BMC Nephrology

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Association of aberrant mineral metabolic markers with fracture risk in chronic kidney disease: a comprehensive meta-analysis

Yao Liu[1,2†], Zhen Xing Zhang[1,2†], Chen Sheng Fu[1,2†], Zhi Bin Ye[1,2*], Hui Min Jin[3,4*] and Xiu Hong Yang[1,2*]

Abstract

Background This meta-analysis aims to investigate the impact of abnormalities in mineral metabolic markers, including serum phosphate and calcium, intact parathyroid hormone (iPTH), and fibroblast growth factor 23 (FGF23) on the risk of fractures in patients with chronic kidney disease (CKD).

Methods A systematic search was conducted across MEDLINE, Web of Science, EMBASE, ClinicalTrials.gov, and the Cochrane Central Register for Controlled Trials. The outcomes were association of mineral metabolic markers with the risk of fractures in patients with chronic kidney disease. Pooled risk estimates and 95% confidence intervals (CIs) were calculated using fixed-effects or random-effects models.

Results Thirty-two studies were included in the meta-analysis. High and low levels of serum phosphate in hemodialysis (HD) patients were both associated with an increased risk of fractures (RR = 1.08, 95% CI 1.02–1.15, $P = 0.013$; RR = 1.13, 95% CI 1.02–1.25, $P = 0.022$, respectively). Similarly, abnormal levels of iPTH in CKD patients, both high and low, were associated with increased fracture risk (RR = 1.25, 95% CI 1.20–1.31, $P < 0.001$; RR = 1.41, 95% CI 1.10–1.82, $P = 0.007$, respectively). Elevated FGF23 levels were also linked to an increased risk of fractures (RR = 1.32, 95% CI 1.06–1.66, $P = 0.015$). While a higher level of calcium exhibited a trend towards reduced fracture incidence without statistical significance (RR = 0.90, 95% CI 0.77–1.05, $P = 0.181$), lower calcium levels tended to increase fracture risk without statistical significance (RR = 1.11, 95% CI 0.99–1.24, $P = 0.087$). Notably, subjects treated with calcium and phosphorus modulating drugs demonstrated a statistically significant reduction in fractures among CKD patients undergoing dialysis (phosphate binders, RR = 0.79, 95% CI 0.70–0.89; cinacalcet, RR = 0.74, 95% CI 0.59–0.93; vitamin D analogues, RR = 0.82, 95% CI 0.74–0.92, respectively).

Conclusion This meta-analysis underscores the association between abnormal mineral metabolic markers, including high serum phosphate, iPTH, and FGF23, and an increased risk of fractures in CKD patients. Notably, both elevated and decreased levels of phosphate and iPTH contribute to fracture risk. The efficacy of active vitamin D, phosphorus

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binders, and cinacalcet in preventing fractures was observed in HD patients but not in the non-dialysis CKD population.

Trial registration PROSPERO CRD42023493951.

Keywords Inorganic phosphate (Pi), Intact parathyroid hormone (iPTH), Fibroblast growth factor 23 (FGF23), Fracture, Chronic kidney disease (CKD)

Introduction

Chronic kidney disease (CKD) stands as a prominent health concern, frequently precipitating heightened cardiovascular and cerebrovascular complications [1]. Early in the trajectory of CKD, disruptions in mineral metabolism emerge, exerting a pivotal influence on the acceleration of metabolic irregularities [2]. Clinical investigations have underscored a discernible association between bone and mineral metabolism aberrations and an augmented susceptibility to fractures [3]. The Dialysis Outcomes and Practice Patterns Study (DOPPS) II, encompassing 12 participating countries, reported an incidence of 8.9 per 1000 patient years for new hip fractures and 25.6 per 1000 for any new fracture among hemodialysis (HD) patients [4].

The primary culprits implicated in elevated fracture risk in CKD include bone loss, secondary hyperparathyroidism (SHPT), deficiency in 1,25-dihydroxydroxy vitamin D, chronic acidosis, and heparin exposure [5]. Numerous clinical studies and reviews have proposed that CKD-mineral and bone disorder (CKD-MBD), marked by conditions such as hyperphosphatemia, compromised activation of vitamin D, SHPT, and elevated fibroblast growth factor 23 (FGF23), significantly contribute to the heightened fracture risk [4, 6–8]. Nevertheless, the precise fracture risk in CKD and its correlation with surrogate markers of CKD-MBD remain elusive. Inconsistencies in findings regarding the association between mineral bone metabolic markers and fracture risk in the CKD population have been documented [4, 9–12].

Thus, the primary objective of this meta-analysis is to affirm the relationship between mineral bone metabolic markers and the risk of fractures in CKD patients. Furthermore, our investigation seeks to elucidate the potential efficacy of phosphorus binders, active vitamin D, and the calcium-sensing receptor agonist-cinacalcet in mitigating fracture risk within both dialysis and non-dialysis CKD populations.

Methods

We adhered to a standardized protocol in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. This study is prospectively registered with PROSPERO under the registration number CRD42023493951, ensuring transparency and methodological rigor in our research process.

