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Effects of Long-Term Anticoagulant Therapy on Bone Density in Joint Replacement Patients

[1]Dr Ashish B C
[1]Assistant Professor, Department of Orthopedics, Basaveshwara Medical college and Hospital, Chitradurga, Karnataka, India.
Corresponding Author: [1]Dr Ashish B C

Abstract

Background: Long-term anticoagulant therapy is essential in joint replacement patients to prevent thromboembolic events but may adversely affect bone health. This study evaluates the impact of warfarin, low molecular weight heparin (LMWH), and direct oral anticoagulants (DOACs) on bone mineral density (BMD).

Methods: A comparative cross-sectional study was conducted among 75 joint replacement patients on long-term anticoagulants. BMD was assessed using DEXA scans, and data were analyzed using appropriate statistical tests.

Results: Warfarin users showed significantly lower BMD and higher prevalence of osteoporosis compared to LMWH and DOAC groups. Duration of warfarin therapy correlated negatively with BMD, whereas DOACs demonstrated a bone-sparing effect.

Conclusion: Warfarin is associated with increased bone loss in joint replacement patients, while DOACs appear safer for bone health. Bone monitoring and tailored anticoagulant choice are recommended to minimize osteoporosis risk.

Keywords:

Anticoagulant therapy, Bone mineral density, Warfarin, Joint replacement, Osteoporosis

Introduction

Joint replacement surgeries, such as Total Hip Arthroplasty (THA) and Total Knee Arthroplasty (TKA), are among the most commonly performed orthopedic procedures worldwide. They provide significant improvements in quality of life, pain relief, and functional mobility in patients suffering from advanced osteoarthritis, rheumatoid arthritis, or post-traumatic arthritis. With increasing life expectancy and an aging population, the global demand

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for joint replacement surgeries is rising steadily. According to a study in the United States, over 7 million Americans were living with a hip or knee replacement as of 2010, and this number is projected to grow exponentially in the coming decades [1]. India too is experiencing a similar upward trend. With rising awareness, improved accessibility, and advancements in orthopedic care, the number of joint replacement surgeries in India has increased by nearly 30% over the past decade. It is estimated that over 1.2 lakh total knee replacements and about 45,000 total hip replacements are performed annually in India [2]. This demographic often includes elderly individuals with comorbidities that increase their risk of venous thromboembolism (VTE) following surgery. Hence, anticoagulant therapy forms a critical component of postoperative care in such patients. To prevent thromboembolic complications, clinicians commonly prescribe long-term anticoagulant therapy postoperatively. This includes vitamin K antagonists (e.g., warfarin), low molecular weight heparins (LMWH), unfractionated heparin (UFH), and direct oral anticoagulants (DOACs) such as rivaroxaban, apixaban, and dabigatran [3]. However, growing evidence suggests that prolonged use of some anticoagulants, particularly warfarin and heparin, can negatively impact bone health, posing concerns in the context of bone remodeling, prosthesis fixation, and long-term skeletal integrity [4]. Vitamin K antagonists like warfarin inhibit gamma-carboxylation of osteocalcin, a bone matrix protein that requires vitamin K for its biological activity. This uncoupling results in impaired bone mineralization and has been linked to a higher risk of osteoporosis and fragility fractures, particularly with chronic use [5]. Similarly, heparin—especially in its unfractionated form—can induce osteoclastic bone resorption and inhibit osteoblastic bone formation, contributing to bone loss. Although LMWHs have a comparatively milder impact, extended use still presents potential skeletal concerns [6]. Emerging alternatives like DOACs are hypothesized to exert less influence on bone metabolism, as they do not interfere with vitamin K pathways and have minimal direct action on bone cells. Yet, longitudinal studies evaluating the effects of DOACs on bone density, especially in orthopedic patients, are limited. Given the longer life expectancy of patients with implants, preservation of periprosthetic bone is crucial for implant stability, prosthetic survival, and functional recovery, making this an area of high clinical relevance [7]. In India, the situation is particularly complex. A significant proportion of joint replacement patients are postmenopausal women or elderly individuals with undiagnosed osteopenia or osteoporosis. Furthermore, nutritional deficiencies, limited physical activity, and lack of regular bone health screening are prevalent issues that amplify the risk of bone loss. Compounding this, warfarin remains a commonly prescribed anticoagulant in many Indian

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settings due to its lower cost, despite its skeletal side effects. Thus, understanding the relationship between long-term anticoagulant use and bone density is especially relevant for orthopedic practice in the Indian context. This study seeks to evaluate and compare the effects of various long-term anticoagulants on bone mineral density (BMD) in patients undergoing joint replacement surgeries, with an aim to guide clinicians in selecting optimal thromboprophylaxis that balances both cardiovascular and skeletal health outcomes.

