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Effectiveness of Calcium and Vitamin D3 Supplementation in Secondary Osteoporosis: A Retrospective Cohort Analysis

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Abstract

Background

Secondary osteoporosis may occur in patients with underlying conditions or exposures that affect bone health. Calcium and vitamin D3 supplementation is frequently used as part of the management of these patients. However, real-world data evaluating changes in bone mineral density (BMD) following supplementation in patients with secondary osteoporosis are limited. This study evaluated changes in BMD following calcium and vitamin D3 supplementation in patients with secondary osteoporosis.

Methods

This retrospective, multicenter cohort study included 12,415 adult patients (≥18 years) diagnosed with secondary osteoporosis across India. Data were collected from electronic medical records. Variables included supplementation patterns, adherence, and treatment regimens. The primary outcome was clinician-assessed change in BMD/T-score during routine clinical follow-up, categorized as improved, unchanged, or declined. Associations between categorical outcomes and baseline/treatment characteristics were evaluated using chi-square tests.

Results

A total of 12,415 patients (mean age 52.2 ± 10.5 years) were included. Calcium and vitamin D3 supplementation were prescribed in 82.6% and 76.8% of patients, respectively, with combination therapy used in 55.1%. Based on clinician assessment, 8,887 patients (71.6%) demonstrated improvement in BMD/T-score, 609 (4.9%) showed no change, and 2,919 (23.5%) experienced a decline during follow-up. Fractures were reported in 2,379 patients (19.2%). Significant associations were observed between BMD/T-score outcomes and supplementation, treatment regimen, adherence, regimen modification, and fracture history (all $p < 0.001$). Combination therapy was associated with the highest proportion of T-score improvement (80.8%), compared with vitamin D3 alone (69.8%) and calcium alone (51.4%) ($p < 0.001$). Higher adherence was significantly associated with improved treatment outcomes ($p < 0.001$). Fractures occurred in 19.2% of patients during follow-up.

Conclusion

Calcium and vitamin D3 supplementation was associated with favorable clinician-assessed BMD outcomes among patients with secondary osteoporosis in routine clinical practice. Combination therapy and high treatment adherence were associated with more favorable outcomes. These findings provide real-world insights into the use of calcium and vitamin D3 supplementation in the management of secondary osteoporosis.

Categories: Oral Medicine, Orthopedics, Epidemiology/Public Health
Keywords: adherence, bone mineral density, calcium, combination therapy, fractures, retrospective study, secondary osteoporosis, supplementation, t-score, vitamin d3

Introduction

Osteoporosis is a chronic skeletal disorder characterized by reduced bone mineral density (BMD) and deterioration of bone microarchitecture, leading to increased bone fragility and susceptibility to fractures. It represents a major global public health concern, particularly in aging populations, with fragility fractures contributing substantially to morbidity, mortality, and healthcare burden. While primary osteoporosis is commonly associated with aging and postmenopausal status, secondary osteoporosis, resulting from underlying medical conditions or pharmacological therapies, is increasingly recognized as a significant and often underdiagnosed contributor to skeletal disease burden [1,2].

Secondary osteoporosis arises due to a wide range of etiologies, including endocrine disorders, inflammatory diseases, gastrointestinal malabsorption syndromes, chronic kidney disease, and prolonged use of medications such as glucocorticoids, anticonvulsants, and proton pump inhibitors. Among these, glucocorticoid-induced osteoporosis remains one of the most common forms, with rapid bone loss and increased fracture risk observed even at relatively low doses [3,4]. Patients with secondary osteoporosis often present at a younger age and may have a more complex clinical profile, necessitating targeted and individualized management strategies.

Calcium and vitamin D3 play fundamental roles in bone metabolism and are considered cornerstone interventions in the prevention and management of osteoporosis. Calcium is essential for maintaining bone mineralization, while vitamin D facilitates intestinal calcium absorption and regulates bone remodeling through its effects on osteoblast and osteoclast activity. Deficiency of either nutrient has been strongly associated with reduced BMD, impaired bone quality, and increased fracture risk [1,5]. Consequently, clinical guidelines universally recommend adequate intake of calcium and vitamin D as part of standard osteoporosis care.

