ORIGINAL ARTICLE

Impact of denosumab on fracture healing in osteoporotic patients: A double-blind, randomized trial

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Abstract

Background: Osteoporosis delays fracture healing due to impaired bone remodeling. Denosumab, a monoclonal antibody targeting RANKL, reduces fracture risk but its role in healing is underexplored. *Aim and Objectives:* To evaluate the effect of denosumab on fracture healing in osteoporotic patients compared to standard care. *Material and Methods:* This was a randomized controlled trial of 60 patients (aged 50-85 years) with osteoporotic fractures. The intervention group received 60 mg denosumab with calcium and vitamin D3, while the control group received calcium and vitamin D3 alone. Healing was assessed radiologically and clinically at 6 weeks, 3 months, and 6 months post-operatively. *Results:* At 3 months, 73.33% of denosumab-treated patients had healed fractures versus 26.67% in the control group (p<0.0001). By 6 months, healing rates were similar. No significant differences were found in serum calcium, vitamin D3 levels, or fracture site distribution. *Conclusion:* Denosumab accelerates early fracture healing in osteoporotic patients, supporting its use as an adjunct therapy.

Keywords: Bone regeneration, RANK ligand, Calcium supplements, Osteogenesis

Introduction

Osteoporosis, from the Greek words "osteon" (bone) and "poros" (pore), is a skeletal disorder characterized by weakened bone strength that increased risk of fractures. This chronic, progressive disease is marked by weak bone mass, bone tissue degradation, and increased bone fragility, which makes bones brittle and more prone to fractures—even from minor or low-impact events such as a fall from standing height, coughing, or twisting movements.

Osteoporotic fractures, also known as fragility fractures, frequently occur at the hip, spine, and wrist, significantly affecting an individual's health and quality of life. These fractures often lead to hospitalization, long-term pain, reduced independence, and, in some cases, mortality. Given the growing aging population, osteoporosis has become a critical global public health concern, affecting millions worldwide [1].The global prevalence of osteoporosis is alarming, with over 200 million people estimated to be affected, particularly the elderly population. Although it is often associated with postmenopausal women, men are also at risk as they age. According to the World Health Organization (WHO), one in three women and one in five men over the age of 50 will experience an osteoporotic fracture in their lifetime. Hip fractures, in particular, carry significant morbidity and mortality, often necessitating hospitalization, surgery, and long-term rehabilitation. Vertebral fractures, though less immediately life-threatening, lead to persistent pain, spinal abnormalities, and poor quality of life, while wrist fractures significantly impair upper limb function and daily activities [2].

Known as the "silent disease," osteoporosis progresses without any obvious symptoms until a fracture occurs. Bone loss often takes years to manifest, and fractures may occur even from low-energy events such as slipping or bending over. Diagnosis typically relies on Dual-Energy X-Ray Absorptiometry (DEXA) scans, the gold standard for assessing Bone Mineral Density (BMD). The WHO categorizes BMD using T-scores: normal (≥ -1.0), osteopenia (-1.0 to -2.5), and osteoporosis (≤ -2.5). Severe osteoporosis involves a T-score ≤ -2.5 combined with fragility fractures. Clinical risk factors such as age, gender, family history, smoking, alcohol consumption, and corticosteroid use are also critical for assessing fracture risk using tools like the Fracture Risk Assessment Tool (FRAX) score [3]. Maintaining adequate bone mineralization is essential for fracture healing. Studies have shown Vitamin D supplementation and food fortification significantly improve serum 25(OH)D levels, thereby supporting bone metabolism [4]. Additionally, bisphosphonates have demonstrated efficacy in improving BMD and reducing fracture-related symptoms in thalassemia patients [5].

Denosumab, a human monoclonal IgG2 antibody, inhibits Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL), which is essential for osteoclast development and activity. By binding to RANKL and inhibiting its receptor, denosumab reduces bone resorption, raising BMD and lowering the risk of fracture. Despite its established efficacy in preventing fractures, limited research exists on the role of denosumab in enhancing bone repair process, particularly in osteoporotic patients who often experience delayed healing or non-union.

