kidney and dialysis

MDPI

Protocol

Global Prevalence of Osteoporosis in Chronic Kidney Disease: Protocol for a Systematic Review

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Abstract: Abnormalities in mineral metabolism, soft tissue calcifications, and bone health are common in people with chronic kidney disease (CKD). In this scenario, osteoporosis is a highly prevalent skeletal disorder characterized by reduced bone strength predisposing patients to adverse health outcomes. We will summarize the evidence of the prevalence of osteoporosis in adults with CKD. Methods: We will perform a comprehensive literature search using MEDLINE, EMBASE, Web of Science, CINAHL, and LILACS databases, without date or language restrictions from inception until January 2021. We will include cross-sectional, case–control, or cohort studies that report prevalence data of osteoporosis in adults aged ≥18 years with CKD in stages 3a–5, including those receiving kidney replacement therapies. We will exclude conference abstracts and experimental studies. The primary outcome will be the prevalence of osteoporosis according to the World Health Organization criteria (*T*-score ≤ −2.5). Two independent reviewers will screen title and abstract, full-text review, critical appraisal of the quality of studies, risk of bias, heterogeneity, and data extraction. The quality of the included studies will be assessed with the Joanna Briggs Institute (JBI) appraisal checklist. The overall prevalence of the studies will be synthesized using random-effects meta-analysis. This systematic review will be reported according to the guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) and the JBI methodological guidance for systematic reviews of observational epidemiological studies. The qualitative and quantitative results will be synthesized and presented in tables, figures or graphs.

Keywords: osteoporosis; chronic kidney disease; osteopenia; bone mineral density; renal osteodystrophy

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1. Introduction

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health [1]. CKD is a worldwide health problem with an estimated global prevalence of 11–13% [2]. This prevalence is rising, driven by an aging population and the increasing incidence of cardiometabolic diseases [2]. In 2017, 1.2 million people died from CKD worldwide, an increase of 29.3% compared to 1990 [3].

Chronic Kidney Disease leads to systemic changes in mineral and bone disorders (MBD), a common and universal complication in the CKD population. According to the Kidney Disease Improving Global Outcomes (KDIGO), the term CKD–MBD is defined as:

> *"A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following: (i) abnormal metabolism of calcium, phosphorus, parathyroid hormone, or vitamin D; (ii) abnormalities in bone turnover, mineralization, volume, linear growth, or strength; (iii) vascular or other soft-tissue calcification [4]."*

The pathophysiology of CKD–MBD is complex and has not been fully elucidated to date, but it involves complex crosstalk between bones and kidneys, the parathyroid gland, the intestine, and other tissues [5,6]. Thus, the mechanisms regulating mineral homeostasis and metabolic processes in bone tissue are modified, which consequently can contribute to the impairment of bone remodeling, bone strength loss, and pathogenesis of CKD-related osteoporosis [7,8]. Moreover, CKD–MBD is associated with an increased risk of cardiovascular calcification, morbimortality, and fracture and contributes to reduced quality of life [4,9–11].

Osteoporosis is considered a form of renal osteodystrophy. Operationally, the World Health Organization (WHO, Geneva, Switzerland) defines osteoporosis as a low bone mineral density (BMD) assessed by dual X-ray absorptiometry (DXA). Increasing evidence suggests that CKD and osteoporosis are highly co-prevalent in different stages of the disease [12–14]. Previous studies showed that CKD progression is associated with reduction of BMD [15–17]. Additionally, in people with CKD, the fracture risk, risk of hospitalization, and mortality are higher than those in the general population [18–20]. Data from the USA shows that the economic burden of osteoporotic fracture in CKD patients exceeded USD 600 million in 2010 [11].

In 2017, the KDIGO Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease—Mineral and Bone Disorder has recommended using DXA to assess osteoporotic fracture risk in people with CKD in stages G3–G5D with risk factors for osteoporosis [21]. Recently, the European Renal Osteodystrophy (EUROD) workgroup has also recommended testing BMD in people with CKD G4–G5D as well as the use of DXA for postmenopausal women, or men aged 50 years or over [22]. These recommendations are an important advance for clinical nephrology practice, as diagnosis of osteoporosis and assessment of fracture risk in people with CKD may reduce the adverse risks of this condition.