Search strategy and study selection

We implemented a comprehensive search strategy to identify relevant literature from multiple databases, including MEDLINE (PubMed, January 1, 1966, to January 31, 2024), Web of Science, EMBASE (January 1, 1966, to January 31, 2024), ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials. The search utilized specific keywords such as "serum phosphate," "parathyroid hormone," "fibroblast growth factor 23," "calcium," "phosphate binders," "cinacalcet," "vitamin D analogues," in conjunction with "chronic kidney disease" and "fracture." Detailed search strategies for each database are outlined in Table S1. Additionally, manual searches of references cited in identified original studies and pertinent review articles were conducted and assessed for inclusion. The stepwise procedures are elucidated in Figure S1.

Inclusion and exclusion criteria

Studies that met the following criteria were included in our meta-analysis: 1) Studies involving patients with CKD. 2) Inclusion of randomized controlled trials (RCTs), non-randomized trials, and prospective or observational studies. 3) Evaluation of fractures associated with high or low levels of serum phosphate, parathyroid hormone, fibroblast growth factor 23 (FGF23), or calcium, as compared to a control group with normal levels of these parameters in CKD patients. 4) Assessment of fractures related to the use of phosphate binders, cinacalcet, or vitamin D analogues, in comparison with a control group receiving placebo or no treatment in CKD patients.

Studies were excluded if they met any of the following criteria: 1) Studies where the outcomes of fractures were not reported. 2) Different publications analyzing the same population or duplicates. 3) Studies involving population post-kidney transplantation.

Data collection

Three researchers (Y Liu, ZX Zhang, CS Fu) performed the search and reviewed the results. Data were independently extracted by the three researchers Y Liu, ZX

Zhang, CS Fu) who reviewed all the study characteristics (i.e., first author's surname, year of publication, study design, sample, follow-up, and outcomes). Any disagreement in data extraction was resolved through a discussion among these researchers in consultation with the other authors (XH Yang, HM Jin and ZB Ye).

Assessment of heterogeneity

Heterogeneity assessment employed Cochran's Q and I^2 statistics. A study was deemed heterogeneous if the *P*-value was less than 0.1 (Cochran's Q). Studies with I^2 values below 50% were categorized as non-heterogeneous, warranting the use of a fixed-effects model in their analysis. Conversely, studies with I^2 values exceeding 50% were considered heterogeneous and were subjected to analysis using a random-effects model.

Risk of bias assessment

The assessment of the quality of included non-randomized controlled trials (non-RCTs) was conducted using the 'Risk of Bias in Non-randomized Studies of Interventions' (ROBINS-I) tool. The studies were evaluated for the risk of bias in seven domains and subsequently ranked as low, moderate, serious, or critical risk of bias.

Statistical analyses

Data analysis was performed utilizing STATA version 17.0 (StataCorp, TX, USA). Risk ratios (RRs) for fractures were computed, and all pooled estimates are presented with corresponding 95% confidence intervals (CIs). Additionally, a sensitivity analysis was conducted, involving the extraction of each study to assess its impact on the overall estimate. To investigate the presence of publication bias, Egger's test was employed. A significance threshold of $P < 0.05$ was set for all statistical analyses.

Results

Study flow and study characteristics

The selection process for inclusion is delineated in Figure S1 and Table S1. A comprehensive screening process identified 196 potentially relevant citations, which were subsequently evaluated, leading to the retrieval of 32 articles for in-depth examination [4, 9–39]. The pertinent characteristics of the 32 included studies are summarized in Table 1. The meticulous risk assessment of these studies utilizing the ROBINS-I tool is presented in detail in Table S2.

Effect of serum inorganic phosphate (Pi) on fracture endpoints

Normal phosphate levels are defined as ranging from 1.13 to 1.78 mmol/L. Phosphate levels above 1.78 mmol/L are considered high, while levels below 1.13 mmol/L are classified as low. These thresholds are based on the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines. The pooled results from nine studies involving CKD patients revealed that high Pi levels posed a heightened risk of fractures compared to the intermediate range (Fig. 1A, RR = 1.08, 95% CI 1.02–1.15, $P = 0.013$). Similarly, results pooled from five studies involving CKD patients undergoing hemodialysis demonstrated that a low level of Pi increased the risk of fractures when compared to the intermediate range (Fig. 1B, RR = 1.13, 95% CI 1.02–1.25, $P = 0.022$).

Effect of iPTH levels on fracture endpoints

The thresholds for high and low PTH levels were chosen based on clinical guidelines (K/DOQI). For dialysis patients, maintaining iPTH levels between 150 and 300 pg/mL is the recommended target range. In our meta-analysis, we defined high PTH as greater than 300 pg/mL and low PTH as below 150 pg/mL. In contrast to the intermediate iPTH levels, a comprehensive analysis of pooled results from 11 studies revealed that elevated iPTH levels significantly increased the risk of fractures in patients with dialysis (Fig. 2A, RR = 1.25, 95% CI 1.20–1.31, $P < 0.001$).

Additionally, findings from 10 studies indicated that lower iPTH levels were associated with an elevated risk of fractures in dialysis patients (Fig. 2B, RR = 1.41, 95% CI 1.10–1.82, $P = 0.007$, $I^2 = 71.5$). Considering the notable heterogeneity, we categorized the studies by study type, which substantially reduced the heterogeneity (Figure S2, cohort study, $I^2 = 47.1\%$; retrospective study, $I^2 = 0.0\%$).