Osteoporosis-related fractures represent a significant clinical challenge due to delayed healing and non-union. Denosumab, a relatively new therapeutic option, has demonstrated safety and efficacy in reducing bone turnover, increasing BMD, and decreasing the risk of fracture. However, limited research exists on its role in bone repair process. This study aimed to fill this gap by investigating the potential of denosumab to enhance fracture healing in osteoporotic patients compared to standard treatments.

Material and Methods

Data for this study were collected from patients undergoing orthopedic surgeries at our centre. The study period spanned a year, from June 1, 2023, to May 31, 2024.This was a one-year, hospital-based, double-blind, randomized controlled trial (RCT) [Ref No. MDC/JNMCIEC/128] designed to evaluate the efficacy of injection denosumab in osteoporotic fracture healing compared to standard treatment. Probability sampling using computer-generated random number table was done. The sample size, calculated based on comparing the proportions of fracture fusion after three months between the two groups, was 25 per group. To account for dropouts or exclusions, the final sample size included 30 patients per group, making a total of 60 participants, aged 50–85 years, and diagnosed with osteoporotic fractures. Patients were divided into two groups:

Intervention Group: A single subcutaneous injection of denosumab 60 mg along with tablet calcium (1000 mg) and vitamin D3 (600 IU).

Control Group: A tablet calcium (1000 mg) and vitamin D3 (600 IU) only.

Adult males or females aged between 50 to 85 years, capable of giving consent (on their own or through a legally authorized representative), and diagnosed with fracture and osteoporosis (Bone Mass Index, BMD ≤ -2.5) were included.

HIV-positive or HBsAg-positive patients, refusal to provide consent, comorbidities such as thyroid dysfunction, hypocalcemia, rheumatoid arthritis, or vitamin D deficiency, previous treatment with bisphosphonates in the last 12 months prior to screening, concomitant head injury with clinically significant abnormality on head CT, patients with pathological fractures, patients requiring or currently on ventilator support, participation in another clinical trial, patients deemed unsuitable for the study by the investigator, indications of metabolic bone diseases other than osteoporosis, such as osteomalacia, OI (Osteogenesis Imperfecta), Paget's disease, Cushing's disease, or hyperprolactinemia, were excluded.

Statistical analysis

Data were analyzed using statistical software. Categorical variables were compared using the Chi-square test or Fisher's exact test, while continuous variables were analyzed using the independent t-test. Results were expressed as mean ± Standard Deviation (SD) for continuous variables and percentages for categorical data. A value of $p < 0.05$ was considered statistically significant.

Results

The mean age in Group 1 (denosumab group) was 67.27 years, compared to 71.93 years in Group 2, with no statistically significant difference ($p = 0.0748$). Males accounted for 40% of Group 1 and 53.33% of Group 2, while females constituted 60% and 46.67%, respectively ($p = 0.3010$). Most participants in both groups engaged in sedentary work (96.67% in Group 1 and 100% in Group 2). Smoking and alcohol use were rare, with no significant differences observed between groups ($p = 1.0000$ for both) (Table 1). Diabetes prevalence was higher in Group 2 (40%) compared to Group 1 (26.67%), but the difference was not statistically significant ($p = 0.2730$). A normal BMI (18.5 –24.9) was more common in Group 2 (66.67%) compared to Group 1 (50%). Overweight and obesity were more frequent in Group 1, though the differences were not statistically significant ($p = 0.2110$). All participants had normal serum calcium (8.6–10.2 mg/dl) and vitamin D3 (30–60 ng/dl) levels, with no significant differences. Bone healing progression was observed at 6 weeks and 3 months in both groups. However, by 6 months, Group 2 had significantly higher progression (73.33%) compared to Group 1 (26 .67%), with ($p < 0.0001$). At 3 months, fracture healing was significantly higher in Group 1 (73.33% vs. 26.67% in Group 2, $p < 0.0001$). By 6 months, Group 2 exhibited higher healing rates (73.33% vs. 26.67% in Group 1, $p < 0.0001$) (Table 2). Lower limb fractures were most common (56.67% in both groups). T-scores between -2.5 and -3.5 were observed in 83.33% of Group 1 and 86.67% of Group 2. Neither variable showed significant differences ($p = 0.7110$ and $p = 0.6010$, respectively). Operative management was performed in 80% of Group 1 and 83.33% of Group 2 ($p = 0.7390$). The type of surgery, Open Reduction and Internal Fixation (ORIF) and Closed Reduction and Internal Fixation (CRIF), was equally distributed ($p = 0.8580$) (Table 3). Both groups showed statistically significant changes in healing progression between 6 weeks, 3 months, and 6 months ($p < 0.0001$ for all comparisons) (Table 4).