Despite the high prevalence of osteoporosis in people with CKD, to our knowledge, there is a lack of published research summarizing the prevalence estimates of osteoporosis in this population at the global level. However, these estimates serve as the basis for the development of preventative and management strategies, as well as providing useful data for health care planning decisions. To fill this gap in the knowledge, we will conduct a systematic review to identify the global prevalence of osteoporosis in adults with CKD.

2. Materials and Methods

2.1. Protocol and Registration

The present protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42020211077. This present study protocol in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement [23]. The proposed systematic review will be reported in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines [24] and the Joanna Briggs Institute (JBI, Adelaide, SA, Australia) methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data [25].

2.2. Eligibility Criteria

The studies will be selected according to the CoCoPop mnemonic criteria (condition, context, and population) recommend by the JBI [25].

2.2.1. Condition

Observational studies that reported the prevalence of osteoporosis. The diagnosis of osteoporosis will be defined using the WHO criteria [26]. Specifically, osteoporosis is defined as T-score ≤ -2.5 the average value for young adults, measured by dual-energy X-ray absorptiometry. Measurements must have been performed in sites of biological relevance, including hip, lumbar spine, femoral neck, or forearm. Studies that defined

osteoporosis according to self-report or other methods (e.g., computerized tomography) will be excluded.

2.2.2. Context

No restriction will be placed on the setting or context of the included studies (e.g., urban vs. rural). Studies in hospital inpatient services, hemodialysis clinics, outpatient programs, community-based facilities, or others will be included.

2.2.3. Participants (Population)

We will include studies that involved CKD people aged ≥18 years older in stages 3a−5 (GFR ≤ 45 mL/min/1.73 m^2), including those receiving kidney replacement therapies (e.g., hemodialysis, peritoneal dialysis, or kidney transplant).

2.2.4. Types of Studies

Eligible studies will be observational studies, including cohort, cross-sectional, and case–control studies, that reported data of the prevalence of osteoporosis in CKD patients using WHO definition criteria. Conference abstracts and letters to editors or any studies that were not published as full reports will be excluded, as well as experimental designs.

2.3. Information Sources and Search Strategy

An electronic search will be carried out in the following databases by one author: MEDLINE (1950−Jan 2021), EMBASE (1947−Jan 2021), Web of Science (1945−Jan 2021), CINAHL (1982−Jan 2021), and LILACS (1982−Jan 2021). The search will be conducted combining terms related to osteoporosis and CKD. A draft search strategy for PubMed/MEDLINE is provided in Table A1. Additionally, reference lists of retrieved studies will be hand-searched. The search will not be restricted to any specific language or date of publication. The studies in languages other than English will be translated adequately using Google translate. The search strategy was peer-reviewed and discussed between all authors and experts in the field.

2.4. Study Selection

Two reviewers (MPD and HSR) will independently screen the title, abstract, and full-text using COVIDENCE software (Veritas Health Innovation, Melbourne, AU, Australia). Discrepancies will be documented using Cohen's kappa coefficient [27] and resolved by discussion between the two reviewers. When necessary, a third assessor will be involved (SGRN). We will include a PRISMA flow diagram to document the screening process [28].

2.5. Data Extraction

Relevant information will be extracted by first author (MPD), using the standardized data extraction method in Excel, and checked by a second author (HSR). Disagreements will be resolved through consensus and, if necessary, a third author will be contacted (SGRN). The following information will be extracted:

i. General information: author(s), year of publication, country, and language;
ii. Study design;
iii. Participants' characteristics: sample size, mean or median age, proportions of female participants, ethnicity, stages of CKD, type of kidney replacement therapy, risk factors for osteoporosis (i.e., comorbidities, pharmacological therapy, and menopause, fracture history) and setting;
iv. Outcome information: prevalence of osteoporosis. Where only primary data (sample size and number of outcomes) are provided, these will be used to calculate the prevalence of the condition. For cohort studies that assess the prevalence of osteoporosis in CKD people, only data from the baseline will be extracted for analysis. Furthermore, the model of the device will be analyzed.

For studies with insufficient data, the author(s) will be contacted via e-mail. We will allow one week for author(s) to reply, and a second e-mail will be sent as a reminder with

an additional seven days for a response. In cases where no response is received, available data will be used.

2.6. Assessment of Methodological Quality

The methodological quality of eligible studies will be evaluated independently by two reviewers (MPD and HSR) using the JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data [25]. The JBI critical appraisal checklist consists of nine items with four possible responses (Yes, No, Unclear, or Not applicable). Any disagreements during the methodological quality assessment will be resolved through consensus and, if necessary, a third author will be contacted (SGRN). Quality scores will be presented in a table.

