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Original

Denosumab for osteoporosis in patients suffering from chronic kidney disease; a review on current data

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Abstract

Osteoporosis presents a significant complication within chronic kidney disease (CKD) patients. This complex scenario has led to the utilization of denosumab, a prescription drug, in its management. Our study delves into the realm of literature containing the conjunction of keywords "CKD" OR "Chronic Kidney Disease" AND "Denosumab" within the title, as indexed in the PubMed database. The accumulated evidence overwhelmingly highlights the advantages of denosumab over bisphosphonates in the context of CKD patients. Moreover, a noteworthy finding emerged; denosumab's administration neither impairs kidney functionality nor exhibits variability in its efficacy across diverse renal function spectrums. Amidst its merits, hypocalcemia is a prominent complication; however, judicious measures can aptly govern its impact in this patient cohort. The pivotal facets of adherence and uninterrupted medication courses warrant particular attention. Nevertheless, caution is imperative, as select studies underscore denosumab's contraindication within CKD patients, particularly in stages 4 and 5.

Keywords: Chronic kidney disease, Denosumab, Osteoporosis, Hypocalcemia

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Introduction

Chronic kidney disease (CKD) refers to a condition affecting the kidneys, with a gradual decline in kidney function that occurs over several months to several years. This disorder is common (about 10% to 13% of the population), irreversible, and progressive (1). In general, patients are asymptomatic at first. Later symptoms may include feeling tired, leg swelling, loss of appetite, vomiting, and confusion. Furthermore, individuals with CKD experience elevated cardiovascular complications, which significantly heighten the chances of mortality and hospitalization (2). The complications associated with kidney hormonal dysfunction encompass conditions such as hypertension, bone disorders, and anemia (3). High blood pressure, diabetes, polycystic kidney, and glomerulonephritis could be mentioned as causes of this disease (4). Diagnosis of CKD is possible through a blood test to measure the estimated glomerular filtration rate (eGFR) and a urine test to measure albumin (5). The available treatment options for CKD include conservative management, which is suitable for patients who do not require dialysis, typically those with a GFR above 15 mL/min.

On the other hand, replacement therapy, such as hemodialysis, peritoneal dialysis, and kidney transplantation, is recommended for patients who require more intensive interventions (1). This disease includes six stages, from 1 to 5. Stage 1 signifies either normal or high GFR, while stage 5 represents end-stage renal disease (ESRD).

Osteoporosis in CKD

Mineral and bone disorders and an elevated susceptibility to fractures and osteoporosis are frequently associated with CKD (6). The diagnostic limit of osteoporosis is a T-score ≤ -2.5, determined by the World Health Organization (7). CKD is an independent risk factor for osteoporosis (7). Fractures, particularly in the hip zone, could be followed by complications and high mortality rates (8-10). The decline in GFR among CKD patients sets off a series of metabolic disorders. It disrupts the normal process of bone remodeling, leading to osteoporosis and a subsequent decrease in bone strength (11). Given the strong association between osteoporosis and CKD, adopting a tailored approach to effectively and safely treat osteoporotic patients with renal failure is crucial while ensuring it does not adversely impact the underlying kidney function (12).

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Implication for health policy/practice/research/ medical education

Denosumab is prescribed in patients with mild to moderate CKD. the evidence shows that it has no adverse effect on kidney function and is safe, but it is contraindicated in severe CKD patients (stages 4 and 5).

Denosumab

Denosumab, marketed under the brand names Prolia and Xgeva, is a medication utilized as an anti-resorptive treatment for osteoporosis and various other bone-related conditions. This bone-modifying medication decreases the probability of skeletal-related events in individuals with bone metastases originating from solid tumors (13). Denosumab is a human monoclonal antibody that inhibits the binding of RANKL(receptor activator of nuclear factor-κB ligand) to RANK, a receptor on the osteoclast surface. Decreasing the binding of RANKL to RANK by denosumab inhibits the formation and function of osteoclasts. As a result, bone resorption is reduced, and bone mass is increased (14,15) (as shown in Figure 1). Unlike antiabsorption drugs like bisphosphonates, this drug is not metabolized or excreted through the kidneys (6). Critical adverse effects associated with this drug include hypocalcemia (low levels of calcium in the blood), osteonecrosis of the jaw, and atypical fractures (13). Cessation of denosumab administration eventuates in a rapid reduction in BMD and reversal of the inhibition of bone remodeling (16).

