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Determinants of Treatment Response and Bone Health Outcomes with Calcium and Vitamin D Supplementation: Influence of Comorbidities, Lifestyle, Absorption and Nutrient Synergy

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Abstract

Background: Calcium and vitamin D are essential for skeletal health, yet treatment responses vary due to comorbidities, lifestyle factors, absorption issues, and nutrient interactions. Real-world data on how Indian physicians evaluate these determinants remain limited. This study examined physician-reported predictors of response, misconceptions, and practical factors influencing clinical outcomes with calcium and vitamin D supplementation.

Methods: A cross-sectional, questionnaire-based study was conducted among 128 physicians across India using a structured 38-item form, of which 13 items relevant to treatment determinants were analysed. Physicians provided anonymised, experience-based responses based on their last 10 patients treated with calcium and vitamin D for osteoporosis or metabolic bone disorders. Key parameters included nutrient synergy, lifestyle advice, comorbidity-related variations, changes in muscle strength and BMD, dosing approaches, absorption barriers, common misconceptions, and methods for assessing long-term effectiveness. Data were summarised using descriptive statistics.

Results: A total of 128 physicians participated in the survey. Vitamin K_2 was most frequently identified as the preferred adjunct to calcium and vitamin D (32.03%), while dietary modification was the most common lifestyle recommendation (42.97%). Comorbidities-particularly chronic kidney disease (37.50%), were perceived as key determinants of therapeutic response. Physicians reported moderate improvements in muscle strength (46.09%) and bone mineral density (39.06%). High fibre intake (42.97%) and proton pump inhibitor use (21.09%) were cited as major factors impairing absorption. Misconceptions included the belief that supplementation is only needed in the elderly (32.81%). Fracture reduction (40.63%) and composite assessments were the most used indicators of long-term effectiveness.

Conclusion: The study highlights that comorbidities, nutrient interactions, lifestyle practices, and absorption factors significantly influence response to calcium and vitamin D supplementation, underscoring the need for individualised strategies and further research to optimise bone health.

Keywords: Calcium; Vitamin D; Vitamin K2; Bone Mineral Density; Chronic Kidney Disease; Supplementation; Absorption

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1. Introduction

The pivotal role of vitamin D in skeletal development and the prevention of rickets has been well recognised since the early 20th century. Calcium, a fundamental component of bone, is absorbed in the small intestine through a process facilitated by vitamin D, and together with phosphorus, contributes to the formation of hydroxyapatite crystals that ensure optimal bone mineralisation and structural strength. Adequate intake and bioavailability of both nutrients are therefore essential for maintaining skeletal integrity across the lifespan. Beyond its classical action of enhancing intestinal calcium absorption, vitamin D also exerts diverse non-skeletal effects, supported by the presence of vitamin D receptors in multiple tissues-including immune cells, the prostate, the brain, and other organ systems-highlighting its broader physiological significance [1,2].

Calcium and vitamin D play interdependent roles in bone metabolism, with calcium serving as the primary mineral component and vitamin D regulating its absorption and utilisation [3]. Evidence demonstrates that these nutrients act synergistically to maintain bone homeostasis, and that the physiological benefits of vitamin D are augmented when calcium intake meets recommended thresholds [4]. Their interaction influences calcium absorption efficiency, vitamin D status, and potentially several skeletal and non-skeletal outcomes [4].

Despite well-established physiological roles, clinical evidence regarding calcium and vitamin D supplementation remains inconsistent. Systematic reviews reveal significant heterogeneity in outcomes across studies evaluating bone mineral density, fracture reduction, cardiovascular risk, cancer prevention, and mortality [5]. Observational associations often do not translate into benefits in randomized controlled trials, and clear dose–response relationships are infrequently demonstrated. While some studies report modest gains in bone mineral density and reductions in non-vertebral fractures with combined supplementation, others find no significant osteogenic effect [6].

Such variability suggests that treatment response is influenced by multiple determinants, including baseline nutrient status, age, comorbidities, gastrointestinal absorption capacity, lifestyle behaviours, concomitant nutrient intake, and methodological variations such as vitamin D assay techniques [5]. Understanding these determinants is crucial for optimising supplementation strategies and identifying patient groups most likely to benefit. Therefore, the present study aims to evaluate physician-reported determinants influencing treatment response and bone health outcomes with calcium and vitamin D supplementation. The objective is to identify key clinical, nutritional, and lifestyle factors that optimize therapeutic effectiveness in routine practice.

