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Hypocalcaemia Induced by Denosumab Therapy: A Cautionary Tale in Osteoporosis Management

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Introduction

Denosumab is a fully human monoclonal antibody widely used in the treatment of osteoporosis due to its potent antiresorptive properties. By inhibiting RANKL (Receptor Activator of Nuclear Factor-κB Ligand), it suppresses osteoclast-mediated bone resorption, thereby increasing bone mineral density and reducing fracture risk. However, this mechanism can also precipitate significant hypocalcaemia, particularly in patients with pre-existing vitamin D deficiency, impaired renal function, or inadequate calcium intake. While often overlooked, denosumab-induced hypocalcaemia can be life-threatening and is increasingly being recognized in clinical settings. This case emphasizes the need for vigilant monitoring and patient education before and during denosumab therapy to avoid this serious complication. The onset of hypocalcaemia following denosumab administration can range from asymptomatic laboratory abnormalities to severe, symptomatic cases involving muscle cramps, tetany, seizures, or cardiac arrhythmias. The risk is particularly heightened in individuals with chronic kidney disease, where impaired calcium-phosphate homeostasis further exacerbates susceptibility. Despite its efficacy in reducing skeletal-related events, the risk of hypocalcaemia necessitates a proactive approach to patient selection and pre-treatment optimization. Baseline assessment of serum calcium, phosphate, vitamin D levels and renal function should be standard practice and any deficiencies must be corrected prior to initiating therapy. Moreover, patients should be counseled about the importance of adhering to prescribed calcium and vitamin D supplementation to mitigate risk throughout treatment [1].

Description

Hypocalcaemia is a known but often underrecognized complication of denosumab therapy, particularly after the initial dose. Unlike bisphosphonates, which gradually inhibit bone resorption, denosumab exerts a rapid and potent antiresorptive effect by binding to and inhibiting RANKL, resulting in abrupt suppression of osteoclast activity and reduced calcium release from bone. This mechanism can lead to symptomatic hypocalcaemia, especially in individuals with underlying risk factors such as vitamin D deficiency, chronic kidney disease, malabsorption syndromes, or hypoparathyroidism. Clinical manifestations may range from perioral numbness and muscle cramps to life-threatening cardiac arrhythmias and seizures. In contrast to bisphosphonates, denosumab's effects are reversible upon discontinuation, allowing serum calcium levels to rebound with appropriate supplementation. However, discontinuation can also result in rebound bone turnover and increased fracture risk if not followed by alternative osteoporosis therapy. This underscores the need for structured treatment transitions, including the initiation of bisphosphonates or other agents, to maintain skeletal protection while minimizing adverse outcomes. Pre-treatment assessment of serum calcium, phosphate, magnesium, 25-hydroxy vitamin D and renal function is critical. Additionally, calcium and vitamin D supplementation should be initiated prior to therapy in at-risk individuals and continued throughout the course of treatment [2].

Lack of patient education and inadequate pre-treatment evaluation remain significant contributors to adverse outcomes. Patients should be clearly informed about the symptoms of hypocalcaemia and the importance of supplementation. Furthermore, follow-up protocols should include biochemical monitoring, particularly within the first two to four weeks after denosumab administration, when the risk of hypocalcaemia is highest. A multidisciplinary approach involving primary care physicians, endocrinologists and nephrologists is essential to manage complex patients with multiple risk factors and optimize treatment safety and efficacy. Future strategies in osteoporosis care with denosumab should focus on personalized risk assessment and predictive modeling. Development of validated risk stratification tools that incorporate renal function, vitamin D status, baseline calcium and comorbidities can help clinicians identify high-risk patients before initiating therapy. These tools could be embedded into electronic medical records to prompt clinicians about necessary labs, supplementation, or alternative treatments when appropriate [3].

Additionally, research into long-acting vitamin D analogs or combination therapies that enhance calcium homeostasis in vulnerable populations could reduce the incidence of hypocalcaemia. Innovations such as point-of-care calcium testing or remote monitoring via wearable devices may also play a role in early detection of metabolic disturbances during treatment. As telemedicine becomes more integrated into chronic disease management, remote patient education and follow-up may provide a scalable solution for monitoring calcium levels and treatment adherence. Policy-wise, updated clinical guidelines should emphasize mandatory baseline biochemical screening and supplementation protocols prior to initiating denosumab. Moreover, incorporating pharmacists and patient navigators into osteoporosis clinics could ensure compliance with supplementation and follow-up. Ultimately, a shift toward individualized care models where treatment plans are adapted to each patient's risk profile and health literacy will be a key to optimizing outcomes and minimizing complications associated with denosumab therapy [4].

As the global population ages and osteoporosis becomes increasingly prevalent, real-world data collection through post-marketing surveillance and large-scale registries will be essential to better understand the incidence, risk factors and outcomes associated with denosumab-induced hypocalcaemia. Such data can inform updates to clinical practice guidelines and identify subpopulations that may require modified dosing regimens or enhanced monitoring protocols. Additionally, collaborative research networks can help evaluate the long-term safety of denosumab in patients with comorbidities such as chronic kidney disease, in whom the risk-benefit balance may differ significantly from that in the general osteoporotic population. Education and training for healthcare professionals should also evolve to reflect these emerging insights. Enhanced curricula and Continuing Medical Education (CME) programs focused on the metabolic complications of osteoporosis therapies particularly in the context of polypharmacy and multimorbidity are needed. Primary care providers, who are often the first to prescribe

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denosumab, should be supported with clear algorithms and decision aids to guide pre-treatment screening, supplementation and follow-up. Leveraging digital health tools and clinical decision support systems can further ensure that safety protocols are consistently applied, ultimately improving patient outcomes and reducing preventable adverse events [5].

Conclusion

Denosumab is a highly effective agent for osteoporosis, but its use is not without risk. Hypocalcaemia, though rare, can be serious and even fatal if not recognized early. This case underscores the importance of pre-treatment screening, vitamin D correction and calcium monitoring before and after denosumab injection, especially in vulnerable populations. Patient education and close follow-up remain pivotal components of safe and effective osteoporosis management. Individualized treatment decisions and ongoing surveillance are essential to minimize risks and ensure optimal outcomes in patients receiving denosumab

Acknowledgment

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Conflict of Interest

None.

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