This medicine is presented in two forms (17):

1. Pre-filled syringe 60 mg/mL
2. Vial 120 mg/1.7 mL

Denosumab in CKD

According to previous information, denosumab is one of the drugs prescribed for the management of osteoporosis. Since osteoporosis is common in CKD, denosumab is also widely prescribed for these patients. This review article aims to investigate this drug in CKD patients.

Search strategy

We investigated seven articles in the PubMed database with the keywords CKD or chronic kidney disease and denosumab in the title since 2020. Review articles and letters to the editor were excluded from our study.

Results

Advantages of usage of denosumab

Previous large clinical trials confirmed the positive effects of long-term use of denosumab in terms of increasing bone mineral density (BMD) and reducing fracture risk (12,18,19). Furthermore, denosumab might have better adherence and cost-effectiveness measured up to oral bisphosphonates (20). The greater increase in BMD by denosumab compared to bisphosphonates and the lack of metabolism and excretion of this drug by the kidneys indicate the advantages of prescribing this drug in CKD patients (21,22). However, it should be known that according to the mechanism of action of denosumab, no bone retention will be observed, even in the case of long-term use of this drug (19).

Comparing the effectiveness of denosumab in people with different kidney function

Results of the study by Broadwell et al confirmed that the effectiveness of denosumab is the same in women with normal kidney function compared to women with mild to moderate CKD. They also stated that there is no significant difference in the safety and effectiveness of denosumab in patients with mild stage compared to moderate stage (12).

Effect of denosumab on kidney function

The study by Broadwell et al also reported that long-term use of denosumab does not have a notable effect on renal function in postmenopausal women who have osteoporosis. According to their previous studies, there is no need to adjust the drug dosage in patients with kidney failure because, as mentioned, this drug does not negatively affect kidney function and will not be removed

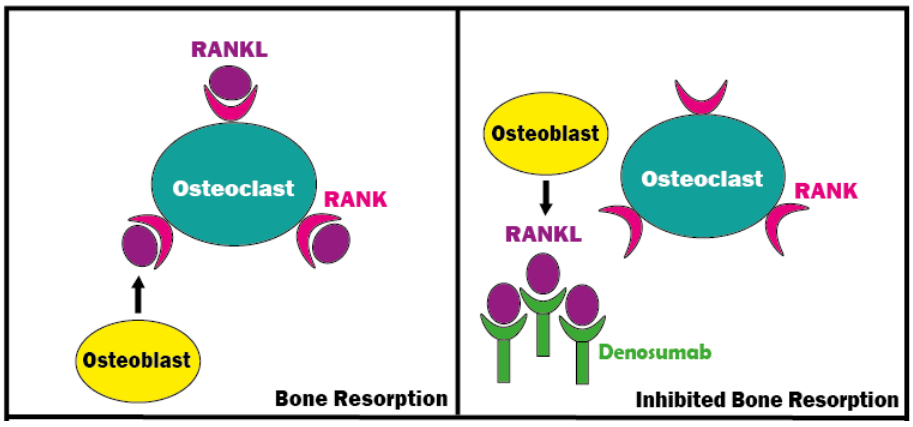

Figure 1. The mechanism of action of denosumab in the treatment of osteoporosis.

during dialysis (12). Moreover, in 2021, by studying the patients' data, Al Adhoubi and Al Salmi concluded that renal function did not deteriorate while using denosumab (23). Another study by Wu et al in 2022 was designed to evaluate denosumab adherence regarding change in renal function among osteoporotic patients with and without CKD. The findings of the two-year study showed that treatment with denosumab in patients with CKD and healthy individuals is not harmful to kidney function. Additionally, according to their laboratory results, the safety of denosumab was proven for mild to moderate CKD patients (6).