Despite strong evidence supporting calcium and vitamin D supplementation in primary osteoporosis, the effectiveness of these interventions in secondary osteoporosis remains less well established. Existing literature largely focuses on controlled clinical trials or specific subgroups, such as postmenopausal women or patients receiving glucocorticoid therapy, with relatively limited data derived from real-world clinical settings [6]. Moreover, response to supplementation in secondary osteoporosis may be influenced by multiple factors, including the underlying etiology, comorbid conditions, medication use, dosing regimens, and patient adherence.

Real-world evidence (RWE) has emerged as a valuable complement to randomized controlled trials by capturing treatment effectiveness in routine clinical practice across diverse patient populations. Such data are particularly important in conditions like secondary osteoporosis, where heterogeneity in patient characteristics and treatment approaches may influence outcomes [7]. However, large-scale real-world studies evaluating the longitudinal impact of calcium and vitamin D3 supplementation on BMD, fracture risk, and treatment response in secondary osteoporosis are scarce.

In this context, the present multicenter retrospective cohort study was conducted to evaluate the effectiveness of calcium and vitamin D3 supplementation in patients with secondary osteoporosis in routine clinical practice across India. The study aims to assess changes in BMD, fracture outcomes, and factors influencing treatment response, including supplementation type, dosing regimens, and adherence. By leveraging a large real-world dataset, this study seeks to provide clinically relevant insights into optimizing management strategies for secondary osteoporosis and improving patient outcomes.

Materials And Methods

Study design

This retrospective, multicenter observational study was conducted to evaluate the effectiveness of calcium and vitamin D3 supplementation in adults with secondary osteoporosis using routinely collected electronic medical records from participating centers. This retrospective multicenter study included patients with secondary osteoporosis managed across 1,753 participating clinical centers in India between May 2024 and November 2025.

Study population

Adults (≥18 years) with a clinical diagnosis of secondary osteoporosis who received calcium and/or vitamin D3 supplementation as part of routine clinical practice were eligible for inclusion. Eligible patients had documented baseline and follow-up clinical data, including BMD measurements, supplementation details, and treatment outcomes. Patients with primary osteoporosis, other primary bone disorders, incomplete medical records, or missing supplementation data were excluded from the analysis.

Secondary osteoporosis was defined as osteoporosis occurring in the presence of an identifiable underlying medical condition, medication exposure, or other clinical factors considered responsible for impaired bone health. Patients with secondary osteoporosis who received calcium and/or vitamin D3 supplementation as part of routine clinical management were eligible for inclusion. Patients with primary osteoporosis or other primary metabolic bone disorders were excluded.

Study objectives

The primary objective was to evaluate the effectiveness of calcium and vitamin D3 supplementation on BMD by assessing changes in T-scores from baseline to follow-up. Secondary objectives included evaluating the association between supplementation type and changes in T-scores, assessing fracture incidence and fracture frequency, identifying factors influencing treatment response, including age, adherence, and dosing regimens, comparing the effectiveness of combination therapy with monotherapy, and evaluating the

impact of treatment modifications on clinical outcomes.

Outcome measures

The primary outcome was clinical improvement in BMD, as assessed and documented by the treating clinician during routine clinical follow-up. Based on the clinician's assessment, BMD/T-score status was categorized as improved, unchanged, or declined compared with baseline. No study-mandated imaging or standardized densitometry protocol was used, as this was a retrospective real-world study.

