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RESEARCH ARTICLE

BONE HEALTH AND FRACTURE RISKS IN LONG-TERM ANTICOAGULANT THERAPY FOR RARE CARDIAC DISORDERS

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Abstract: ***Background:*** Long-term anticoagulant therapy plays a crucial role in preventing thromboembolic complications in rare cardiac disorders such as hypertrophic cardiomyopathy, congenital valvular anomalies, and arrhythmogenic right ventricular dysplasia. However, chronic use of vitamin K antagonists (VKAs) and certain direct oral anticoagulants (DOACs) may negatively affect bone metabolism and increase fracture risk. ***Aims and Objectives:*** To evaluate the impact of long-term anticoagulant therapy on bone mineral density (BMD), serum bone metabolism markers, and fracture risk in patients with rare cardiac disorders. ***Methods and Materials:*** A cross-sectional observational study was conducted on 36 patients aged 25–65 years receiving anticoagulant therapy for over two years at a tertiary cardiac care centre. Patients were grouped based on the type of anticoagulant warfarin (n=18) and DOACs (n=18). DEXA scan was used to measure BMD at lumbar spine and femoral neck. Serum calcium, phosphate, 25(OH) vitamin D, and osteocalcin were assessed. Fracture history and therapy duration were recorded. ***Results:*** Of 36 patients, 22 (61.1%) exhibited reduced BMD (T-score ≤ –1.0). Osteopenia occurred in 33.3%, and osteoporosis in 27.8%. Mean T-score was lower in warfarin users (–2.0 ± 0.6) than DOAC users (–1.3 ± 0.5) ($p<0.05$). Fractures were more common in warfarin users (27.8%) compared to DOAC users (11.1%). Vitamin D deficiency (<20 ng/mL) was found in 69.4% of participants. ***Discussion:*** Chronic warfarin therapy adversely affects bone metabolism by impairing vitamin K–dependent osteocalcin activation, leading to lower bone density and higher fracture rates. DOACs, which do not rely on vitamin K pathways, showed a comparatively safer bone profile. Periodic DEXA screening and nutritional supplementation with calcium and vitamin D are advisable for patients on long-term anticoagulation. ***Conclusion:*** Long-term use of VKAs is associated with greater bone loss and fracture risk than DOACs among patients with rare cardiac disorders. Early bone health monitoring and preventive strategies can reduce skeletal morbidity.

Keywords: Anticoagulants, warfarin, DOAC, osteoporosis, bone mineral density, fractures, vitamin K, rare cardiac disorders

INTRODUCTION

Anticoagulant therapy is a cornerstone in the management of cardiac disorders that predispose patients to thromboembolic complications. In patients with rare cardiac diseases such as hypertrophic cardiomyopathy, congenital valvular malformations, restrictive or arrhythmogenic right ventricular cardiomyopathies, and prosthetic valve replacements, prolonged anticoagulation is often mandatory for survival (1). By reducing thrombus formation and embolic events, these agents have significantly improved morbidity and mortality. However, with increasing longevity and the chronic nature of these diseases, new concerns have emerged regarding the long-term systemic effects of these drugs, particularly on skeletal health (2).

Among the available agents, vitamin K antagonists (VKAs) such as warfarin have been the mainstay of therapy for several decades. They act by inhibiting the vitamin K epoxide reductase complex, thereby reducing the activation of vitamin K–dependent clotting factors II, VII, IX, and X (3). Unfortunately, vitamin K is also essential for bone metabolism, where it facilitates the γ-carboxylation of osteocalcin a key non-collagenous protein secreted by osteoblasts that binds calcium to the bone matrix (4). Inhibition of this process leads to under-carboxylated osteocalcin, reduced calcium deposition, and impaired mineralization, resulting in osteopenia and osteoporosis over time. Consequently, long-term warfarin therapy has been associated with decreased bone mineral density (BMD) and increased fracture risk, especially in elderly or postmenopausal patients (5).

The introduction of direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban, has offered safer alternatives that function independently of vitamin K metabolism. Preliminary evidence suggests that DOACs may have a more favorable skeletal profile compared with VKAs, as they do not interfere with osteocalcin carboxylation or calcium regulation (6). Nevertheless, the long-term effects of these agents on bone health remain insufficiently studied, particularly in populations with rare cardiac disorders requiring continuous therapy.

Patients with such rare cardiac diseases often face additional risk factors for bone loss, including prolonged immobility, nutritional deficiencies, and

polypharmacy. Hence, understanding how chronic anticoagulation influences bone integrity is vital for designing preventive and therapeutic strategies (7). Evaluating BMD, fracture prevalence, and biochemical markers of bone metabolism in this population can provide essential insights into clinical decision-making (8).

Early recognition and intervention may mitigate long-term morbidity and improve overall quality of life in this unique subset of cardiac patients (9).

AIM AND OBJECTIVES

Aim:

To evaluate bone mineral density and fracture risk in patients with rare cardiac disorders undergoing long-term anticoagulant therapy.