2. Methods

2.1. Study design

This physician-based study was conducted to assess real-world clinical determinants of treatment response and bone health outcomes associated with calcium and vitamin D supplementation in India. The study evaluated physician-reported patterns related to nutrient synergy, lifestyle influences, comorbidity-driven variations in response, physiological impact on muscle strength and bone mineral density, absorption-related limitations, patient misperceptions, and methods used to assess long-term treatment effectiveness. All study procedures were conducted in accordance with the principles of Good Clinical Practice (GCP).

2.2. Study instrument

A structured surveillance form consisting of 38 questions was developed using current literature, expert clinical insights, and routine practice standards. Of these, 13 questions were analysed in this study. The questionnaire focused on key determinants of response to calcium and vitamin D supplementation, including nutrient combinations, recommended lifestyle measures, clinical predictors of treatment outcomes, frequently observed comorbidities, patient groups benefiting most from therapy, perceived impact on muscle strength, preferred calcium sources, changes in bone mineral density, factors guiding dose selection, limitations affecting absorption, common patient misperceptions, the influence of vitamin D deficiency in diabetes, and methods used to assess long-term effectiveness. Physicians provided responses based on their experience with their last 10 patients receiving calcium and vitamin D for osteoporosis or metabolic bone disorders. Only anonymised, experience-based information was collected, with no patient identifiers recorded. The study protocol received approval from the institutional ethics committee and was conducted in accordance with Good Clinical Practice (GCP) guidelines.

2.3. Data collection method

Participating physicians were informed about the study objectives and the procedure for completing the structured form. The surveillance form was provided either electronically or in person based on the physician's preference. All responses reflected routine clinical practice and the physicians' experiential assessment of patient outcomes.

2.4. Data analysis

Responses were entered into Microsoft Excel, and descriptive statistics were applied. Findings were summarised using frequencies and percentages.

3. Results

A total of 128 physicians participated in the survey. Responses related to nutrient synergy, lifestyle recommendations, and predictors of treatment response are summarized in Table 1. According to 32.03% of physicians, vitamin K2 was the most suitable nutrient to combine with calcium and vitamin D, followed by phosphorus (28.91%). Dietary modifications (42.97%) were the most frequently recommended lifestyle measure, while a considerable proportion of physicians endorsed a comprehensive approach involving diet, sunlight exposure, and exercise (37.50%). Physicians most frequently reported the presence of comorbidities (42.19%) as the key determinant factor influencing patient response to therapy, followed by adherence to supplementation (25.00%). About 37.50% of physicians observed chronic kidney disease as a common comorbidity in patients receiving calcium and vitamin D supplementation, followed by osteoarthritis (28.91%) and hypertension (20.31%) (Table 1).

Table 1 Physician responses on nutrient synergy, lifestyle recommendations, and patient-level predictors influencing calcium and vitamin D supplementation

Question	Options	Response (N=128)
Which additional nutrient is most beneficial when combined with calcium and vitamin D for optimal bone health in these 10 patients?	Vitamin K2	41 (32.03)
	Phosphorus	37 (28.91)
	No additional supplementation needed	26 (20.31)
	Magnesium	24 (18.75)
What lifestyle modification do you most frequently recommend alongside calcium and vitamin D supplementation?	Dietary modifications	55 (42.97)
	Sunlight exposure	17 (13.28)
	Weight-bearing exercise	8 (6.25)
	All of the above	48 (37.50)
Among your last 10 patients, which factor most affected their response to calcium and vitamin D supplementation?	Presence of other comorbidities	54 (42.19)
	Adherence to supplementation	32 (25.00)
	Baseline Vitamin D levels	22 (17.19)
	Type of formulation used	20 (15.63)
	Presence of other comorbidities	54 (42.19)
What is the most common comorbidity observed in patients receiving calcium and vitamin D supplementation?	Chronic kidney disease	48 (37.50)
	Osteoarthritis	37 (28.91)
	Hypertension	26 (20.31)
	Cardiovascular disease	17 (13.28)

Data given as n (%).

According to 36.72% physicians, patients with recurrent fractures benefited the most from high-dose vitamin D, followed by those with chronic kidney disease (32.03%). With respect to preferred calcium sources, most of the physicians indicated that calcium carbonate supplements were most commonly used (34.38%), followed by calcium

citrate (27.34%). Regarding the impact of supplementation on bone mineral density, physicians most frequently reported moderate improvement over time (39.06%), while around 29.69% observed significant improvement. For dosing decisions, the largest proportion of physicians opted for standard dosing for all patients (37.50%), whereas others-based dosing on dietary intake and risk factors (23.44%) (Table 2).