Denosumab-induced hypocalcemia

In 2023, Hsu et al monitored patients suffering from CKD and ESRD in Taiwan (3208 patients were included in their study). The purpose of this research was to set up integrated multidisciplinary care to abate the occurrence of severe hypocalcemia associated with denosumab in these patients. In order to establish this care plan, a multidisciplinary team was assembled, consisting of orthopedists, nursing consultants specialized in osteoporosis, nephrologists, dialysis nurses, and dieticians (11). Their previous studies stated that patients with advanced CKD and ESRD primarily experience CKD-MBD (chronic kidney disease-mineral and bone disorder), which encompasses secondary hyperparathyroidism, calcification of blood vessels or soft tissues, and renal osteodystrophy (24,25). Their research showed the benefits of implementing a management approach that includes calcium and vitamin D supplements that help reduce the risk of denosumab-induced hypocalcemia in these patients. They provided evidence that increased dialysate calcium concentration and calcium and vitamin D supplementation in dialysis patients can significantly prevent denosumab-induced hypocalcemic complications. They concluded that if physicians and health care staff are fully aware of denosumab-induced hypocalcemia and management approaches for this complication, and if integrated multidisciplinary care is implemented to monitor these patients, denosumab-induced hypocalcemia will be optimally managed (26).

In a case report published in 2023, Kouroglou et al documented a case from Greece involving a 38-year-old woman. The patient had a medical history of systemic lupus erythematosus, lupus nephritis stage III/IV, osteopenia, amenorrhea since 2013, and osteonecrosis of the left hip. She presented to the nephrology department with symptomatic hypocalcemia, with a corrected calcium level of 4.5 mg/dL. The patient's medical records revealed that she had taken oral calcium carbonate combined with cholecalciferol for one month before initiating denosumab treatment. After receiving three doses of denosumab, the patient's corrected calcium level in venous blood was within the normal range following the first and second doses of the medication. However, after 19 days of receiving the third subcutaneous dose, the patient experienced severe hypocalcemia, leading her to seek emergency medical attention and subsequently visit the nephrology department. This showed the resistance to treatment. Therefore, she was admitted to the hospital. She started taking calcium carbonate, intravenous calcium gluconate, and cholecalciferol. The patient was discharged with the given diet, however six days later, when she returned for a laboratory examination, she was hospitalized due to hypocalcemia. A more intensive diet, including calcium carbonate, cholecalciferol, alfacalcidol, and calcium gluconate, was applied during the second hospitalization. After maintaining the diet for four days, her serum calcium level reached an acceptable level for discharge. The medical team advised her to continue calcium carbonate, cholecalciferol, and alfacalcidol in a certain amount. The interesting and remarkable thing was that despite the intense administration of calcium, hypercalciuria did not occur. Two months later, the patient's serum calcium level had decreased again, but she was not admitted to the hospital because she was asymptomatic. The treatment team decided to change the regimen gradually. They concluded that close monitoring and a more aggressive calcium replacement regimen are needed in CKD patients treated with denosumab to prevent severe hypocalcemia, possibly leading to other complications and hospitalization (27).

Broadwell et al, in their article, cited several studies that focused on hypocalcemia associated with denosumab. In these studies, it was stated that using any anti-osteoporosis drug leads to hypocalcemia. As a result, hypocalcemia is also a known complication among patients receiving denosumab and affects about 13%-15% of this population. Likewise, this complication is more common in advanced CKD patients and is often observed after the first dose (28–31). Therefore, they suggested that consideration should be given to the administration of calcium and vitamin D supplements by patients during the treatment period, the use of high-calcium dialysis, and weekly monitoring of blood tests for calcium in the first month after initiation of denosumab (12).

In 2022, Horikawa et al conducted a study in Japan to investigate the association between the incidence of hypocalcemia and the stage of CKD in elderly osteoporotic patients receiving denosumab therapy. Serum-adjusted calcium and phosphate concentrations were measured by their team one week after the start of denosumab treatment. According to the serum calcium level, they were divided into two groups; the normal group and the denosumab-associated hypocalcemia (DAH) group. Denotes chewable tablets were prescribed for patients with low calcium levels. This tablet contained precipitated calcium carbonate, cholecalciferol, and magnesium carbonate. The study's findings indicated that a low eGFR

might be a contributing factor associated with DAH. This implies that renal dysfunction may also play a role in the occurrence of DAH. The results of their intervention study proved that adequate intake of calcium and vitamin D can prevent hypocalcemia. They concluded the following may be associated with hypocalcemia during donosumab (32).