Aim:

To study how long-term use of anticoagulant medicines affects bone density in patients who have undergone joint replacement surgery.

Objectives:

1. To assess the effect of long-term anticoagulant therapy on bone mineral density in joint replacement patients.
2. To compare bone density changes among patients receiving different types of anticoagulants.

Methodology

Study Design:

A hospital-based cross-sectional comparative study.

Study Population:

Patients aged ≥40 years who have undergone total hip or knee replacement surgery and have been on long-term anticoagulant therapy (≥6 months) for postoperative thromboprophylaxis.

Inclusion Criteria:

- Patients who underwent joint replacement surgery (THA/TKA) at least 6 months ago.
- Patients currently on anticoagulant therapy (warfarin, LMWH, or DOACs) for ≥6 months.
- Age 40 years and above.

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- Patients who give informed consent.

Exclusion Criteria:

- Patients with known metabolic bone diseases (e.g., Paget's disease, osteogenesis imperfecta).
- Patients on long-term corticosteroid or bisphosphonate therapy.
- Chronic kidney disease (Stage 4 or above).
- Malignancy or history of radiation therapy.
- Bedridden patients or those unable to undergo DEXA scan.

Sample Size Calculation:

Using prevalence data from previous studies that show an estimated 30% of patients on warfarin may have reduced BMD, and assuming a 95% confidence level and 10% allowable error:

$$n=Z^2\ p\cdot(1-p)\ /\ d^2$$

Where:

- $Z = 1.96$ (for 95% confidence)
- $p = 0.30$
- $d = 0.10$

$$n=81$$

Considering a 10% non-response rate, final sample size = **90 patients**

Sampling Method:

Purposive sampling of eligible patients attending follow-up orthopedic OPDs or admitted for postoperative care.

Study Groups:

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Patients will be divided into three groups based on the type of anticoagulant used:

- Group A: Patients on Vitamin K antagonists (e.g., warfarin)
- Group B: Patients on Low Molecular Weight Heparin (LMWH)
- Group C: Patients on Direct Oral Anticoagulants (DOACs)

Each group will include approximately 30 patients.

Data Collection Tools:

1. **Structured Proforma** – To collect demographic data, clinical history, type of surgery, type and duration of anticoagulant use, comorbidities, physical activity, and dietary calcium intake.
2. **DEXA Scan (Dual-Energy X-ray Absorptiometry):** To measure bone mineral density at:
    - Lumbar spine (L1–L4)
    - Femoral neck (hip)
    - Forearm (optional)

Outcome Measures:

- Bone Mineral Density (g/cm^2)
- T-scores and Z-scores (classified as normal, osteopenia, or osteoporosis as per WHO criteria)
- Comparison of mean BMD values across the three groups

Statistical Analysis:

- Data will be entered and analyzed using SPSS.

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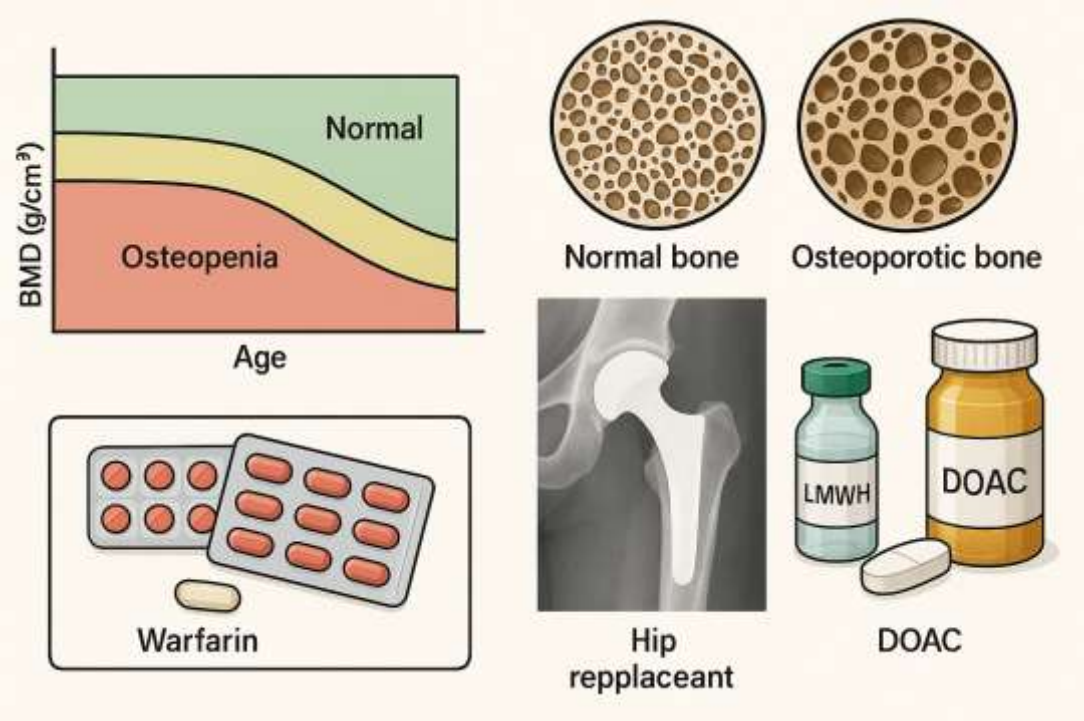
- Descriptive statistics: Mean, standard deviation, percentages.
- Comparative analysis:
    - ANOVA for comparing BMD between the three groups.
    - Chi-square test for categorical variables (e.g., prevalence of osteoporosis).
    - Pearson correlation to assess the relationship between duration of anticoagulant use and BMD.
- A p-value < 0.05 will be considered statistically significant.