Table 2 Physician perspectives on high-risk subgroups, BMD response, dosing decisions, misperceptions, and long-term evaluation of calcium and vitamin D supplementation

Question	Options	Response (N=128)
Based on your last 10 patients, which patient benefits most from high-dose vitamin D?	Patients with recurrent fractures	47 (36.72)
	Patients with chronic kidney disease	41 (32.03)
	Patients with severe Vitamin D deficiency	24 (18.75)
	No significant difference	16 (12.50)
What is the most preferred source of calcium in your patients?	Calcium carbonate supplements	44 (34.38)
	Calcium citrate supplements	35 (27.34)
	Dairy products	31 (24.22)
	Fortified foods	18 (14.06)
Based on your last 10 patients, how does calcium and vitamin D supplementation influence BMD over time?	No significant effect	10 (7.81)
	Mild improvement	30 (23.44)
	Moderate improvement	50 (39.06)
	Significant improvement	38 (29.69)
How do you decide the appropriate dose of calcium and vitamin D supplementation for these 10 patients?	Standard dosing for all patients	48 (37.50)
	Based on dietary intake & risk factors	30 (23.44)
	As per clinical guidelines	26 (20.31)
	Based on serum calcium & Vitamin D levels	24 (18.75)
What is the most common misperception among patients regarding calcium and vitamin D supplementation?	It is only needed in elderly patients	42 (32.81)
	Higher doses → faster bone strengthening	38 (29.69)
	It can completely prevent osteoporosis	24 (18.75)
	It is unsafe for long-term use	24 (18.75)
How do you assess the long-term effectiveness of calcium and vitamin D supplementation in these 10 patients?	Reduction in fracture risk	52 (40.63)
	BMD tests	21 (16.41)
	Symptomatic relief	4 (3.13)
	All of the above	51 (39.84)

Data given as n (%). BMD, bone mineral density.

Physicians also highlighted common patient misconceptions, most notably the belief that supplementation is only needed in elderly individuals (32.81%), followed by the misconception that higher doses lead to faster bone strengthening (29.69%). In evaluating long-term effectiveness, physicians most frequently relied on a reduction in fracture risk (40.63%), though nearly an equal proportion reported using a combination of fracture risk, BMD testing, and symptom improvement (39.84%) (Table 2).

The majority of physicians (46.09%) reported moderate improvement in muscle strength with calcium and vitamin D supplementation in postmenopausal women and patients with diabetes, while approximately one-fourth observed significant improvement (25.78%) (Figure 1). The most commonly reported factor limiting the absorption of calcium and vitamin D was high fiber intake (42.97%), followed by the use of proton pump inhibitors (PPIs) (21.09%) and low

dietary fat intake (20.31%), while around 15.63% of physicians indicated that all factors collectively contributed to impaired absorption (Figure 2). With regard to the impact of vitamin D deficiency on bone health in diabetic patients, physicians most frequently reported that deficiency either worsened musculoskeletal pain (32.81%) or increased fracture risk in combination with pain (32.81%) (Figure 3).

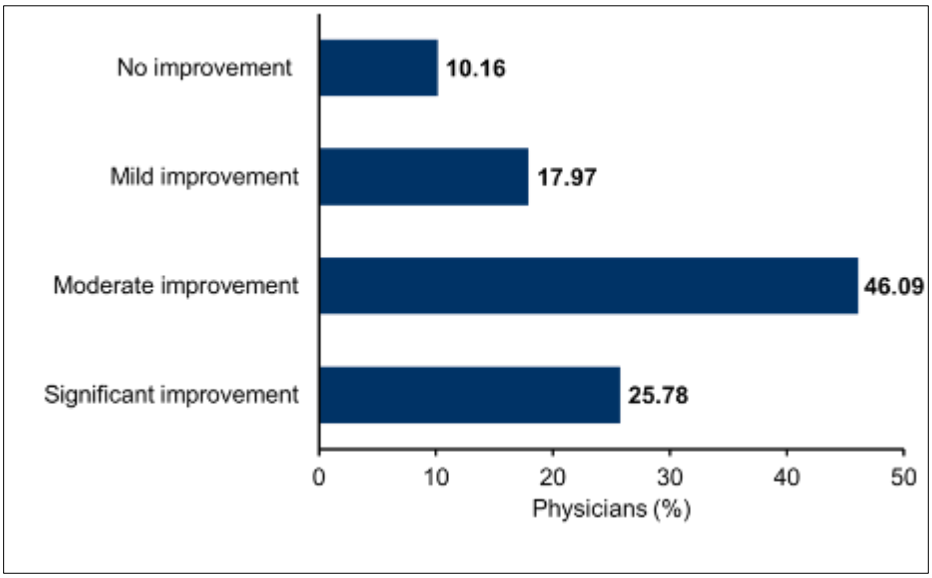

Figure 1 Impact of calcium and vitamin D supplementation on muscle strength in postmenopausal women and patients with diabetes