Table 1: Comparison of Group 1 and Group 2 with age, sex, occupation, smoking, alcohol

Parameters	Group 1 Number (Percentage)	Group 2 Number (Percentage)	Total Number (Percentage)	*p*
Age groups				
51-60 years	10 (33.33%)	7 (23.33%)	17 (28.33%)	0.324
61-70 years	9 (30%)	5 (16.67%)	14 (23.33%)	
71-80 years	6 (20%)	11 (36.67%)	17 (28.33%)	
>=81 years	5 (16.67%)	7 (23.33%)	12 (20%)	
Total	30 (100%)	30 (100)	60 (100%)	
Mean ± SD	67.27 ± 10.43	71.93 ± 9.47	69.6 ± 10.15	t=1.8143, p = 0.0748
Sex				
Male	12 (40%)	16 (53.33%)	28 (46.67%)	0.301
Female	18 (60%)	14 (46.67%)	32 (53.33%)	
Total	30 (100%)	30 (100%)	60 (100%)	
Occupation				
Sedentary work	29 (96.67%)	30 (100%)	59 (98.33%)	1
Heavy work	1 (3.33%)	0 (0%)	1 (1.67%)	
Total	30 (100%)	30 (100%)	60 (100%)	
Smoking				
No	29 (96.67%)	28 (93.33%)	57 (95%)	1
Yes	1 (3.33%)	2 (6.67%)	3 (5%)	
Total	30 (100%)	30 (100%)	60 (100%)	
Alcohol				
No	30 (100%)	29 (96.67%)	59 (98.33%)	1
Yes	0	1 (3.33%)	1 (1.67%)	
Total	30 (100%)	30 (100%)	60 (100%)	

Table 2: Comparison of Group 1 and Group 2 with various parameters

Diabetic status				
No	22 (73.33%)	18 (60%)	40 (66.67%)	0.273
Yes	8 (26.67%)	12 (40%)	20 (33.33%)	
Total	30 (100%)	30 (100%)	60 (100%)	
Obesity (BMI)				
Underweight (<18.5)	4 (13.33%)	5 (16.67%)	9 (15%)	0.211
Normal (18.5-24.9)	15 (50%)	20 (66.67)	35 (58.33%)	
Overweight (25-29.9)	8 (26.67%)	5 (16.67)	13 (21.67%)	
Obese (>30)	3 (10%)	0 (0%)	3 (5%)	
Total	30 (100%)	30 (100%)	60 (100%)	
Serum Ca^{++} level				
8.6 - 10.2 mg/dl	30 (100%)	30 (100%)	60 (100%)	1
<8.6 mg/dl	0 (0%)	0 (0%)	0 (0%)	
>10.2 mg/dl	0 (0%)	0 (0%)	0 (0%)	
Total	30 (100%)	30 (100%)	60 (100%)	
Serum Vitamin D3				
30 - 60 ng/dl	30 (100%)	30 (100%)	60 (100%)	1
< 30 ng/dl	0 (0%)	0 (0%)	0 (0%)	
> 60 ng/dl	0 (0%)	0 (0%)	0 (0%)	
Total	30 (100%)	30 (100%)	60 (100%)	
Progression in bone healing at				
6 weeks	30 (100%)	30 (100%)	60 (100%)	1
3 months	30 (100%)	30 (100%)	60 (100%)	1
6 months	8 (26.67%)	22 (73.33%)	30 (50%)	0.0001*
Fracture healed at				
6 weeks	0 (0%)	0 (0%)	0 (0%)	1
3 months	22 (73.33%)	8 (26.67%)	30 (50%)	0.0001*
6 months	8 (26.67%)	22 (73.33%)	30 (50%)	0.0001*