Effect of FGF23 levels on fracture endpoints in CKD patients without dialysis

No pertinent literature was found to explore the impact of FGF23 on fracture endpoints in CKD patients undergoing dialysis. Consequently, our focus was directed towards CKD patients without dialysis. This meta-analysis was conducted on six study arms that reported fracture endpoints. The pooled results revealed that elevated FGF23 levels (> 58 pg/ml) were associated with an increased risk of fracture outcomes (RR = 1.32, 95% CI 1.06–1.66, $P = 0.015$, Fig. 3).

Effect of serum corrected calcium on fracture endpoints in CKD patients on dialysis

In our meta-analysis, we explored the impact of serum calcium on fracture endpoints in CKD patients undergoing dialysis. The K/DOQI guidelines recommend that the target range for serum calcium is 2.1–2.51 mmol/L. Low calcium was defined as levels below 2.1 mmol/L, intermediate calcium as levels between

Table 1 The pertinent characteristics of the 32 included studies

Study	N	Age (years)	Sex (male%)	CKD stages	Study type	Follow up	Basline level of Pi	Basline level of iPTH	Basline level of Ca	Basline level of FGF23	Outcomes
Atsumi et al. 1999 [12]	187	54.2 ± 8.8	100	5	retrospective study	/	5.6 ± 1.4 mg/dL	218.7 ± 289.9 pg/mL	4.8 ± 0.4 mEq/L	/	vertebral fracture
Coco et al. 2000 [13]	1,272	58 ± 0.4	49	5	retrospective study	10 years	/	/	/	/	hip fracture
Stemman-Breen et al.2000 [9]	4,952	59.7 ± 15.6	51.7	5	cohort study	3.16 years	5.93 ± 2.02 mg/dL	323.8 ± 552.0 pg/mL	9.14 ± 1.12 mg/dL	/	hip fracture
Cunningham et al.2005 [14]	1,184	53.7 ± 14.4	62	5	RCT	≥ 6 months	6.2 ± 1.6 mg/dL	711 ± 481 pg/mL	9.9 ± 0.8 mg/dL	/	fracture
Danese et al. 2006 [10]	9,007	61.7 ± 15.5	57.5	5	cohort study	3 years	5.9 ± 3.1 mg/dL	375.2 ± 947.8 pg/mL	9.5 ± 2.1 mg/dL	/	hip, vertebral, and pelvic fractures
Jadoul et al. 2006 [4]	12,782	≥ 18	/	5	practice patterns study	/	/	/	/	/	hip or other bone fractures
Kanda et al. 2012 [15]	105	73.2 ± 7.7	67.6	1–4	cross-sectional study	/	1.1 ± 0.2 mmol/L	143.6 ± 139.4 ng/L	2.4 ± 0.1 mmol/L	78.0 ± 101.7 pg/mL	vertebral fracture
Jovanovich et al.2013 [11]	3,337	78 ± 5	40	3–5	prospective study	9.6 (5.1,11.0) years	/	/	/	70 RU/mL	hip fracture
Lane et al. 2013 [16]	5,994	≥ 65	100	3–5	prospective case-cohort study	5.3 years	2.69–3.70 mg/dL	3.19 ± 0.41 mg/dL	/	4.2–111.1 pg/mL	fracture
Chen et al. 2014 [17]	64,124	≥ 50	49.02	5	cohort study	10 years	/	/	/	/	hip fracture
Isakova et al. 2015 [18]	2,786	74.7 ± 2.9	49	3–5	prospective cohort study	5 years	3.6 ± 0.5 mg/dL	33.7 (25.1,45.8) pg/mL	8.9 ± 0.4 mg/dL	46.7(36.7,60.2) pg/mL	fracture
Moe et al. 2015 [19]	3,883	55.0 (35,74)	58.5	5	placebo-controlled study	5 years	6.3(4.9,8.3) mg/dL	694.5 (362.0,1707.0) pg/mL	9.8(9.0,10.7) mg/dL	/	fracture
Fishbane et al.2016 [20]	142,407	≥ 18	52–54	5	cohort study	3 years	4.0–7.3 mg/dL	197.5 (105.6,347.2) pg/mL	8.3–9.9 mg/dL	/	hip and femur fractures
Dey et al. 2017 [21]	2,096	> 18	58.4	5	retrospective study	3 years	1.2 ± 0.42 mmol/L	37.3 ± 28.32 pmol/L	2.41 ± 0.17 mmol/L	/	symptomatic fracture
Evans et al. 2018 [22]	3,526	66.8	64.6	3–5	cohort study	37 months	1.6(1.3,2.0) mmol/L	316(202,548) ng/L	2.37(2.25,2.50) mmol/L	/	fracture
Hutchison et al. 2018 [23]	10,120	57.1 ± 14.6	58.1	5	observational cohort study	5 years	/	/	/	/	fracture

Table 1 (continued)