2.7. Data Synthesis

The systematic review will provide summary tables and narrative synthesis to explain the characteristics and findings of the included studies (e.g., characteristics of studies, condition, context, and population). We will estimate pooled prevalence of osteoporosis using a random-effects meta-analysis model. However, to minimize extreme prevalence estimates of studies in the pooled prevalence, we will stabilize the variance of individual studies with the use of the Freeman–Tukey double arcsine transformation. The results of the meta-analysis will be presented with a 95% confidence interval (CI), and additionally list the proportions (expressed as a percentage), with their 95% CI, found in the individual studies included in the meta-analysis show graphically in a forest plot. Statistical heterogeneity will be determined by visual inspection of the forest plots and quantified considering I-squared (I^2) statistic. The I^2 values of 0−25%, 50%, and 75% will be considered evidence of low-, moderate-, and high heterogeneity, respectively. In case of sufficient included studies, a meta-analysis will be conducted for exploratory analysis, which will be undertaken based on: location (continent/country), gender (e.g., male vs. female); age (middle-age adult vs. older adult); race/ethnic background (e.g., black vs. white vs. Asian); bone site (e.g., femoral neck vs. lumbar spine); stages of CKD (e.g., stage 3a vs. 4, or hemodialysis vs. peritoneal dialysis); risk factor (e.g., secondary hyperparathyroidism, specific ages of both genders, pre-/post-menopausal woman), or quality of studies included (e.g., high risk of bias vs. low risk of bias). Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, NJ, USA, EUA) will be used to conduct all analyses.

2.8. Meta-Bias

Depending on the data, we will assess the presence of publication bias using funnel plots and with Begg's and Egger's test, with $p < 0.10$ indicating significant publication bias [29]. Besides, in case of heterogeneity in the included studies, we will perform sensitive analysis or metaregression to explore potential sources. These characteristics (e.g., age group, sex, study setting, year of study, geographic location, and study quality) significantly associated with the heterogeneity ($p < 0.05$) will be included in a multivariate hierarchical model.

Author Contributions: M.P.D.: Original draft preparation, supervision, and final revision; H.S.R. and S.G.R.N.: Substantial contributions to the conception and design of the work; L.S.A.: Writing reviewing, methodology, and writing reviewing; J.L.V.: Revising the paper critically for important intellectual content and final approval; R.M.L.: Draft preparation, revising the paper critically for important intellectual content and final approval. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Ethical review and approval were not applicable since this is a protocol paper for a PROSPERO-registered systematic review. The findings of this study will be disseminated through relevant peer-reviewed publication(s), online repositories/media, and conference presentation(s), where appropriate.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. Search strategy. MEDLINE (PubMed). Search conducted 4 February 2021.

Query	Search	Records Retrieved
#1	exp renal insufficiency, chronic/	117,737
#2	((kidney or renal) adj5 (insufficienc * or failure *)).tw,kf.	126,769
#3	(end?stage renal or end?stage kidney or chronic kidney or chronic renal).tw,kf.	89,087
#4	exp Renal Replacement Therapy/	213,825
#5	((renal or kidney) adj3 (transplant * or replacement *)).tw,kf.	100,712
#6	(predialysis or pre-dialysis or dialysis or hemodialys * or h?emofiltration or h?emodiafiltration or peritoneal dialys *).tw,kf.	154,361
#7	or/1–6	430,190
#8	exp osteoporosis/ or bone density/	89,564
#9	(osteoporo* or bone densit* or bone mineral densit* or bone mass or bone quantit* or bone quality or bone deminerali* or bone strength or bone los*).tw,kf.	139,285
#10	or/8–9	156,695
#11	7 and 10	3709
#12	exp animals/ not humans/	4,776,757
#13	11 not 12	3544
#14	exp clinical trial/	879,988
#15	13 not 14	3257
#16	review.pt.	2,750,483
#17	15 not 16	2330