Data collection

Demographic and clinical information, including age, sex, baseline BMD category, fracture history, supplementation details, treatment regimen, adherence, and follow-up outcomes, were extracted from EMRs using standardized data collection procedures. Clinical outcomes included changes in clinician-assessed BMD, measured T-scores, fracture occurrence during follow-up, and changes in fracture frequency. Treatment information included calcium and vitamin D3 dosage, supplementation regimen, combination therapy, treatment modifications, and physician-assessed adherence.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are summarized as frequencies and percentages. Associations between categorical variables were evaluated using the chi-square test. BMD/T-score outcomes were categorized as improved, unchanged, or declined based on the treating clinician's assessment and were analyzed in relation to baseline clinical characteristics, supplementation, treatment regimen, adherence, regimen modification, and fracture history. Subgroup analyses evaluated treatment response according to supplementation type, treatment regimen, adherence, fracture history, and other baseline characteristics. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 27.0 (Released 2020; IBM Corp., Armonk, New York, United States), and a two-sided p-value <0.05 was considered statistically significant.

Ethical considerations

The study protocol was approved by the Ethics Committee Deoyani Multispeciality Hospital. Owing to the retrospective observational design, the requirement for informed consent was waived. Patient data were anonymized prior to analysis, and all study procedures were conducted in accordance with applicable ethical and regulatory requirements to ensure confidentiality and data integrity.

Results

Baseline characteristics

A total of 12,415 patients with a clinical diagnosis of secondary osteoporosis recorded at the participating centers were included in the retrospective analysis. The mean age was 52.2 ± 10.5 years, and 8,221 patients (66.2%) were female. Based on baseline T-scores recorded in the clinical records, 4,467 patients (36.0%) had T-scores in the normal range, 4,128 (33.3%) had T-scores above the normal range, 1,765 (14.2%) had osteopenic-range T-scores, and 2,055 (16.6%) had osteoporotic-range T-scores. The baseline demographic and BMD characteristics of the study population are summarized in Table *1*.

Variable	n (%) / mean ± SD
Gender	
Male	4,194 (33.8)
Female	8,221 (66.2)
Age (years)	52.2 ± 10.5

TABLE 1: Baseline characteristics of study population (N = 12,415).

Supplementation pattern and treatment characteristics

Calcium supplementation was prescribed to 10,251 patients (82.6%), while 9,530 (76.8%) received vitamin D3 supplementation. Combination therapy with calcium and vitamin D3 was used in 6,838 patients (55.1%), whereas calcium monotherapy and vitamin D3 monotherapy were used in 2,901 (23.4%) and 2,676 (21.6%) patients, respectively. Treatment regimens were modified during follow-up in 1,814 patients (14.6%), while 10,601 patients (85.4%) had no regimen modification. The distribution of supplementation doses and

adherence categories is shown in Table 2 and Figure 1.

Treatment characteristic	n (%)
Calcium supplementation	10,251 (82.6)
Vitamin D3 supplementation	9,530 (76.8)
Combination therapy	6,838 (55.1)
Calcium monotherapy	2,901 (23.4)
Vitamin D3 monotherapy	2,676 (21.6)
Regimen modified during follow-up	1,814 (14.6)
No regimen modification	10,601 (85.4)

TABLE 2: Treatment characteristics (N = 12,415).

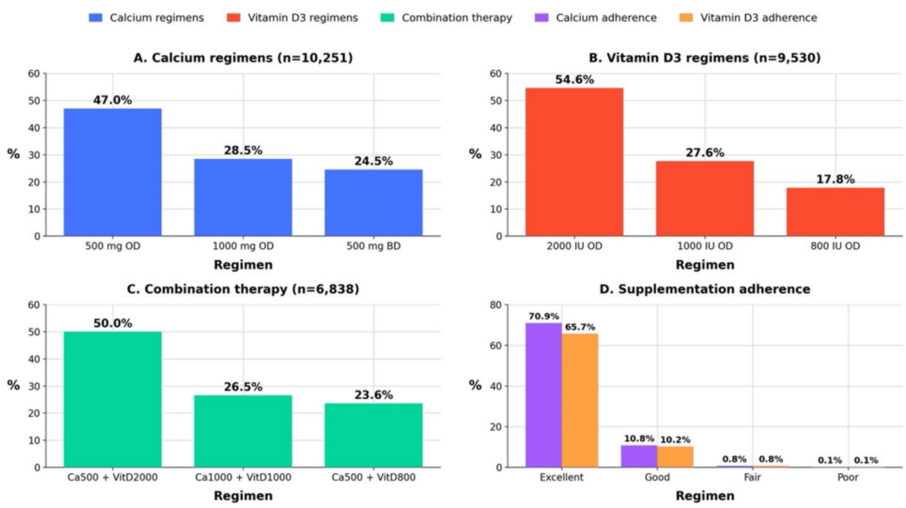


FIGURE 1: Supplement regimens and adherence.