Study	N	Age (years)	Sex (male%)	CKD stages	Study type	Follow up	Basline level of Pi	Basline level of iPTH	Basline level of Ca	Basline level of FGF23	Outcomes
Desbiens et al. 2019 [24]	17,608	40–69	48.4–51.3	2–3	cross-sectional study	/	/	/	/	/	fracture
Geng et al. 2019 [25]	5,108	68 ± 17	48	3–4	prospective study	23 ± 10 years	/	105 ± 100 pg/mL	/	/	fracture
Kwon et al. 2019 [26]	89,533	≥ 18	58.0	1–5	cohort study	5 years	/	/	/	/	fracture
Wakasugi et al. 2019 [27]	135,984	64.9 ± 12.2	61.7	5	prospective cohort study	1 year	5.3 ± 1.4 mg/dL	124(65,206) pg/mL	9.4 ± 0.8 mg/dL	/	hip fracture
Jansz et al. 2020 [28]	146	52 ± 13	67	5	prospective cohort study	3 years	1.32 ± 0.48 mmol/L	1.32 ± 0.48 pmol/L	2.35 ± 0.13 mmol/L	/	vertebral fracture
Matias et al. 2020 [29]	341	68.7 ± 13.6	60.0	5	retrospective study	51 months	4.3 ± 1.2 mg/dL	329 pg/mL	9.1 ± 0.6 mg/dL	/	fracture
Ribeiro et al. 2020 [30]	126	58.10 ± 6,66	58.2	2–3	prospective study	7 years	4.52 ± 0.15 mg/dL	177.05 ± 16.34 pg/mL	9.08 ± 0.50 mg/dL	304.63 ± 27.02 RU/mL	fracture
Ogata et al. 2021 [31]	2,135	69 (63,75)	59.5	5	RCT	3 years	5.3 ± 1.4 mg/dL	114.0 (63.0,175.2) pg/dL	9.2 ± 0.7 mg/dL	/	hip fracture
Fusaro et al. 2021 [32]	387	67 (55,74)	63	5	cross-sectional study	2.7 ± 0.5 years	4.7(3.9,5.7) mg/dL	290(171,446) pg/mL	9.1(8.7,9.5) mg/dL	/	vertebral fracture
Fusaro et al. 2021 [33]	387	67 (52,74)	63.8	5	cross-sectional study	> 4 years	4.84 ± 1.32 mg/dL	245 (144.5,361) pg/mL	9.13 ± 0.66 mg/dL	/	vertebral fracture
Xie et al. 2021 [34]	521	67.2 (57,78)	45.5	5	retrospective case–control study	1439 days	/	/	/	/	fracture
Yoshida et al. 2021 [35]	1,342	51–84	62.1	5	retrospective, follow-up study	5 years	3.5–6.7 mg/dL	122 (67,188) g/mL	7.9–9.9 mg/dL	/	fracture
Desbiens et al. 2022 [36]	312	53 (48,61)	49.3	3	case-cohort study	70 months	0.86–1.43 mmol/L	17.3 (11.6,23.1) ng/L	2.24–2.50 mmol/L	80(73,91) RU/mL	fracture
Murashima et al. 2022 [37]	208,512	65.3 ± 12.4	62.4	5	prospective cohort study	1.8 years	5.20 ± 1.43 mg/dL	128(66,215) pg/mL	9.30 ± 0.87 mg/dL	/	hip fracture
Young et al. 2022 [38]	4,401	63 ± 9	66.1	2–3	observational study	2.35(1.88,2.93) years	/	/	/	/	fracture

Table 1 (continued)

Study	N	Age (years)	Sex (male%)	CKD stages	Study type	Follow up	Basline level of Pi	Basline level of iPTH	Basline level of Ca	Basline level of FGF23	Outcomes
Barrera-Baena et al.2023 [39]	6,274	64.0 ± 14.4	60.7	5	observational cohort study	3 years	5.4 ± 1.4 mg/dL	210.0 (108.0,375.0) pg/mL	9.1 ± 0.7 mg/dL	/	fracture

RCT Randomized Clinical Trial

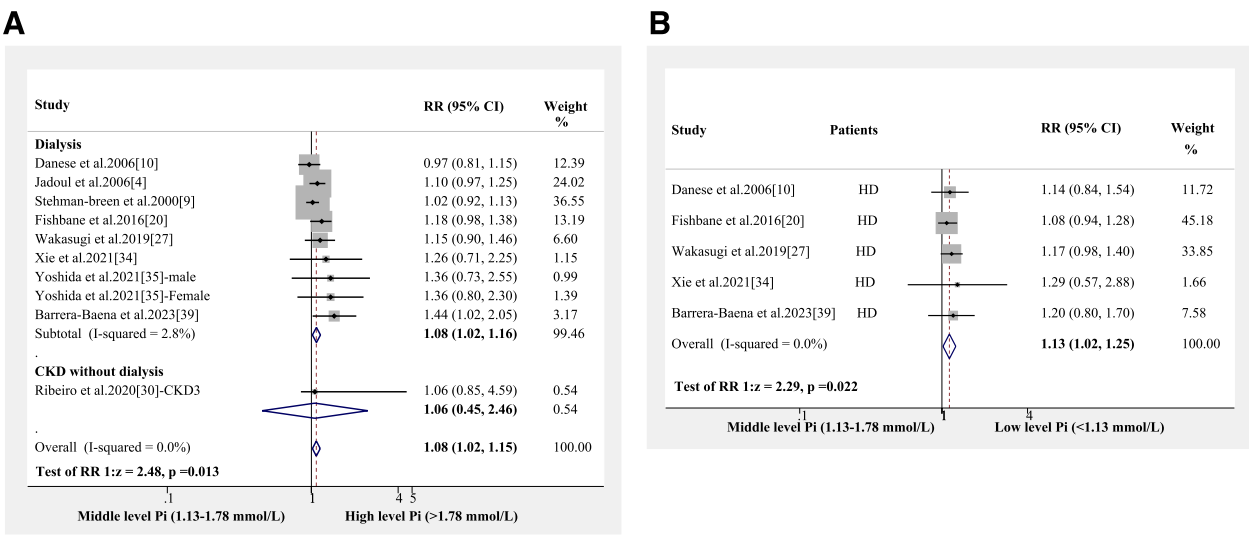

Fig. 1 Risk ratios (RRs) for fractures in CKD patients associated with inorganic phosphate (Pi) levels from pooled studies. **A** Pooled results from studies assessing fractures associated with high Pi. **B** Pooled results from studies assessing fractures associated with low Pi

