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Meta-Analysis

Role and efficacy of denosumab in osteoporotic patients undergoing joint replacement surgery

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ABSTRACT

Osteoporosis is a prevalent skeletal disorder characterized by decreased bone mass and structural deterioration, significantly increasing the risk of fractures. In joint replacement surgeries, compromised bone quality in osteoporotic patients poses substantial challenges, including an elevated risk of periprosthetic fractures and implant instability. Denosumab, a monoclonal antibody targeting receptor activator of nuclear factor-kappa B ligand (RANKL), has emerged as a potent antiresorptive agent with the potential to enhance surgical outcomes in these patients. This study systematically reviews and evaluates the role and efficacy of denosumab in improving bone mineral density (BMD), minimizing periprosthetic bone loss (PBL), and enhancing implant stability in osteoporotic patients undergoing joint replacement surgery. A comprehensive literature search was conducted utilizing PubMed, MEDLINE, and Cochrane Library databases, including randomized controlled trials (RCTs) and cohort studies evaluating the impact of denosumab on BMD, PBL, and implant stability in osteoporotic patients undergoing joint replacement. Six major RCTs were included in the analysis, consistently demonstrating that denosumab enhances BMD, reduces PBL, and improves implant stability. These findings suggest that denosumab is an effective therapeutic option for optimizing surgical outcomes in osteoporotic patients undergoing joint replacement, supporting its integration into perioperative management strategies.

Keywords: Denbri, Joint replacement surgery, Total hip replacement, Total knee replacement, Denosumab, Osteoporosis, Bone mineral density

INTRODUCTION

Osteoporosis is a chronic, progressive skeletal disorder characterized by decreased bone mass, deterioration of bone microarchitecture, and an increased susceptibility to fractures.[1] It is one of the most common metabolic bone disorders worldwide, affecting approximately 200 million people, particularly postmenopausal women and elderly individuals.[2] Known as the "silent disease," osteoporosis often remains asymptomatic until a fracture occurs, significantly impairing patient quality of life.[3] Hip, vertebral, and wrist fractures are the most common osteoporotic fractures, with hip fractures being the most debilitating due to their high morbidity and mortality rates.[4]

Osteoporosis is primarily caused by an imbalance between bone resorption and bone formation, where osteoclastic activity exceeds osteoblastic activity, leading to net bone loss.[5] Various factors, including age, hormonal changes, genetic predisposition, nutritional deficiencies, and certain medications, contribute to the development of osteoporosis.[6] A bone mineral density (BMD) that is 2.5 standard deviations below the mean value for a young, healthy adult is considered osteoporosis by the World Health Organization (WHO).[7] In the context of orthopedic

surgery, particularly joint replacement, osteoporosis presents unique challenges to joint replacement surgeons. Compromised bone quality can adversely affect implant stability, increasing the risk of periprosthetic fractures, implant loosening, and failure.[8] Periprosthetic fractures are difficult to manage due to poor bone quality, which hinders implant fixation and stability.[9] This is particularly concerning in elderly patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA), where long-term implant survival is crucial. Denosumab, a fully human monoclonal antibody, has emerged as a potent antiresorptive agent for osteoporosis management. It functions by inhibiting the receptor activator of nuclear factor-kappa B ligand (RANKL), a key regulator of osteoclast formation, function, and survival.[10] By blocking RANKL, it reduces bone resorption and enhances BMD (Figure 1).[11] Unlike bisphosphonates, which primarily reduce bone turnover, denosumab provides a more direct inhibition of osteoclast formation, making it a versatile and potent option for osteoporosis management.[12] This study aims to systematically review and evaluate the role and efficacy of denosumab in improving BMD, minimizing periprosthetic bone loss (PBL), and enhancing implant stability in osteoporotic patients undergoing joint replacement surgeries.

METHODS

A systematic review was conducted, covering the study period from January 2005 to January 2025, using PubMed, MEDLINE, and Cochrane Library databases. The search strategy incorporated terms such as "denosumab," "osteoporosis", "joint replacement", "arthroplasty", "periprosthetic bone loss", and "implant stability". Eligible studies were restricted to randomized controlled trials (RCTs) and cohort studies that specifically assessed the impact of denosumab on BMD, PBL, and implant stability in osteoporotic patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA). A total of six major RCTs met the inclusion criteria and were selected for detailed analysis.