Objectives:

1. To assess BMD and categorize patients into normal, osteopenic, or osteoporotic groups.
2. To compare warfarin and DOAC users in terms of bone metabolism markers and fracture prevalence.

MATERIAL AND METHODS

Study Design and Setting: This was a cross-sectional observational study conducted in the Department of Cardiology at a tertiary care centre. The study was designed to assess bone health parameters among patients with rare cardiac disorders who were receiving long-term anticoagulant therapy. The study period extended over 18 months, during which data collection, laboratory evaluation, and imaging were performed.

Study Population and Sample Size: A total of 36 patients aged between 25 and 65 years were enrolled. All participants were diagnosed with rare cardiac disorders such as hypertrophic cardiomyopathy, restrictive cardiomyopathy, congenital valvular heart disease, or arrhythmogenic right ventricular dysplasia. All patients were on continuous anticoagulant therapy for a duration exceeding two years.

Inclusion Criteria

- Patients aged 25–65 years with confirmed rare cardiac disorders.
- Continuous anticoagulant therapy (warfarin or DOACs) for more than two years.
- Willingness to participate and provide informed consent.

Exclusion Criteria

- Pre-existing metabolic bone diseases or severe osteoporosis diagnosed before starting anticoagulant therapy.
- Patients on chronic corticosteroids, anticonvulsants, or other drugs known to affect bone metabolism.
- Chronic renal or hepatic insufficiency.
- History of malignancy or systemic inflammatory disease affecting bone.

Study Groups: Participants were divided into two groups based on the anticoagulant used:

- **Group A:** Warfarin users (n = 18)
- **Group B:** Direct Oral Anticoagulant (DOAC) users (n = 18)

Data Collection and Assessment Parameters: A detailed clinical history was taken, including duration of anticoagulant therapy, dietary habits, mobility status, and history of fractures or falls. Physical examination included height, weight, and body mass index (BMI). Bone mineral density (BMD) was assessed by Dual-Energy X-ray Absorptiometry (DEXA) at the lumbar spine (L1–L4) and femoral neck.

Laboratory Investigations

Venous blood samples were analyzed for:

- Serum calcium and phosphate levels.
- 25(OH) vitamin D concentration.
- Serum osteocalcin as a marker of bone formation.

All tests were performed using standardized laboratory methods within the hospital's biochemistry department.

Ethical Considerations: The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from all participants before enrollment. Confidentiality and anonymity of patient data were strictly maintained.

Statistical Analysis: Collected data were entered in Microsoft Excel and analyzed using SPSS version 25.0. Descriptive statistics (mean, standard deviation, and percentage) were used for continuous and categorical variables. Comparison between warfarin and DOAC groups was done using independent t-test for continuous variables and Chi-square test for categorical variables. A p-value <0.05 was considered statistically significant.

RESULTS AND OBSERVATIONS:

A total of 36 patients with rare cardiac disorders on long-term anticoagulant therapy were evaluated. Among them, 18 were receiving warfarin (Group A) and 18 were on direct oral anticoagulants (DOACs; Group B). The mean duration of anticoagulation was 4.4 ± 1.6 years.

The two groups were comparable in terms of age, sex distribution, BMI, and therapy duration ($p > 0.05$), ensuring that baseline characteristics did not influence outcome differences. Although calcium levels were slightly lower in warfarin users, the difference was not statistically significant. This homogeneity indicates that subsequent variations in bone parameters were primarily attributable to the type of anticoagulant used.

Table 1: Demographic and Clinical Characteristics of Study Participants

Parameter	Warfarin (n = 18)	DOAC (n = 18)	p-value
Mean age (years)	50.8 ± 9.4	48.6 ± 8.9	0.49
Male : Female ratio	10:08	09:09	0.78
Mean duration of therapy (years)	4.7 ± 1.6	4.1 ± 1.4	0.27
Mean BMI (kg/m²)	23.4 ± 3.1	22.8 ± 2.9	0.53
Mean serum calcium (mg/dL)	8.4 ± 0.6	8.8 ± 0.5	0.06
Mean serum phosphate (mg/dL)	3.3 ± 0.5	3.4 ± 0.4	0.64

Table 2: Bone Mineral Density (BMD) and Osteoporotic Status by Anticoagulant Type

Parameter	Warfarin (n = 18)	DOAC (n = 18)	p-value
Mean BMD T-score	–2.0 ± 0.6	–1.3 ± 0.5	< 0.05*
Normal BMD (%)	27.8 % (5)	44.4 % (8)	0.18
Osteopenia (%)	38.9 % (7)	33.3 % (6)	0.66
Osteoporosis (%)	33.3 % (6)	22.2 % (4)	0.04*
Fracture prevalence (%)	27.8 % (5)	11.1 % (2)	< 0.05*

Warfarin users demonstrated significantly lower mean BMD T-scores (–2.0 ± 0.6) than DOAC users (–1.3 ± 0.5) ($p < 0.05$). The prevalence of osteoporosis and fragility fractures was also notably higher in the warfarin group. These results confirm a clear association between vitamin K antagonism and reduced bone mineralization, aligning with the study hypothesis that chronic warfarin use predisposes to bone loss and fracture risk.