2.1 and 2.51 mmol/L, and high calcium as levels above 2.51 mmol/L. When compared to the intermediate calcium levels, a higher calcium level appeared to confer a potential benefit in reducing the incidence of fractures, although this trend lacked statistical significance (RR = 0.90, 95% CI 0.77–1.05, $P = 0.181$; Fig. 4A). Conversely, lower calcium levels exhibited a tendency to increase the risk of fractures, though again without statistical significance (RR = 1.11, 95% CI 0.99–1.24, $P = 0.087$; Fig. 4B).

Effect of phosphate binders, cinacalcet, and vitamin D analogues on fracture endpoints in CKD patients

As depicted in Fig. 5A, individuals treated with medications addressing abnormal calcium and phosphorus metabolism exhibited statistically significant reductions in fractures among CKD patients undergoing dialysis (phosphate binders, RR = 0.79, 95% CI 0.70–0.89; cinacalcet, RR = 0.74, 95% CI 0.59–0.93; vitamin D analogues, RR = 0.82, 95% CI 0.74–0.92; respectively) compared to control groups. However, in non-dialysis patients, there was a limited number of studies investigating the effects of these drugs on final fracture endpoints. The pooled results from three studies on drugs and fracture endpoints were inconclusive, suggesting that calcium and phosphorus-modulating drugs were not associated with a decreased risk of fracture when compared to control groups in CKD patients not undergoing dialysis (Fig. 5B; phosphate binders, RR = 1.07, 95% CI 0.90–1.27; vitamin D analogues, RR = 0.95, 95% CI 0.66–1.37; respectively).

Sensitivity analysis and publication bias

The sensitivity analysis indicated that the exclusion of any individual study from the meta-analysis did not alter the overall conclusions (Figure S3). Publication bias was assessed using Egger's test for studies exceeding 10 in number. Consequently, no publication bias was detected in the pooled studies (high Pi with fracture, $P = 0.065$; high iPTH with fracture, $P = 0.555$; calcium and phosphorus-modulating drugs treatment with fracture, $P = 0.070$; Figure S4).

Discussion

This meta-analysis represents the inaugural attempt to elucidate the association between mineral bone metabolic markers and the risk of fractures in CKD. Our findings indicate that elevated phosphorus, high iPTH, and increased FGF-23, as well as decreased phosphorus and diminished iPTH, are all associated with an elevated risk of fractures in the CKD population.

As has been previously suggested, existing literature proposes that bone loss is a primary contributor to fractures [2, 3, 12]. Experimental CKD studies demonstrate distinct regulatory roles of high serum Pi and iPTH in bone loss and vascular calcification [40]. The Wnt/β-Catenin signaling pathway is crucial for normal bone mineralization, osteoblastic activity, osteocyte function, and overall bone health [41]. In CKD, this pathway is dysregulated, contributing to impaired bone remodeling and fragility. Wnt signaling is involved in osteoblast differentiation and bone matrix production, as well as osteocyte viability and communication, all of which are vital for bone integrity [42, 43]. Recent studies have

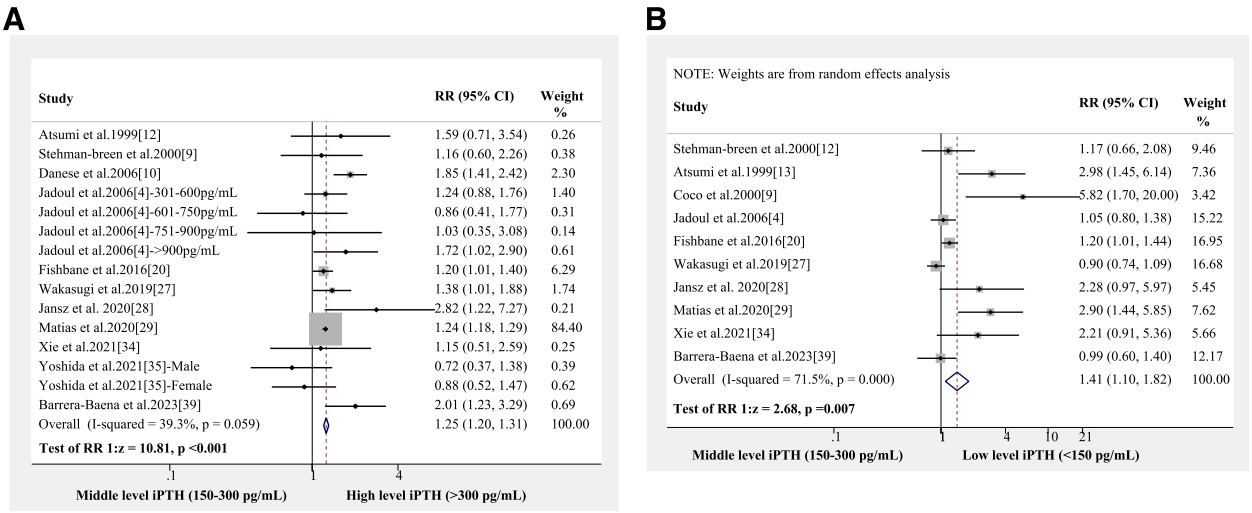

Fig. 2 Risk ratios (RRs) for fractures in dialysis patients associated with intact parathyroid hormone (iPTH) levels from pooled studies. **A** Pooled results from studies assessing fractures associated with high iPTH. **B** Pooled results from studies assessing fractures associated with low iPTH