Inclusion criteria

Studies published between January 2005 and January 2025, RCTs and cohort studies, studies involving osteoporotic patients undergoing THA or TKA, studies that explicitly assessed the impact of denosumab on BMD, PBL, and implant stability, and articles published in English were included.

Exclusion criteria

Studies involving patients without osteoporosis, non-randomized studies, case reports, reviews, and meta-analyses, studies that did not specifically report outcomes related to BMD, PBL, or implant stability, articles with incomplete data or lacking clear outcome measures, and studies published in languages other than English were excluded.

Statistical analysis

The data was evaluated utilizing the Review Manager (RevMan) 5.4 software. Continuous variables, such as changes in BMD and PBL, were expressed as mean differences (MD) with 95% confidence intervals (CIs), and a random-effects model was applied due to the expected heterogeneity among studies. Statistical significance was defined at a threshold of $p<0.05$. Heterogeneity was assessed using the I^2 statistic. Subgroup analysis was performed specifically for THA and TKA patients to evaluate the impact of denosumab on periprosthetic BMD and implant stability across different joint types.

RESULTS

Denosumab has consistently demonstrated significant efficacy in enhancing BMD, reducing PBL, and improving implant stability in osteoporotic patients undergoing joint replacement surgery. The findings from multiple RCTs and cohort studies provide strong evidence supporting the use of denosumab in this patient population.

Bone mineral density improvement

The FREEDOM trial, a landmark study involving 7,808 postmenopausal women, demonstrated that denosumab significantly increased BMD at the lumbar spine by 21.7% and at the total hip by 9.2% over three years.[13] These benefits were further confirmed in the FREEDOM extension study, which showed that BMD gains were sustained for up to 10 years without plateauing.[14] Such long-term BMD preservation is particularly important in osteoporotic patients, where bone loss is a continuous concern. Beyond the lumbar spine and hip, denosumab has shown significant benefits in enhancing periprosthetic BMD, which is critical for implant stability. Aro et al conducted a study on patients undergoing THA and reported that denosumab significantly increased periprosthetic BMD around the femoral component.[15] Similarly, Nyström et al found that THA patients treated with denosumab exhibited a 32% higher BMD in Gruen zone 7, a critical region for implant fixation, compared to those receiving placebo (Figure 1).[16] This highlights the role of denosumab in maintaining bone density around orthopedic implants.

Reduction in periprosthetic bone loss and enhanced implant stability

Periprosthetic bone loss is a major concern in joint replacement surgery, as it can lead to implant loosening and failure. Denosumab has consistently demonstrated its ability to minimize PBL around orthopedic implants, thus preserving bone integrity. Murahashi et al showed that denosumab significantly reduced PBL around the tibial component in TKA, maintaining bone density and enhancing implant fixation.[17] This effect is particularly important, as excessive PBL is a key predictor of implant failure. Ledin et al further confirmed that denosumab

reduced early tibial component migration in TKA, an important indicator of long-term implant success.[18] The ability of denosumab to prevent early migration and maintain periprosthetic bone is a critical factor in ensuring implant stability. In another study, Nakura et al demonstrated that denosumab outperformed risedronate, a commonly used bisphosphonate, in maintaining BMD around THA implants (19) (Table 1). This comparative advantage underscores the superior antiresorptive efficacy of denosumab. By increasing periprosthetic BMD and minimizing PBL, denosumab provides better support for the implant, reducing the risk of micromotion, which is a common cause of implant loosening. These findings are of particular importance for elderly patients, where bone quality is compromised, and implant longevity is critical.[18,19]