References

1. KDIGO CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int. Suppl.* **2013**, *3*, 1–150. [CrossRef]
2. Hill, N.R.; Fatoba, S.T.; Oke, J.L.; Hirst, J.A.; O'Callaghan, C.A.; Lasserson, D.S.; Hobbs, F.D.R. Global Prevalence of Chronic Kidney Disease—A Systematic Review and Meta-Analysis. *PLoS ONE* **2016**, *11*, e0158765. [CrossRef] [PubMed]
3. Bikbov, B.; Purcell, C.A.; Levey, A.S.; Smith, M.; Abdoli, A.; Abebe, M.; Adebayo, O.M.; Afarideh, M.; Agarwal, S.K.; Agudelo-Botero, M.; et al. Global, Regional, and National Burden of Chronic Kidney Disease, 1990–2017: A Systematic Analysis for the Global Burden of Disease Study 2017. *Lancet* **2020**, *395*, 709–733. [CrossRef]
4. Moe, S.; Drüeke, T.; Cunningham, J.; Goodman, W.; Martin, K.; Olgaard, K.; Ott, S.; Sprague, S.; Lameire, N.; Eknoyan, G. Definition, Evaluation, and Classification of Renal Osteodystrophy: A Position Statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* **2006**, *69*, 1945–1953. [CrossRef]
5. Waziri, B.; Duarte, R.; Naicker, S. Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD): Current Perspectives. *Int. J. Nephrol. Renovasc. Dis.* **2019**, *12*, 263–276. [CrossRef]
6. Elder, G.J. Pathophysiology of CKD-MBD. *Clin. Rev. Bone Miner. Metab.* **2012**, *10*, 128–141. [CrossRef]
7. Zheng, C.-M.; Zheng, J.-Q.; Wu, C.-C.; Lu, C.-L.; Shyu, J.; Yung-Ho, H.; Wu, M.-Y.; Chiu, I.-J.; Wang, Y.-H.; Lin, Y.-F.; et al. Bone Loss in Chronic Kidney Disease: Quantity or Quality? *Bone* **2016**, *87*, 57–70. [CrossRef]
8. Hsu, C.-Y.; Chen, L.-R.; Chen, K.-H. Osteoporosis in Patients with Chronic Kidney Diseases: A Systemic Review. *Int. J. Mol. Sci.* **2020**, *21*, 6846. [CrossRef]
9. Covic, A.; Vervloet, M.; Massy, Z.A.; Torres, P.U.; Goldsmith, D.; Brandenburg, V.; Mazzaferro, S.; Evenepoel, P.; Bover, J.; Apetrii, M.; et al. Bone and Mineral Disorders in Chronic Kidney Disease: Implications for Cardiovascular Health and Ageing in the General Population. *Lancet Diabetes Endocrinol.* **2018**, *6*, 319–331. [CrossRef]
10. Block, G.A. Mineral Metabolism, Mortality, and Morbidity in Maintenance Hemodialysis. *J. Am. Soc. Nephrol.* **2004**, *15*, 2208–2218. [CrossRef] [PubMed]
11. Kim, S.M.; Long, J.; Montez-Rath, M.; Leonard, M.; Chertow, G.M. Hip Fracture in Patients with Non-Dialysis-Requiring Chronic Kidney Disease. *J. Bone Miner. Res.* **2016**, *31*, 1803–1809. [CrossRef] [PubMed]
12. Klawansky, S.; Komaroff, E.; Cavanaugh, P.F.; Mitchell, D.Y.; Gordon, M.J.; Connelly, J.E.; Ross, S.D. Relationship between Age, Renal Function and Bone Mineral Density in the US Population. *Osteoporos. Int.* **2003**, *14*, 570–576. [CrossRef] [PubMed]