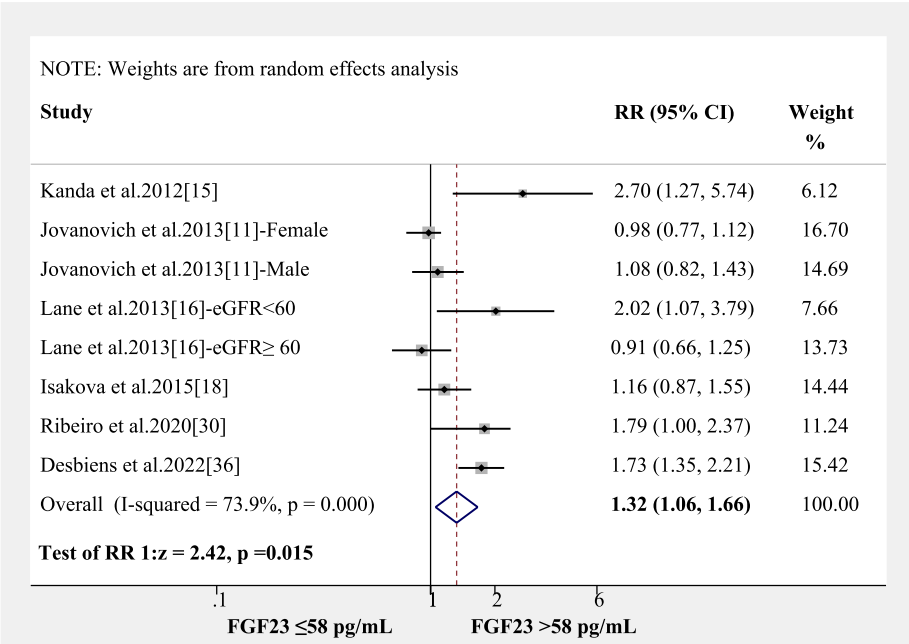

Fig. 3 Risk ratios (RRs) for fractures in CKD patients without dialysis associated with fibroblast growth factor-23 (FGF23) levels from pooled studies

shown that FGF23 inhibits the Wnt pathway, exacerbating bone loss in CKD [44]. Elevated FGF23 levels in uremic models suppress Wnt signaling, leading to reduced osteoblastic activity and bone formation. Additionally, iPTH enhances FGF23 expression, further inhibiting Wnt signaling, which results in a cycle of bone resorption and mineralization defects [45]. Besides Wnt/β-Catenin, other pathways like RANK/RANKL/OPG also contribute to CKD-related bone disorders [46]. These pathways collectively influence bone fragility in CKD, highlighting the need for targeted therapies to modulate them and improve bone health in this population.

In pre-dialysis CKD patients, an iPTH level below 70 pg/ml was associated with a high risk of low bone mineral density (BMD), and patients with adynamic bone disease (ABD) and osteomalacia (OM) exhibited lower trabecular bone volume. Low turnover bone disease, as manifested by ABD and OM, emerged as a hallmark of

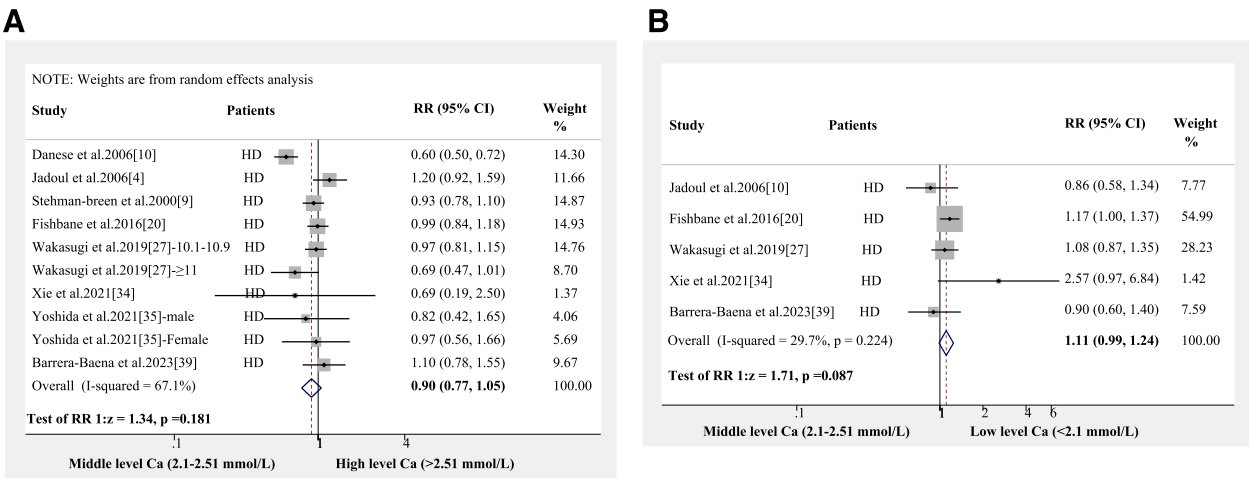

Fig. 4 Risk ratios (RRs) for fractures in CKD patients with dialysis associated with calcium (Ca) levels from pooled studies. **A** Pooled results from studies assessing fractures associated with high Ca. **B** Pooled results from studies assessing fractures associated with low Ca