Figure generated using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA); the image was enhanced using Perplexity AI (Perplexity AI, Inc., San Francisco, CA).

BMD and fracture outcomes

Based on the clinician's assessment, 8,887 patients (71.6%) demonstrated improvement in BMD/T-score, 609 (4.9%) showed no change, and 2,919 (23.5%) experienced a decline during follow-up. Fractures were reported in 2,379 patients (19.2%), while 10,036 (80.8%) remained fracture-free during the study period. These overall clinical and BMD outcomes are presented in Table 3.

Outcome	n (%)
T-score change (clinician-assessed)	
Improved	8,887 (71.6)
No change	609 (4.9)
Declined	2,919 (23.5)
Fractures during study	
Yes	2,379 (19.2)
No	10,036 (80.8)

TABLE 3: Clinical/BMD outcomes (N = 12,415).

BMD/T-score change was categorized as improved, no change, or declined based on the treating clinician's assessment during routine clinical follow-up.

BMD: bone mineral density.

Factors associated with T-score change

Fracture occurrence during follow-up was significantly associated with T-score outcomes (p<0.001). Patients who remained fracture-free had a higher proportion of T-score improvement than those who experienced fractures (74.2% vs. 60.4%) and a lower proportion of T-score decline (20.9% vs. 34.6%) (Table *4*). Supplementation type was also significantly associated with T-score outcomes (p<0.001). Patients receiving calcium supplementation demonstrated a higher proportion of T-score improvement than those not receiving calcium (75.1% vs. 54.8%) and a lower proportion of T-score decline (21.0% vs. 35.4%). Similarly, patients receiving vitamin D3 had higher T-score improvement (77.5% vs. 52.2%) and lower T-score decline (18.9% vs. 38.9%) than those not receiving vitamin D3. Among the mutually exclusive treatment strategies, combination therapy showed the highest proportion of improvement (80.8%), followed by vitamin D3 alone (69.8%) and calcium alone (51.4%) (Table *5*).

Variable	Improved, n (%)	No change, n (%)	Declined, n (%)	Total	p-value
Fractures during study					
No	7,450 (74.2)	489 (4.9)	2,097 (20.9)	10,036	<0.001
Yes	1,437 (60.4)	120 (5.0)	822 (34.6)	2,379	

TABLE 4: Association of fracture-related variables with clinician-assessed T-score change.

Pearson $\chi^2 = 204.065$; df = 2; $p < 0.001$.

Variable	Improved, n (%)	No change, n (%)	Declined, n (%)	Total	p-value
Calcium supplementation					
Yes	7,701 (75.1)	397 (3.9)	2,153 (21.0)	10,251	<0.001
No	1,186 (54.8)	212 (9.8)	766 (35.4)	2,164	
Vitamin D3 supplementation					
Yes	7,382 (77.5)	350 (3.7)	1,798 (18.9)	9,530	<0.001
No	1,505 (52.2)	259 (9.0)	1,121 (38.9)	2,885	
Type of therapy					
Combination (Ca + Vit D)	5,528 (80.8)	221 (3.2)	1,089 (15.9)	6,838	
Vitamin D alone	1,869 (69.8)	127 (4.7)	680 (25.4)	2,676	<0.001
Calcium alone	1,490 (51.4)	261 (9.0)	1,150 (39.6)	2,901	
Total	8,887 (71.6)	609 (4.9)	2,919 (23.5)	12,415	

TABLE 5: Association of supplementation type with clinician-assessed T-score change.

