials.

Conclusion

The use of sevelamer decreased serum calcium levels and serum phosphorus levels in hemodialysis patients compared with patients in the comparison and placebo groups, respectively. In addition, a significant reduction in serum phosphorus levels was observed in patients who had taken sevelamer for a maximum of three months compared to those in the comparison group. The use of sevelamer was effective in the short term; however, no conclusive result was obtained on the optimal dose of sevelamer or the best type of sevelamer that reduces serum phosphorus levels. Therefore, researchers are suggested to compare the effects of sevelamer (carbonate and hydrochloride) and the effects of high and low doses of sevelamer on serum phosphorus levels in CKD and hemodialysis patients.

Limitations of the study

Lack of access to the full text of some articles, lack of presentation of results by patients' sex and age, and uneven distribution of studies in different subgroups are the main limitations of the study.

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Authors' contribution

Conceptualization: Mohammad Hossein Taklif and Arash Izadpanah Ghahremani.
Data curation: Hamidreza Khodabandeh and Fatemeh Vashahi Torfi.
Formal analysis: Fatemeh Vashahi Torfi and Hamidreza Khodabandeh.
Investigation: Elnaz Hajian, Arash Izadpanah Ghahremani and Mohammad Hossein Taklif.
Methodology: Mohamad Khaledi, and Sara Abbasian.
Project management: Elnaz Hajian.
Resources: Farshad Gharebakhshi, Mohamad Khaledi and Seyedeh Mahsa Shariati Sough.
Supervision: Farshad Gharebakhshi.

Validation: Farshad Gharebakhshi and Seyedeh Mahsa Shariati Sough.
Visualization: Sara Abbasian and Arash Izadpanah Ghahremani.
Writing–original draft: Hamidreza Khodabandeh, Elnaz Hajian, Mohamad Khaledi, Seyedeh Mahsa Shariati Sough, and Fatemeh Vashahi Torfi.
Writing–reviewing and editing: Mohammad Hossein Taklif, Farshad Gharebakhshi, Arash Izadpanah Ghahremani and Sara Abbasian.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author. This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD42023406804).

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None.

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