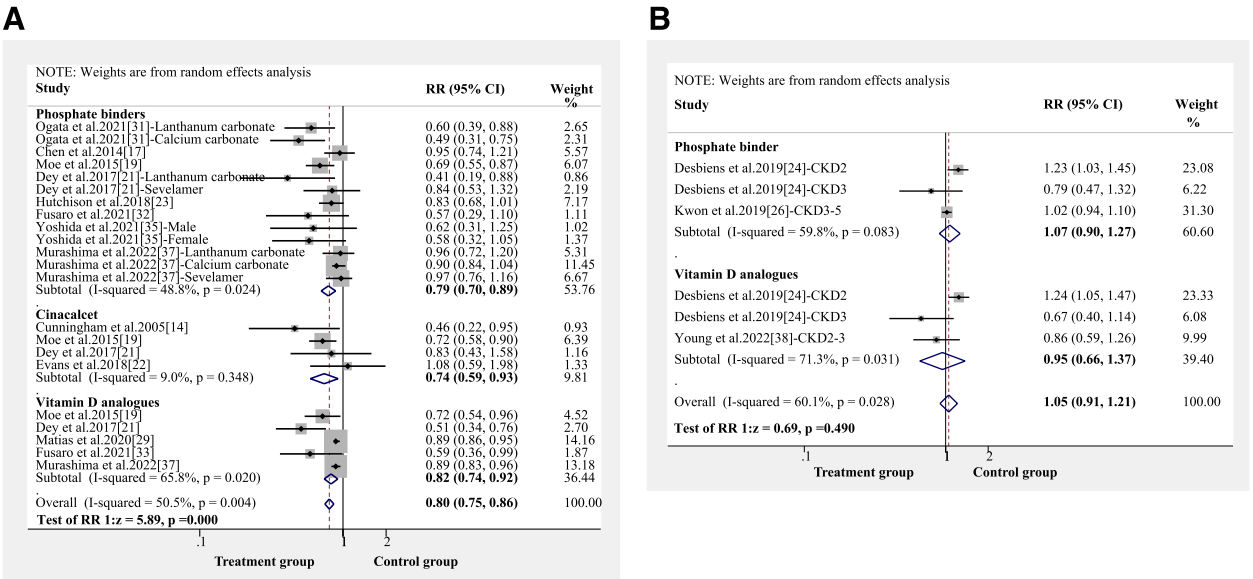

Fig. 5 Risk ratios (RRs) for fractures in CKD patients associated with drug treatments from pooled studies. **A** Pooled results from studies assessing fractures in CKD patients with dialysis of drug treatments. **B** Pooled results from studies assessing fractures in CKD patients without dialysis of drug treatments

bone loss [47]. Bone histomorphometric analysis also indicated an independent correlation between serum FGF23 levels and bone volume parameters in rats with experimentally induced CKD [48].

The mechanism by which hyperphosphatemia induces an elevated risk of fractures is not fully elucidated. Potential mechanisms include the suppression of osteoblastic proliferation through insulin-like growth factor 1 and osteopontin gene expression [49]. Hyperphosphatemia has also been implicated in increasing osteoblast apoptosis and reducing bone formation [50], as well as inhibiting bone resorption through the stimulation of osteoblast-produced osteoprotegerin [51].

Conversely, it is noteworthy that hypophosphatemia is associated with an increased risk of fractures in CKD population. Phosphate plays crucial roles in numerous biological processes, and chronic hypophosphatemia leads to impaired mineralization of the bone matrix, resulting in conditions such as rickets and osteomalacia, as observed in X-Linked Hypophosphatemia (XLH) and FGF23-related hypophosphatemic diseases [52]. Bones from mice with XLH exhibit enlarged osteocyte

lacunae, enhanced osteocyte expression of genes related to bone remodeling, and impaired canalicular structure [53]. In vitro studies have demonstrated that hypophosphatemia leads to rickets by impairing caspase-mediated apoptosis of hypertrophic chondrocytes [54]. However, research on the relationship between hypophosphatemia and osteoblasts is limited. Future studies on low phosphorus and osteoblasts may provide insights into why low phosphorus increases the risk of fractures.

The efficacy of phosphate binders in reducing the risk of fractures in CKD patients has been a subject of controversy. Phosphate binders encompass calcium-based phosphate binders (CPB) and non-calcium-based phosphate binders (NCPB), including sevelamer and lanthanum. Early studies with small sample sizes in hemodialysis patients suggested that NCPB was associated with lower BMD at the lumbar spine and distal radius compared to CPB [55]. However, another small sample study in incident hemodialysis patients found no significant differences in lumbar and femoral BMD between lanthanum carbonate and calcium carbonate groups [56].