13. Nickolas, T.L.; McMahon, D.J.; Shane, E. Relationship between Moderate to Severe Kidney Disease and Hip Fracture in the United States. *J. Am. Soc. Nephrol.* **2006**, *17*, 3223–3232. [CrossRef] [PubMed]
14. Najar, M.S.; Mir, M.M.; Muzamil, M. Prevalence of Osteoporosis in Patients with Chronic Kidney Disease (Stages 3–5) in Comparison with Age- and Sex-Matched Controls: A Study from Kashmir Valley Tertiary Care Center. *Saudi J. Kidney Dis. Transpl.* **2017**, *28*, 538–544. [CrossRef]
15. Aggarwal, H.K.; Jain, D.; Yadav, S.; Kaverappa, V. Bone Mineral Density in Patients with Predialysis Chronic Kidney Disease. *Ren. Fail.* **2013**, *35*, 1105–1111. [CrossRef]
16. Huang, J.F.; Zheng, X.Q.; Sun, X.L.; Zhou, X.; Liu, J.; Li, Y.M.; Wang, X.Y.; Zhang, X.L.; Wu, A.M. Association between Bone Mineral Density and Severity of Chronic Kidney Disease. *Int. J. Endocrinol.* **2020**, *2020*. [CrossRef]
17. de Carvalho, K.S.B.; Vasco, R.F.V.; Custodio, M.R.; Jorgetti, V.; Moysés, R.M.A.; Elias, R.M. Chronic Kidney Disease Is Associated with Low BMD at the Hip but Not at the Spine. *Osteoporos. Int.* **2019**, *30*, 1015–1023. [CrossRef]
18. Iseri, K.; Qureshi, A.R.; Dai, L.; Ripsweden, J.; Heimbürger, O.; Barany, P.; Bergström, I.; Stenvinkel, P.; Brismar, T.B.; Lindholm, B. Bone Mineral Density at Different Sites and 5 Years Mortality in End-Stage Renal Disease Patients: A Cohort Study. *Bone* **2020**, *130*, 115075. [CrossRef]
19. Yenchek, R.H.; Ix, J.H.; Shlipak, M.G.; Bauer, D.C.; Rianon, N.J.; Kritchevsky, S.B.; Harris, T.B.; Newman, A.B.; Cauley, J.A.; Fried, L.F. Bone Mineral Density and Fracture Risk in Older Individuals with CKD. *Clin. J. Am. Soc. Nephrol.* **2012**, *7*, 1130–1136. [CrossRef]
20. Tentori, F.; McCullough, K.; Kilpatrick, R.D.; Bradbury, B.D.; Robinson, B.M.; Kerr, P.G.; Pisoni, R.L. High Rates of Death and Hospitalization Follow Bone Fracture among Hemodialysis Patients. *Kidney Int.* **2014**, *85*, 166–173. [CrossRef]
21. Ketteler, M.; Block, G.A.; Evenepoel, P.; Fukagawa, M.; Herzog, C.A.; McCann, L.; Moe, S.M.; Shroff, R.; Tonelli, M.A.; Toussaint, N.D.; et al. Executive Summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: What's Changed and Why It Matters. *Kidney Int.* **2017**, *92*, 26–36. [CrossRef] [PubMed]
22. Evenepoel, P.; Cunningham, J.; Ferrari, S.; Haarhaus, M.; Javaid, M.K.; Lafage-Proust, M.-H.; Prieto-Alhambra, D.; Torres, P.U.; Cannata-Andia, J.; Vervloet, M.; et al. European Consensus Statement on the Diagnosis and Management of Osteoporosis in Chronic Kidney Disease Stages G4–G5D. *Nephrol. Dial. Transplant.* **2021**, *36*, 42–59. [CrossRef] [PubMed]
23. Moher, D.; Shamseer, L.; Clarke, M.; Ghersi, D.; Liberati, A.; Petticrew, M.; Shekelle, P.; Stewart, L.A. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 Statement. *Syst. Rev.* **2015**, *4*, 1. [CrossRef]
24. Stroup, D.F.; Berlin, J.A.; Morton, S.C.; Olkin, I.; Williamson, D.; Rennie, D.; Moher, D.; Becker, B.J.; Sipe, T.A.; Thacker, S.B. Meta-Analysis of Observational Studies in Epidemiology: A Proposal for Reporting. *JAMA* **2000**, *283*, 2008–2012. [CrossRef]
25. Munn, Z.; Moola, S.; Lisy, K.; Riitano, D.; Tufanaru, C. Methodological Guidance for Systematic Reviews of Observational Epidemiological Studies Reporting Prevalence and Cumulative Incidence Data. *Int. J. Evid. Based Healthc.* **2015**, *13*, 147–153. [CrossRef] [PubMed]
26. Kanis, J.A.; Melton, L.J.; Christiansen, C.; Johnston, C.C.; Khaltaev, N. The Diagnosis of Osteoporosis. *J. Bone Miner. Res.* **2009**, *9*, 1137–1141. [CrossRef] [PubMed]
27. Landis, J.R.; Koch, G.G. The Measurement of Observer Agreement for Categorical Data. *Biometrics* **1977**, *33*, 159. [CrossRef] [PubMed]
28. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *J. Clin. Epidemiol.* **2009**, *62*, 1006–1012. [CrossRef]
29. Egger, M.; Smith, G.D.; Schneider, M.; Minder, C. Bias in Meta-Analysis Detected by a Simple, Graphical Test. *BMJ* **1997**, *315*, 629–634. [CrossRef] [PubMed]