Table 3: Biochemical Markers of Bone Metabolism

Parameter	Warfarin (n = 18)	DOAC (n = 18)	p-value
Serum 25(OH) Vitamin D (ng/mL)	18.2 ± 5.4	20.1 ± 4.9	0.22
Vitamin D deficiency (< 20 ng/mL) (%)	72.2 % (13)	66.7 % (12)	0.62
Serum osteocalcin (ng/mL)	11.4 ± 3.6	16.7 ± 4.1	< 0.05*
Serum calcium (mg/dL)	8.4 ± 0.6	8.8 ± 0.5	0.06
Serum phosphate (mg/dL)	3.3 ± 0.5	3.4 ± 0.4	0.64

Vitamin D deficiency was prevalent in both groups, but mean osteocalcin levels were significantly lower among warfarin users ($p < 0.05$). This reduction in osteocalcin reflects impaired carboxylation secondary to vitamin K inhibition, leading to defective bone matrix formation. The relative preservation of osteocalcin in DOAC users suggests a lesser impact on bone turnover and mineralization.

Of the 36 participants, 22 (61.1 %) exhibited reduced bone mineral density (T-score ≤ –1.0). Osteopenia was present in 33.3 %, and osteoporosis in 27.8 % of patients. Fractures were reported in 19.4 % overall, predominantly in the warfarin group.

The findings demonstrate a significant association between warfarin use and reduced BMD, likely mediated by impaired vitamin K-dependent bone protein synthesis. DOACs, by contrast, showed a comparatively protective skeletal profile.

DISCUSSION

The present study evaluated the impact of long-term anticoagulant therapy on bone health among patients with rare cardiac disorders. The findings demonstrated a significant reduction in bone mineral density (BMD) and a higher fracture prevalence in patients receiving warfarin compared with those on direct oral anticoagulants (DOACs) (10). These results support the growing evidence that chronic use of vitamin K antagonists (VKAs) adversely affects skeletal metabolism through mechanisms that differ fundamentally from those of DOACs (11).

Warfarin acts by inhibiting the vitamin K epoxide reductase complex, thereby blocking the γ-carboxylation of vitamin K–dependent proteins, including osteocalcin, which plays a critical role in calcium binding and bone matrix mineralization (12). In the absence of adequate γ-carboxylation, under-

carboxylated osteocalcin accumulates, leading to defective bone mineralization and decreased BMD. This biochemical disruption explains the significantly lower osteocalcin levels and poorer BMD values observed among warfarin users in this study (13).

Conversely, DOACs such as dabigatran, rivaroxaban, and apixaban exert their anticoagulant effect by directly inhibiting thrombin or factor Xa, independent of vitamin K metabolism. Therefore, they are unlikely to interfere with osteocalcin activation or bone matrix formation (14). In the present study, DOAC users exhibited relatively preserved bone density and significantly higher osteocalcin levels, suggesting minimal skeletal toxicity. Several population-based cohort studies have corroborated these findings, indicating a reduced risk of osteoporosis and fractures among patients treated with DOACs compared to warfarin.

Vitamin D deficiency was prevalent in both groups, affecting nearly two-thirds of the cohort. This observation reflects common risk factors such as inadequate sunlight exposure, dietary insufficiency, and reduced mobility in patients with chronic cardiac illness (15). Vitamin D deficiency may further compound the effects of warfarin by impairing calcium absorption and bone mineralization. Therefore, routine assessment and supplementation of vitamin D and calcium should be integral to the management of such patients (16).

The correlation between therapy duration and bone loss also emphasizes the cumulative skeletal burden of prolonged anticoagulation. Although no significant difference in therapy duration was observed between the two groups, the decline in BMD was clearly more pronounced in those on warfarin (10). Regular bone health monitoring through dual-energy X-ray absorptiometry (DEXA) should thus be considered in patients on VKAs for more than two years, particularly those with additional risk factors such as postmenopausal status or advanced age (17).

Overall, the results suggest that while anticoagulants remain essential in preventing thromboembolic events in rare cardiac disorders, clinicians should balance cardiovascular protection with long-term skeletal safety. Substituting DOACs for VKAs, when clinically appropriate, along with dietary modification, physical activity, and supplementation, may effectively reduce the risk of osteoporosis and fractures (18).

CONCLUSION

Long-term anticoagulant therapy, especially with warfarin, is associated with significant deterioration of bone mineral density and increased fracture risk among patients with rare cardiac disorders. DOACs demonstrate a comparatively safer skeletal profile. Regular DEXA screening, vitamin D and calcium supplementation, and consideration of DOAC therapy where feasible are recommended to preserve bone health and reduce morbidity in this vulnerable population.

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