A prospective two-year study in chronic dialysis patients, using dual X-ray absorptiometry (DXA) and quantitative computed tomography (QCT) to measure BMD changes, indicated that vitamin D analogs and phosphate binders did not protect against bone loss [57]. Cinacalcet showed protective effects in univariate analysis but not in multivariable analysis [57]. There are limited trials investigating bone histomorphometric changes through bone biopsy after phosphate binder therapy. A 54-week randomized study with 119 hemodialysis patients comparing the effects of sevelamer hydrochloride and calcium carbonate on bone demonstrated that sevelamer did not result in statistically significant changes in bone turnover or mineralization compared to calcium carbonate. However, sevelamer was associated with increased bone formation and improved trabecular architecture [58]. In a small trial with hemodialysis patients, cinacalcet treatment decreased iPTH and reduced activation frequency, bone formation rate/bone surface, and fibrosis surface/bone surface [59]. Despite the prevalent use of paricalcitol or doxercalciferol in stage 5 CKD patients, there is limited prospective human research on their effects on bone. A six-month prospective trial demonstrated that calcitriol treatment decreased bone turnover, bone resorption and formation, and reduced woven osteoid and fibrosis. It also improved mineralization and parameters of bone architecture in hemodialysis patients [60]. In rats with CKD, calcitriol positively influenced bone microarchitecture, achieving normal trabecular connectivity [61].

Considering that excessive suppression of iPTH may increase fracture risk, iPTH levels should be monitored during treatment with vitamin D analogs and cinacalcet. Maintaining an appropriate balance between therapeutic benefits and potential risks is essential. Future research should focus on determining the optimal therapeutic range for iPTH suppression to ensure that the fracture risk reduction achieved with these therapies is not compromised by overly aggressive suppression of iPTH.

This meta-analysis is subject to several potential limitations. Firstly, the majority of studies included are observational or prospective/retrospective trials, with only two randomized controlled trials (RCTs). A meta-analysis incorporating high-quality RCT data would enhance the persuasiveness of the findings. Secondly, there is notable heterogeneity in the analysis of the association between low iPTH levels and fracture risk (I squared = 71.5, Fig. 2B), likely due to variations in study design (Figure S2). Future RCTs should further investigate and confirm the association of low iPTH with an increased risk of fractures in CKD population. Thirdly, the limited number of papers addressing low phosphate (5 papers), as well as the effects of vitamin D analogues (5 papers) and cinacalcet (4 papers) on fracture risk in the CKD population, underscores the need for more clinical trials to validate the association of low phosphate with the risk of fractures and to further establish the protective effects of vitamin D analogues and cinacalcet on bone.

In summary, our meta-analysis reveals that elevated serum phosphate, iPTH, and FGF23 are associated with an increased risk of fractures, while low phosphate and low iPTH also contribute to an elevated risk of fractures in CKD population. Regarding calcium levels, while higher calcium levels showed a trend towards reducing fracture risk, this finding was not statistically significant. Similarly, lower calcium levels tended to increase fracture risk, but again, this was not statistically significant. To better understand the relationship between these factors and fracture risk, further research is warranted, particularly regarding the impact of calcium levels on fracture risk in CKD patients. Future studies should consider larger sample sizes and longer follow-up periods to validate these trends and explore potential clinical intervention strategies. Given the limited data available on non-dialysis CKD populations, future research should focus on conducting trials specifically targeting this group to better understand the efficacy of treatments such as phosphate binders, cinacalcet, and vitamin D analogs in non-dialysis patients. Addressing this gap will provide valuable insights and guide clinical decision-making in the management of mineral bone disorders in this population.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-025-03992-w.

Supplementary Material 1: Figure S1. Study selection process.

Supplementary Material 2: Figure S2. Pooled results from studies assessing fractures associated with low iPTH by study type.

Supplementary Material 3: Figure S3. The sensitivity analyses of studies. (A) The sensitivity analyses of studies assessing fractures associated with high Pi. (B) The sensitivity analyses of studies assessing fractures associated with low Pi. (C) The sensitivity analyses of studies assessing fractures associated with high iPTH. (D) The sensitivity analyses of studies assessing fractures associated with low iPTH. (E) The sensitivity analyses of studies assessing fractures associated with fibroblast growth factor-23 (FGF23). (F) The sensitivity analyses of studies assessing fractures associated with high Ca. (G) The sensitivity analyses of studies assessing fractures associated with low Ca. (H) The sensitivity analyses of studies assessing fractures in CKD patients with dialysis of drug treatments. (I) The sensitivity analyses of studies assessing fractures in CKD patients without dialysis of drug treatments.

Supplementary Material 4: Figure S4. The Egger's publication bias plot of studies. (A) The Egger's publication bias plot of studies assessing fractures associated with high Pi. (B) The Egger's publication bias plot of studies assessing fractures associated with high iPTH. (C) The Egger's publication bias plot of assessing fractures in CKD patients with dialysis of drug treatments.

Supplementary Material 5.

Acknowledgements
NA.

Authors' contributions
HM Jin and ZB Ye conceived and designed the study. Y Liu, ZX Zhang, CS Fu selected the articles, extracted and analysed the data. XH Yang wrote the first draft of the manuscript. XH Yang, HM Jin and ZB Ye interpreted the data and contributed to the writing of the final version of the manuscript. All authors agreed with the results and conclusions of this Article. Y Liu, ZX Zhang, CS Fu contributed equally to this paper.

Funding
No funding was received.

Data availability
Data associated with the study has not been deposited into a publicly available repository. Data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 21 September 2024 Accepted: 29 January 2025
Published online: 11 February 2025

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