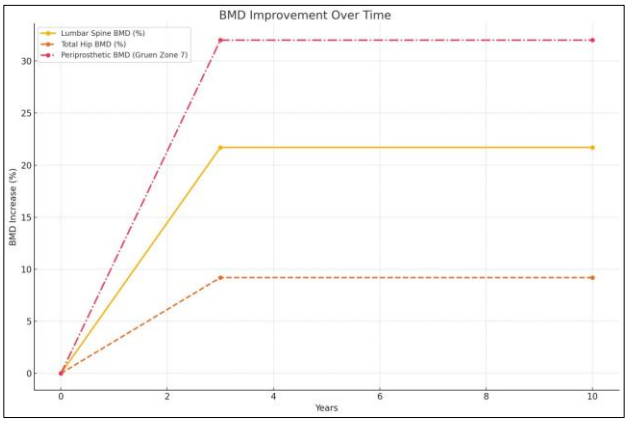

Figure 1: BMD improvement over time.

Table 1: Periprosthetic bone loss reduction and implant stability.

Study	PBL reduction	Implant stability
Murahashi et al[17]	Significant reduction	Enhanced fixation
Ledin et al[18]	Reduced early migration	Improved stability
Nakura et al[19]	Outperformed risedronate	Superior to risedronate

DISCUSSION

Denosumab has emerged as a highly effective therapeutic agent for optimizing surgical outcomes in osteoporotic patients undergoing joint replacement surgery. Its ability to enhance BMD, reduce PBL, and improve implant stability is primarily ascribed to its unique mechanism of action. Denosumab is a fully human monoclonal antibody that targets the RANKL, a key regulator of osteoclast formation, function, and survival.[20] By inhibiting RANKL, denosumab directly suppresses osteoclast activity, leading to a profound decrease in bone resorption and a consistent rise in BMD. The FREEDOM trial remains the cornerstone of evidence supporting denosumab's efficacy, demonstrating significant increases in BMD at the hip, with these benefits sustained for up to 10 years.[13,14] This long-term bone preservation is crucial for osteoporotic patients, where ongoing bone loss is a significant challenge. In the context of joint replacement, maintaining periprosthetic BMD is essential for ensuring implant stability and reducing the risk of implant failure. Studies by Aro et al and Nyström et al have confirmed that denosumab enhances periprosthetic BMD around orthopedic implants, including THA and TKA.[15,16] These findings are significant because periprosthetic bone loss is a major contributor to implant loosening and failure. Its ability to maintain bone density around implants translates directly into improved implant stability, which is critical for long-term surgical success. Denosumab's superiority over traditional bisphosphonates is another critical aspect of its efficacy. While bisphosphonates reduce bone turnover by inhibiting osteoclast activity indirectly, denosumab directly targets RANKL, providing more effective suppression of bone resorption.[21] This direct mechanism of action results in a more consistent and significant increase in BMD, making it an ideal choice for patients with compromised bone quality. Despite its benefits, denosumab use must be carefully managed due to the risk of rebound bone loss upon discontinuation. Rebound bone loss is characterized by a rapid increase in bone turnover and a significant decline in BMD, which can increase fracture risk.[22] To mitigate this risk, transition strategies, such as switching to bisphosphonates, are recommended for maintaining BMD gains. Regular monitoring of serum calcium levels is also essential, specifically in patients with renal impairment. This study has several strengths. First, it is based on a comprehensive review of high-quality RCTs, providing robust evidence of denosumab's efficacy. Second, the inclusion of studies with large sample sizes, such as the FREEDOM trial, ensures the reliability of the findings. However, the study also has limitations. The analysis is limited to the existing literature, and the long-term safety profile of denosumab in the context of joint replacement remains to be fully explored. Additionally, the potential for rebound bone loss upon discontinuation of denosumab is a significant concern, necessitating careful management. Future research should focus on optimizing the use of denosumab in the perioperative management of osteoporotic patients undergoing joint replacement. This includes exploring the benefits of combining denosumab with anabolic agents, developing standardized protocols for managing rebound bone loss, and investigating the long-term safety of denosumab in elderly patients with multiple comorbidities.

CONCLUSION

Denosumab is a highly effective therapeutic option for managing osteoporosis in patients undergoing joint replacement surgery. Its ability to enhance bone mineral density, reduce periprosthetic bone loss, and improve implant stability makes it an invaluable tool in orthopaedic practice. Proper patient selection, continuous monitoring, and effective transition strategies are essential.

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