Pearson χ^2 tests: calcium supplementation, $\chi^2 = 388.343$, df = 2; Vitamin D3 supplementation, $\chi^2 = 701.347$, df = 2; type of therapy, $\chi^2 = 879.406$, df = 4; all $p < 0.001$.

Association of treatment regimen and regimen modification with T-score change

T-score outcomes varied significantly across the evaluated supplementation regimens and according to whether the treatment regimen was modified during follow-up (all $p < 0.001$). Among calcium regimens, 1,000 mg once daily had the highest proportion of T-score improvement (81.0%) and the lowest proportion of decline (11.6%). For vitamin D3, the 1,000 IU regimen showed the highest improvement rate (75.8%) and the lowest decline rate (17.3%). Among combination regimens, calcium 1,000 mg plus vitamin D3 1,000 IU was associated with the highest proportion of improvement (81.5%) and the lowest proportion of decline (11.1%). Patients whose regimen was not modified had a higher proportion of T-score improvement than those whose regimen was modified (72.6% vs. 65.6%) (Table *6*; Figure *2*).

Variable	Improved, n (%)	No change, n (%)	Declined, n (%)	Total	p-value
Calcium regimen					
1,000 mg once daily	2,864 (81.0)	260 (7.4)	410 (11.6)	3,534	
500 mg once daily	3,830 (65.6)	213 (3.6)	1,795 (30.8)	5,838	<0.001
500 mg twice daily	2,193 (72.1)	136 (4.5)	714 (23.5)	3,043	
Vitamin D3 regimen					
2,000 IU	4,785 (70.6)	281 (4.1)	1,709 (25.2)	6,775	
1,000 IU	2,600 (75.8)	239 (7.0)	593 (17.3)	3,432	<0.001
800 IU	1,502 (68.0)	89 (4.0)	617 (27.9)	2,208	
Combination therapy regimen					
Ca 1000 + Vit D 1000	2,679 (81.5)	242 (7.4)	365 (11.1)	3,286	
Ca 500 + Vit D 2000	4,321 (69.7)	264 (4.3)	1,617 (26.1)	6,202	<0.001
Ca 500 + Vit D 800	1,887 (64.5)	103 (3.5)	937 (32.0)	2,927	
Regimen change					
No	7,697 (72.6)	493 (4.7)	2,411 (22.7)	10,601	<0.001
Yes	1,190 (65.6)	116 (6.4)	508 (28.0)	1,814	
Total	8,887 (71.6)	609 (4.9)	2,919 (23.5)	12,415	

TABLE 6: Association of regimen and treatment modifications with clinician-assessed T-score change.

Pearson χ^2 tests: calcium regimen, $\chi^2 = 479.892$, df = 4; vitamin D3 regimen, $\chi^2 = 137.763$, df = 4; combination therapy regimen, $\chi^2 = 448.845$, df = 4; regimen change, $\chi^2 = 38.462$, df = 2; all $p < 0.001$.

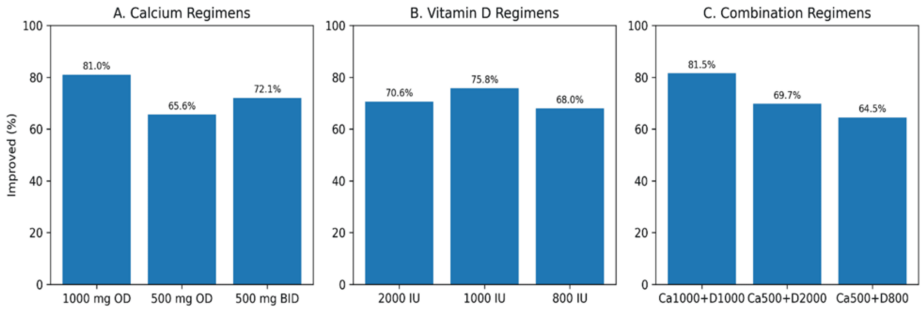


FIGURE 2: Clinical improvement rates across supplementation regimen.

Figure generated using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA); the image was enhanced using Perplexity AI (Perplexity AI, Inc., San Francisco, CA).