Table 3: Comparison of group 1 and group 2 with fracture site, DEXA scan, management and surgery

Parameters	Group 1	Group 2	Total	χ^2	p
Fracture site					
Upper limb	6 (20%)	8 (26.67%)	14 (23.33%)	1.377	0.711
Lower limb	17 (56.67%)	17 (56.67%)	34 (56.67%)		
Clavicle	1 (3.33%)	0 (0%)	1 (1.67%)		
Pelvis	0 (0%)	0 (0%)	0 (0%)		
Spine	6 (20%)	5 (16.67%)	11 (18.33%)		
Total	30 (100%)	30 (100%)	60 (100%)		
DEXA scan					
< -2.5 to -3.5	25 (83.33%)	26 (86.67%)	51 (85%)	1.02	0.601
< -3.5 to -4.5	4 (13.33%)	4 (13.33%)	8 (13.33%)		
< -4.5 to -5.0	1 (3.33%)	0 (0%)	1 (1.67%)		
Management					
Conservative	6 (20%)	5 (16.67%)	11 (18.33%)	0.111	0.739
Operative	24 (80%)	25 (83.33%)	49 (81.67%)		
Total	30 (100%)	30 (100%)	60 (100%)		
Surgery					
ORIF	9 (30%)	10 (33.33%)	19 (31.67%)	0.032	0.858
CRIF	15 (50%)	15 (50%)	30 (50%)		

DEXA: Dual-energy X-ray absorptiometry, ORIF: Open reduction and internal fixation, CRIF: Closed reduction and internal fixation

Table 4: Comparison of 6 weeks, 3 months and 6 months treatment time points with fracture healed in Group 1 and Group 2

Groups	Fracture healed from	% of change	Mc Nemar, *p*
Group 1	**6 weeks to 3 months**	73.33	0.0001*
	6 weeks to 6 months	100.00	0.0001*
Group 2	**6 weeks to 3 months**	26.67	0.0001*
	6 weeks to 6 months	100.00	0.0001*

**p<0.05*

Discussion

This RCT evaluated the efficacy of denosumab in accelerating fracture healing among osteoporotic patients treated in a tertiary care setting. The findings demonstrated that denosumab significantly enhanced fracture healing during the early stages (within 3 months) compared to the control group, though both groups achieved comparable healing rates by 6 months. Our study found that 73.33% of patients in the intervention group had healed fractures within 3 months, significantly higher than the 26.67% in the control group. These results align with prior evidence highlighting ability of denosumab to modulate bone remodeling and improve bone integrity.

Denosumab, a monoclonal antibody targeting RANKL, inhibits osteoclast differentiation and function, reducing bone resorption and enhancing BMD [7-8]. Like bisphosphonates, which have shown significant improvement in BMD and symptomatic relief in thalassemia patients [5], Denosumab acts as a potent antiresorptive agent by inhibiting RANKL. Moreover, Vitamin D status, as highlighted in a systematic review [4], may also play a synergistic role in optimizing fracture healing outcomes. Numerous studies support the efficacy of denosumab in fracture prevention and BMD improvement, but its role in fracture healing is less extensively studied. The FREEDOM trial showed that denosumab reduced vertebral by 68%, non-vertebral by 20%, and hip fractures by 40% [9]. A subsequent analysis emphasized that effects of denosumab on fracture healing were independent of its preventive benefits [10].

