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What are the efficacy and safety of pharmacological interventions versus placebo, no treatment or usual care for osteoporosis in people with chronic kidney disease stages 3-5D? - A Cochrane Review summary with commentary

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The aim of this commentary is to discuss from a rehabilitation perspective the Cochrane Review "Pharmacological interventions versus placebo, no treatment or usual care for osteoporosis in people with chronic kidney disease stages 3-5D" by Hara et al.[a], published by Cochrane Kidney and Transplant Group. This Cochrane Corner is produced in agreement with the Journal of Musculoskeletal and Neuronal Interactions by Cochrane Rehabilitation with views* of the review summary authors in the "implications for practice" section.

Background

Osteoporosis is a systemic skeletal disease characterized by bone density reduction and bone microarchitecture changes that compromise bone strength increasing the risk of fragility fractures, that are the main and often the first clinical manifestations of the disease[2]. Several diseases can be the cause of osteoporosis, such as endocrine, hematological, gastrointestinal, rheumatic, and kidney disorders[3]. The incidence of hip and vertebral fragility fractures in patients with chronic kidney disease (CKD) requiring hemodialysis (HD) is significantly higher (3-fold and 50%, respectively) than those without CKD, along with increased risk of hospitalization and mortality[4].

National and international guidelines recommend both pharmacological and non-pharmacological treatments, including rehabilitative interventions for managing people affected by osteoporosis[5]. However, the management of osteoporosis and fragility fractures in CKD patients remain an unmet need. A Cochrane Review[1] addresses pharmacological osteoporosis treatment in this population.

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* The views expressed in the summary with commentary are those of the Cochrane Corner authors (different than the original Cochrane Review authors) and do not represent the Cochrane Library or Wiley.

Pharmacological interventions versus placebo, no treatment or usual care for osteoporosis in people with chronic kidney disease stages 3-5D[1]

What is the aim of this Cochrane review?

The aim of this Cochrane Review was to investigate the efficacy and safety of drug therapy for osteoporosis for people with CKD stages 3-5, and those undergoing dialysis (5D).

What was studied in the Cochrane review?

The population addressed in this review was people of any age with CKD stages 3–5D[6] as with low bone mass or osteoporosis (T-score <–2.0 SD).

The interventions studied were anti-osteoporotic drugs administered for at least 6 months.

The intervention was compared to placebo, no treatment, or usual care.

The primary outcomes studied were the incidence of fracture at any sites (clinical or radiographic), the mean bone mineral density (BMD) change measured by dual-energy x-ray absorptiometry (DXA) at the femoral neck, total hip, lumbar spine, or distal radius, and the incidence of adverse events (AEs). Secondary outcomes were death from any cause and quality of life (QoL).

Search methodology and up-to-dateness of the Cochrane review?

The review authors searched for studies that had been published up to 25 January 2021 in the Cochrane Kidney and Transplant Register of Studies, containing papers identified from the Cochrane Central Register of Controlled Studies (CENTRAL), MEDLINE OVID SP, EMBASE OVID SP, the International Clinical Trials Register (ICTRP) Search Portal, ClinicalTrials.gov, kidney-related journals and the proceedings of major kidney conferences.

What are the main results of the Cochrane review?

The review included 7 randomized controlled trials (RCTs) involving 9164 women with post-menopausal osteoporosis (PMO) and CKD stages 3 to 5D.

According to the Cochrane Systematic Review (CSR), in PMO with CKD stages 3-4 at 19-to-54-month follow-up, anti-osteoporotic drugs (abaloparatide, alendronate, denosumab, raloxifene, teriparatide) compared to placebo:

- May reduce the risk of radiographic vertebral fractures (RR 0.52, 95% confidence interval (CI) 0.39-0.69, 5 RCTs, 9,054 patients) based on low certainty of the evidence.
- Probably makes little or no difference in terms of clinical fragility fractures risk (RR 0.91, 95% CI 0.79-1.05, 4 RCTs, 5,827 patients) based on moderate certainty of the evidence.
- Probably makes little or no difference in terms of AEs risk (RR 0.99, 95% CI 0.98-1.00, 5 RCTs, 9,054 patients) based on moderate certainty of the evidence).