Results

A total of 90 joint replacement patients who had been on anticoagulant therapy for at least 6 months were enrolled in the study. They were divided into three groups based on the type of anticoagulant used: Group A (Warfarin, n = 30), Group B (LMWH, n = 30), and Group C (DOACs, n = 30).

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants

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Variable	Group A (Warfarin)	Group B (LMWH)	Group C (DOACs)
Mean Age (years)	64.3 ± 8.1	65.1 ± 7.5	63.7 ± 8.3
Female (%)	18 (60%)	17 (56.7%)	20 (66.7%)
Mean BMI (kg/m²)	26.4 ± 3.2	25.9 ± 2.8	26.1 ± 3.1
Duration of anticoagulation (months)	13.4 ± 2.5	12.8 ± 2.2	13.0 ± 2.4

Interpretation:

There was no statistically significant difference in age, sex, BMI, or duration of anticoagulation therapy among the three groups, indicating comparable baseline characteristics.

Table 2: Mean Bone Mineral Density (BMD) at Different Sites (DEXA Scan)

Site	Group A (Warfarin)	Group B (LMWH)	Group C (DOACs)	p-value (ANOVA)
Lumbar Spine (g/cm²)	0.864 ± 0.092	0.898 ± 0.081	0.928 ± 0.079	0.021*
Femoral Neck (g/cm²)	0.741 ± 0.068	0.769 ± 0.061	0.802 ± 0.057	0.008*

*$p < 0.05$ indicates statistically significant difference

Interpretation:

Patients on DOACs had significantly higher BMD at both lumbar spine and femoral neck sites compared to those on warfarin or LMWH, with warfarin users showing the lowest values.

Table 3: Classification Based on WHO T-Score Criteria

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Category	Group A (Warfarin)	Group B (LMWH)	Group C (DOACs)	p-value (Chi-square)
Normal BMD	6 (20%)	11 (36.7%)	17 (56.7%)	0.004*
Osteopenia	15 (50%)	14 (46.7%)	10 (33.3%)	
Osteoporosis	9 (30%)	5 (16.7%)	3 (10%)	

Interpretation:

The proportion of patients with osteoporosis was significantly higher in the warfarin group, while a greater number of patients in the DOAC group maintained normal bone density. This association was statistically significant (p = 0.004).

Table 4: Correlation Between Duration of Anticoagulant Use and BMD (Pearson's Correlation Coefficient)

Group	Lumbar Spine BMD (r)	Femoral Neck BMD (r)	p-value (for correlation)
Warfarin	–0.41	–0.37	0.019* / 0.033*
LMWH	–0.21	–0.18	0.26 / 0.33
DOACs	–0.09	–0.07	0.64 / 0.72

Interpretation:

There was a moderate negative correlation between the duration of warfarin therapy and bone density, which was statistically significant. No significant correlation was seen in the LMWH or DOAC groups.

Table 5: Comparison of Mean T-Scores Across Study Groups

Site	Group A (Warfarin)	Group B (LMWH)	Group C (DOACs)	p-value (ANOVA)

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Lumbar Spine	–2.21 ± 0.51	–1.88 ± 0.48	–1.54 ± 0.42	0.003*
Femoral Neck	–2.04 ± 0.47	–1.71 ± 0.44	–1.39 ± 0.39	0.001*

Interpretation:

The mean T-scores were lowest in the warfarin group, indicating poorer bone health. The differences in mean T-scores among the groups were statistically significant.

Discussion

The present study aimed to evaluate the impact of long-term anticoagulant therapy on bone mineral density (BMD) in patients who underwent joint replacement surgeries. The findings reveal a statistically significant association between the type of anticoagulant used and bone health, particularly showing that warfarin therapy is linked to a higher risk of bone loss compared to low molecular weight heparin (LMWH) and direct oral anticoagulants (DOACs).