Treatment adherence and T-score outcomes

Treatment adherence was significantly associated with T-score outcomes ($p < 0.001$). The proportion of patients with T-score improvement was highest among those with excellent adherence (73.6%) and progressively decreased with lower adherence, reaching 65.8% among those with good adherence, 62.1% among those with fair adherence, and 42.0% among those with poor adherence. The corresponding proportions with T-score decline were 23.3%, 23.3%, 28.1%, and 30.4%, respectively (Table 7; Figure 3).

Adherence level	Improved, n (%)	No change, n (%)	Declined, n (%)	Total	p-value
Excellent	7,103 (73.6)	301 (3.1)	2,252 (23.3)	9,656	
Good	1,512 (65.8)	251 (10.9)	536 (23.3)	2,299	
Fair	243 (62.1)	38 (9.7)	110 (28.1)	391	<0.001
Poor	29 (42.0)	19 (27.5)	21 (30.4)	69	
Total	8,887 (71.6)	609 (4.9)	2,919 (23.5)	12,415	

TABLE 7: Association of overall supplementation adherence with clinician-assessed T-score change (N = 12,415).

Pearson $\chi^2 = 357.430$; df = 6; $p < 0.001$.

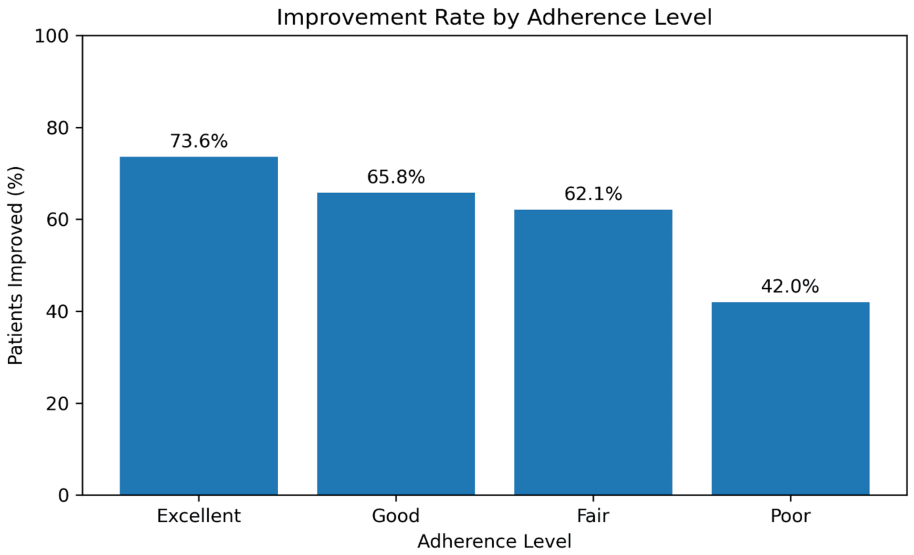


FIGURE 3: Adherence to supplementation and improvement in clinician-assessed T-score.

Figure generated using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA); the image was enhanced using Perplexity AI (Perplexity AI, Inc., San Francisco, CA).

Discussion

This large retrospective, real-world cohort study evaluated the clinical outcomes associated with calcium and vitamin D3 supplementation in patients with secondary osteoporosis, with particular emphasis on clinician-assessed changes in BMD/T-score and fracture outcomes. These findings are consistent with current clinical guidelines that recommend calcium and vitamin D as the foundation of osteoporosis management to support bone health and reduce fracture risk [1,2,8,9]. The higher rate of clinician-assessed improvement compared with T-score improvement may reflect routine clinical practice, where treatment response is evaluated using a combination of densitometric findings, symptom improvement, functional status, and overall fracture risk.

Combined calcium and vitamin D3 supplementation was associated with higher rates of T-score improvement than either calcium or vitamin D3 alone. This observation is biologically plausible because vitamin D facilitates intestinal calcium absorption and contributes to bone mineralization. Similar findings have been reported in previous clinical studies and meta-analyses evaluating combined supplementation for osteoporosis management and fracture prevention [5,6,9].