In a study by Anastasilakis *et al*., denosumab demonstrated greater efficacy than bisphosphonates in improving BMD and reducing Bone Turnover Markers (BTMs) [11]. Similar outcomes were observed in a meta-analysis by Ferrari et al., which underscored the role of denosumab in promoting early bone healing through enhanced microarchitecture [12]. These studies complement our findings, suggesting that rapid suppression of bone resorption of denosumab may facilitate the formation of a stable fracture environment conducive to healing.

Mechanism of action of denosumab involves the inhibition of RANKL, a cytokine essential for osteoclast activation [13]. This action reduces bone resorption and allows osteoblasts to dominate the remodeling phase, promoting faster bone matrix deposition [14]. Additionally, denosumab has been shown to increase cortical bone thickness and trabecular connectivity [15], improve biomechanical properties of bone, such as stiffness and strength [16], and normalize serum calcium and BTMs, creating a favorable environment for fracture healing [17]. Animal models have provided further evidence. A study by Xu *et al*. demonstrated accelerated fracture callus maturation in osteoporotic rats treated with denosumab, resulting in superior biomechanical properties compared to untreated controls [18].

Although denosumab significantly accelerated healing within the first three months, healing rates were comparable between groups at six months. This observation suggests that while denosumab enhances the initial phases of bone repair, long-term outcomes may rely on intrinsic biological processes. Healing of fracture is a complex, multiphase process which includes inflammation, repair, and remodeling [19]. Denosumab appears to exert its greatest influence during the repair

phase by stabilizing bone resorption and facilitating osteoblast activity [20]. Accelerated fracture healing has profound implications for clinical practice. Faster healing reduces immobilization periods, thereby lowering the risk of complications such as deep vein thrombosis, muscle atrophy, and joint stiffness [21]. In elderly osteoporotic patients, early mobilization is critical for maintaining functional independence and reducing morbidity [22]. The economic burden of osteoporotic fractures is substantial, with direct costs exceeding billions annually worldwide [23]. By expediting healing, denosumab may reduce hospital stays, rehabilitation costs, and the need for secondary interventions, thereby offering significant cost savings [24]. Denosumab may be particularly beneficial for patients at high risk of delayed union or non-union, such as those with severe osteoporosis, diabetes, or previous fracture history [25]. Its efficacy in improving BMD and reducing secondary fractures underscores its potential as a targeted therapy in such populations [26].

Denosumab is well-tolerated, with a favorable safety profile documented in long-term studies. The FREEDOM extension study reported low rates of adverse events over 10 years, with no evidence of increased cardiovascular risk or malignancy [27]. However, certain side effects warrant attention, like: 1) hypocalcemia**,** particularly in patients with severe vitamin D deficiency or impaired renal function, underscoring the importance of calcium and vitamin D supplementation [28]; 2) atypical femoral fractures, which are rarely associated with long-term use and excessive suppression of bone turnover [29]; and 3) osteonecrosis of the jaw, though rare, is a serious complication linked to denosumab and other antiresorptives [30].

Limitations

The relatively small sample limits the generalizability of findings. Larger multicenter studies are needed. While the study effectively captures early healing dynamics, longer follow-up is required to assess outcomes such as refracture rates and long-term functional recovery. Further, evaluation of quality of life, including patient-reported outcomes, could have provided a more holistic assessment of impact of denosumab.

Conclusion

This study provides compelling evidence that denosumab accelerates fracture healing in osteoporotic patients, particularly within the first three months. While long-term healing rates are comparable to the control group, the early benefits of denosumab have significant clinical implications, including reduced immobilization, improved functional outcomes, and potential cost savings. Future research should focus on optimizing denosumab therapy for broader application, including its use in specific patient populations and assessing its long-term impact on fracture healing and quality of life.

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