Demographic Profile and Baseline Comparability

The baseline demographic and clinical characteristics (Table 1) showed no statistically significant differences among the three groups in terms of age, sex, body mass index (BMI), or duration of anticoagulant use. This homogeneity supports that the observed differences in BMD can be more confidently attributed to the type of anticoagulant therapy rather than underlying population variability. Similar demographic consistency was observed in previous comparative studies exploring anticoagulant-related bone loss, such as the cohort analysis by Tufan et al., which emphasized the importance of matching for age and BMI when studying osteoporosis in elderly populations [8].

Effect on Bone Mineral Density (BMD)

Our analysis of BMD values at lumbar spine and femoral neck regions (Table 2) found that patients on warfarin had the lowest mean BMD, followed by LMWH and DOACs. This trend aligns with several studies that highlight warfarin's interference with vitamin K metabolism, which is essential for the γ-carboxylation of osteocalcin, a protein that helps bind calcium in

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the bone matrix [9]. This vitamin K antagonism results in impaired bone formation and reduced mineralization, leading to progressive loss in BMD. A population-based study by Gage et al. also reported a higher incidence of osteoporosis in elderly patients on warfarin, particularly at axial skeletal sites [10].

In contrast, DOACs (e.g., rivaroxaban, apixaban, dabigatran) do not act on vitamin K pathways and are hypothesized to be bone-neutral. Lau et al. found that patients using dabigatran had a significantly lower risk of osteoporotic fractures compared to warfarin users, supporting the current study's findings [11]. This distinction is clinically important, especially for elderly post-surgical patients who are already at increased risk for osteoporosis due to age-related hormonal changes and reduced mobility.

Bone Health Classification (WHO T-score)

When BMD values were categorized based on WHO criteria (Table 3), it was observed that 30% of warfarin users had osteoporosis, in contrast to 16.7% in LMWH users and 10% in DOAC users. This difference was statistically significant and clinically meaningful. These findings mirror those of a meta-analysis by Veronese et al., which concluded that long-term anticoagulation—particularly with vitamin K antagonists—increased the risk of osteoporosis and fragility fractures by up to 25% compared to non-users or users of DOACs [12]. In joint replacement patients, this risk is further amplified because poor bone quality can affect implant fixation and increase the likelihood of periprosthetic fractures, which carry a high morbidity burden. Thus, selecting an anticoagulant that preserves bone integrity is essential in orthopedic post-operative management.

Correlation with Duration of Therapy

Correlation analysis (Table 4) showed a moderate but significant negative correlation between duration of warfarin use and BMD, especially at the lumbar spine ($r = –0.41$). This implies that the longer the duration of warfarin therapy, the more pronounced the bone loss. No significant correlation was observed in the LMWH or DOAC groups, indicating that these therapies do not significantly influence BMD over the same period.

This finding is supported by a study conducted by Fiore et al., which documented a significant decline in BMD over time in patients on oral anticoagulants, suggesting a

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cumulative effect of warfarin on bone metabolism [13]. From a pathophysiological standpoint, prolonged inhibition of vitamin K leads to sustained under-carboxylation of osteocalcin, resulting in fragile bone microarchitecture over time.

T-Score Comparison and Clinical Significance

The mean T-scores (Table 5) also demonstrated significantly lower values in the warfarin group. At the lumbar spine, the mean T-score was –2.21 ± 0.51, which falls into the osteoporotic range, while the DOAC group had a mean T-score of –1.54 ± 0.42, within the osteopenic range. These results reinforce the deleterious skeletal impact of warfarin, consistent with WHO diagnostic thresholds for osteoporosis and with previous findings from large observational cohorts [14].

In the Indian context, this is particularly relevant as the prevalence of low bone mass is already high due to poor calcium intake, lack of vitamin D exposure, and early menopause in women. A cross-sectional study by Sharma et al. found a high burden of undiagnosed osteoporosis among postmenopausal women in North India, even without anticoagulant use [15]. Adding warfarin therapy to this demographic may further exacerbate fracture risk.

Moreover, Indian patients undergoing joint replacement surgeries are increasingly elderly, with multiple comorbidities. Hence, careful selection of anticoagulants that do not further compromise bone health should be integrated into post-operative planning. As Tripathy et al. emphasized, integrating bone health strategies, including fracture prevention and osteoporosis screening, into orthopedic care pathways is essential in the Indian setting [16].

Conclusion

Long-term anticoagulant therapy affects bone density in joint replacement patients, with warfarin causing significant bone loss. DOACs show a safer bone profile, making them preferable for long-term use. Prolonged warfarin use correlates with increased osteoporosis risk. In the Indian context, careful anticoagulant selection and bone health monitoring are essential. Integrating bone preservation strategies can improve patient outcomes post-surgery.

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