1. Old age
2. Low eGFR
3. Low serum calcium status

In 2021, Al Adhoubi and Al Salmi worked on an article in Oman. By observing the incidence of hypocalcemia, they suggested close monitoring of patients and medication adjustment (23).

Importance of medication continuity

In 2022, Wu et al published an article evaluating denosumab adherence and its impact on renal function among osteoporotic patients, both with and without CKD. The patients were categorized into two groups based on their adherence to the denosumab treatment plan: the high-adherence (HA) and low-adherence (LA) groups. They mentioned that following instructions and persistence are important in using anti-osteoporosis drugs, such as denosumab, to reduce the risk of fractures. In their study population, only 63.5% had high adherence, which indicates that more than one-third were at high risk of fractures. The results showed high adherence to denosumab treatment was associated with better survival (6). Also, to improve medication adherence, some strategies were presented by Kobayashi et al. These strategies include (33):

1. Dental care
2. Using combined drugs to prevent side effects
3. Educating patients on the benefits of medication and the necessity of adherence

Discontinuing medication

From the article cited by Broadwell et al (12), it should be considered that individuals are at risk of relapse of bone turnover and fracture after discontinuation of denosumab. Therefore, in people with a contraindication for denosumab or should stop taking the drug, the treatment should be replaced with another antiabsorption agent to prevent the above complications (19).

In a separate research conducted in 2023, Iseri et al, investigated the effects of long-term denosumab treatment and discontinuation on the cortical bone in the hip region of patients undergoing dialysis. The evidence and findings derived from the study demonstrated that the BMD of both the cortical and trabecular components in the hip area exhibited significant increases after the initiation of denosumab treatment. However, following the discontinuation of denosumab, these BMD measurements experienced a noteworthy reduction (34). Another study mentioned that denosumab is a reversible agent, and treatment discontinuation is associated with decreased BMD and increased fracture risk (19,35).

Contraindications in CKD patients

According to previous study by Horikawa et al (32) and citing previous articles, they stated that denosumab is contraindicated in patients with severe CKD stages 4 and 5 (36).

Conclusion

According to the information, osteoporosis is common in CKD, and denosumab is the prescribed drug. In addition to increasing bone density, compared to bisphosphonates, it is not metabolized or excreted through the kidneys. This drug is prescribed in patients with mild to moderate CKD, and the evidence shows that it has no adverse effect on kidney function and is safe, but it is contraindicated in severe CKD patients (stages 4 and 5). Hypocalcemia is one of the complications associated with this drug, leading to other complications and, in some cases, hospitalization. To prevent this complication, the following points should be taken into account:

1. Close monitoring of patients
2. Aggressive diet to replace calcium with calcium and vitamin D supplements
3. Awareness of doctors and health care professionals about hypocalcemia related to denosumab and approaches to manage this complication in patients with CKD
4. Setting up multidisciplinary integrated care

The necessity of educating patients is also needed to improve patient adherence. It is essential to highlight that discontinuing denosumab treatment is linked to a decrease in BMD and an increased risk of fractures, essentially reversing the positive effects of the treatment. Therefore, in cases where a patient with CKD has a contraindication or needs to discontinue denosumab, it is necessary to switch to another antiresorptive agent to prevent a reversal in bone turnover and an elevated risk of fractures that may occur after denosumab discontinuation.

Authors' contribution

Conceptualization: Fateme Sharafeddin, Sasan Zandi Esfahan.
Data curation: Fateme Sharafeddin.
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Project administration: Sasan Zandi Esfahan, Fateme Sharafeddin.
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Validation: Fateme Sharafeddin, Sasan Zandi Esfahan.
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Writing—original draft: Fateme Sharafeddin, Sasan Zandi Esfahan. **Writing—review & editing:** Fateme Sharafeddin, RK. Golnaz Goudarzi.

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 authors.

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