Differences in treatment response were also observed across supplementation regimens. Calcium 1000 mg once daily and vitamin D3 1000 IU daily were associated with higher proportions of T-score improvement

than the other evaluated regimens. Because treatment allocation was based on routine clinical practice rather than randomization, these findings should be interpreted cautiously and may reflect differences in baseline patient characteristics, physician prescribing preferences, adherence, or vitamin D status. Previous studies have similarly suggested that the effectiveness of supplementation depends on individual patient characteristics rather than dose alone [6].

Treatment adherence was strongly associated with favorable T-score outcomes, with patients demonstrating excellent adherence achieving the highest rates of improvement. These findings are consistent with previous reports identifying poor adherence as a major determinant of suboptimal treatment outcomes in osteoporosis, where long-term therapy is frequently challenged by the asymptomatic nature of disease progression [2,10]. The results reinforce the importance of strategies that promote sustained adherence during long-term osteoporosis management.

Patients who experienced fractures during follow-up had lower rates of T-score improvement and higher rates of T-score decline than those who remained fracture-free. These findings indicate an association between fracture occurrence and clinician-assessed T-score outcomes during follow-up; however, given the retrospective nature of the study and the absence of a formal pre- versus post-treatment assessment of fracture frequency, the findings should not be interpreted as evidence of a reduction in fracture frequency.

An important strength of this study is its large sample size and multicenter real-world design, which reflects routine clinical practice across diverse healthcare settings. Unlike randomized controlled trials, RWE provides valuable information regarding treatment patterns, adherence, and clinical outcomes in heterogeneous patient populations, thereby complementing evidence generated from controlled clinical studies [7]. These findings are particularly relevant in India, where vitamin D insufficiency and inadequate calcium intake remain common and continue to contribute substantially to osteoporosis risk [11].

Despite its strengths, this study has several limitations. Its retrospective observational design and the absence of a control group preclude causal inference, and potential confounding factors, including concomitant osteoporosis therapies, underlying disease severity, and lifestyle-related factors, could not be fully accounted for [3,4]. In addition, reliance on medical records and clinician-reported assessments may have introduced variability in data quality and outcome evaluation. Multivariable analyses to identify independent factors associated with treatment response and fracture occurrence were not performed in this study; therefore, the observed associations should be interpreted cautiously, and future studies incorporating prespecified multivariable models are warranted.

Notwithstanding these limitations, the study provides valuable RWE from a large, multicenter cohort representative of routine clinical practice. The findings demonstrate that calcium and vitamin D3 supplementation is associated with favorable BMD and T-score outcomes, with combination therapy and better treatment adherence showing the most favorable results. These observations support current guideline recommendations and provide practical evidence to inform the management of secondary osteoporosis. Further prospective, controlled studies are warranted to confirm these findings and optimize supplementation strategies across different patient populations.

Conclusions

Calcium and vitamin D3 supplementation was associated with favorable clinician-assessed T-score outcomes in this large real-world cohort of patients with secondary osteoporosis. Combination supplementation and good treatment adherence were associated with more favorable outcomes. Fractures were recorded during follow-up; however, the study was not designed to assess fracture prevention or reduction in fracture frequency. These findings provide real-world insights into the use of calcium and vitamin D3 supplementation in routine management of secondary osteoporosis. Prospective controlled studies are warranted to further evaluate these observations.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Rahul Pathak, Mayur Rabhadiya, Srisanat Rao, Pritam Kamble

Acquisition, analysis, or interpretation of data: Rahul Pathak, Mayur Rabhadiya, Srisanat Rao, Pritam Kamble

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Critical review of the manuscript for important intellectual content: Rahul Pathak, Mayur Rabhadiya, Srisanat Rao, Pritam Kamble

Supervision: Rahul Pathak, Mayur Rabhadiya, Srisanat Rao, Pritam Kamble

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Ethics Committee Deoyani Multispeciality Hospital issued approval IND/OP/01. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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