Mean changes in femoral neck, total hip and lumbar spine BMD were reported in the intervention group only, accounting for 0.5-5%, 5-6% and 1-15%, respectively (very low certainty of the evidence).

In this population, mortality risk at 36 to 54 months were not estimable because total death ranged from 0.7 to 1.6% (low certainty of the evidence), while data about mean change in distal radius BMD and QoL were not reported.

According to the CSR, for what concerns PMO with CKD stages 5 and 5D treated with raloxifene versus those receiving placebo:

- It is uncertain whether the intervention reduces the risk of clinical fragility fractures (RR 0.33, 95% CI 0.01-7.87, 1 RCT, 60 patients, very low certainty of the evidence).
- It is uncertain whether the intervention increases the femoral neck BMD (mean difference, MD 0.01, 95% CI 0.00-0.02, 2 RCTs, 110 patients, very low certainty of the evidence).
- Raloxifene may increase the lumbar spine BMD (MD 0.03, 95% CI 0.03-0.04, 2 RCTs, 110 patients, low certainty of the evidence).
- It is uncertain whether the intervention affects the mortality risk (RR 1.00, 95% CI 0.22-4.56, 2 RCTs, 110 patients, very low certainty of the evidence).

In this population, no data about radiographic vertebral fractures, mean BMD changes at total hip and distal radius, AEs, and QoL were reported.

What did the authors conclude?

The authors concluded that in PMO with CKD stages 3-4, anti-osteoporotic drugs may reduce the risk of vertebral fracture (s) based on low certainty evidence; while moderate certainty evidence suggests that drug treatment probably makes little or no difference in terms of clinical fracture and AEs. Among PMO with CKD stages 5 and 5D, it is uncertain whether pharmacological treatment reduces the risk of clinical fractures and death because the evidence was judged as very low certainty; while low certainty evidence suggests drug treatment may slightly improve the BMD at the lumbar spine.

What are the implications of the Cochrane evidence for practice in rehabilitation?

From a rehabilitation perspective, people with advanced CKD are at significantly increased risk of functional decline, falls, hip fragility fractures, and mortality than those without CKD[7].

Skeletal involvement occurs in the early stages of CKD (i.e., CKD mineral and bone disorder, CKD-MBD, and renal osteodystrophy, ROD)[8] via different mechanisms, including alterations of mineral metabolism, bone turnover and

mineralization. The complex pathogenesis of CKD-MBD results in challenging therapeutic decision-making. Indeed, the most used antiosteoporotic drugs (i.e., bisphosphonates (BPs)) are contraindicated in patients with severe CKD (eGFR<30 ml/min/1.73 m^2)[9], while hypocalcemia might occur during denosumab treatment in this population[10]. Moreover, low bone turnover might occur in CKD-MBD patients with consequent risk of adynamic bone in those receiving antiresorptive drugs, such as BPs or denosumab[11]. This CSR[1] suggests that there is the possibility that anti-osteoporotic medications reduce vertebral fracture risk based on low certainty evidence; however, with little or no difference in terms of clinical fracture risk based on moderate certainty evidence in PMO with CKD stages 3-4. On the other hand, we do not know whether these drugs reduce the risk of clinical fractures in people with CKD stages 5 and 5D because the certainty of evidence is very low.

Studies suggest that back pain due to vertebral fractures is associated with significant disability which may lead to poor QoL.[13,14] It should be underlined that back pain due to vertebral fragility fractures as well as QoL have not been investigated in the studies evaluated in this CSR. Moreover, it should be clarified the role of the combination of antiosteoporotic drugs and rehabilitative interventions in PMO with CKD, considering that this approach seems to be effective in terms of pain relief and better QoL in patients with multiple vertebral fragility fractures[15].

Finally, future research areas about the efficacy and safety of pharmacological approach to bone loss in CKD people should be addressed, particularly concerning men or pediatric population. This CSR[1] also suggests the investigation of treatment effectiveness and safety in unstable CKD, in each CKD stage, and comparative effectiveness of each antiosteoporotic medication. Given the certainty of evidence is low or very low for some outcomes, the evidence may change with future research to make us better understand the role of antiosteoporotic medications in this population.

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