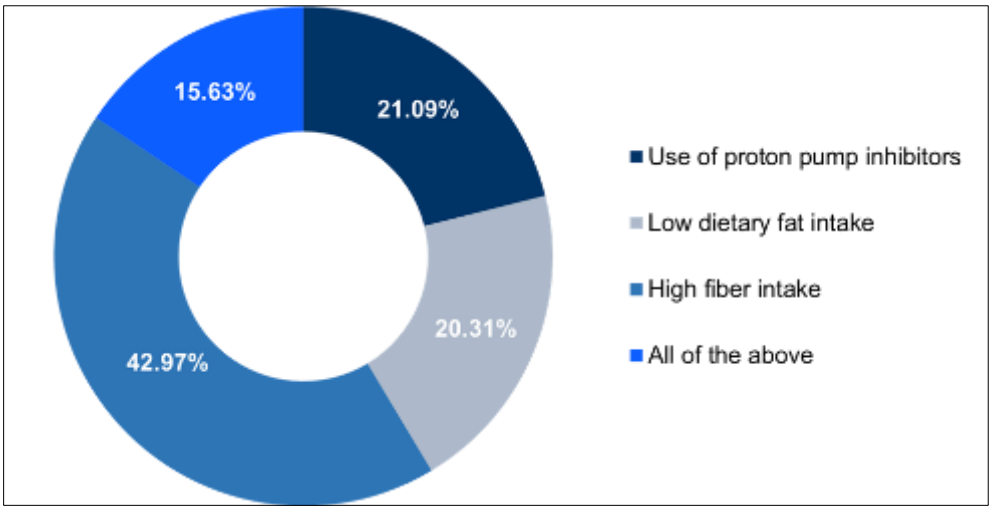

Figure 2 Key factors limiting absorption of calcium and vitamin D

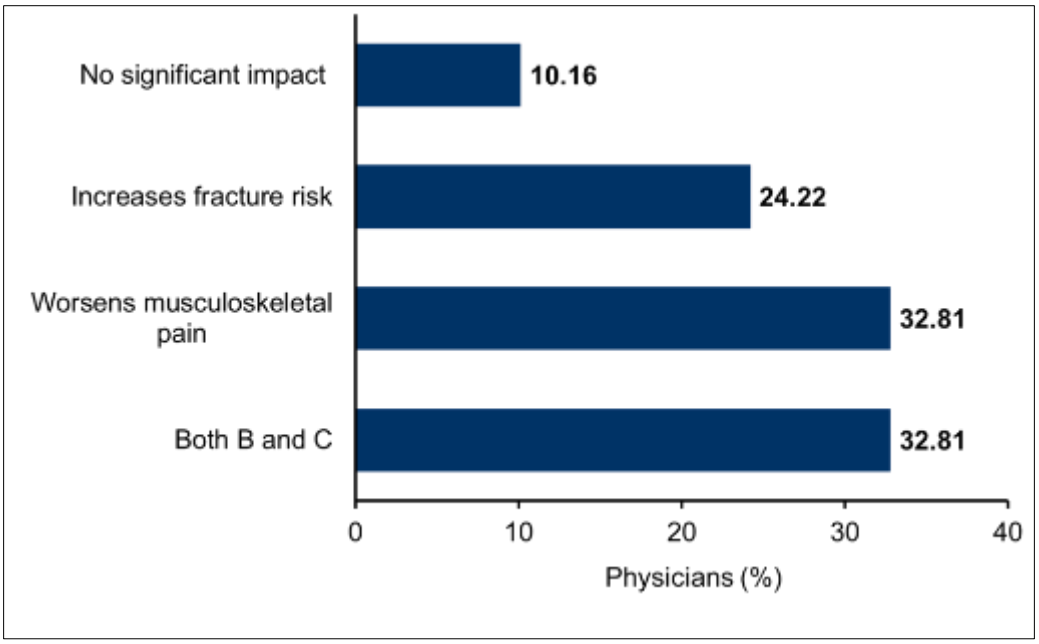

Figure 3 Impact of vitamin D deficiency on bone health in diabetic patients

4. Discussion

Effective calcium and vitamin D supplementation is influenced by multiple patient- and treatment-related factors, including nutrient synergy, lifestyle practices, comorbidities, and absorption, all of which are critical for optimizing bone health outcomes. The present study found that physicians most frequently identified vitamin K_2 as the preferred adjunct to calcium and vitamin D supplementation. This finding is consistent with existing evidence demonstrating that calcium alone offers limited fracture-preventive benefit, whereas vitamin K_2 enhances bone quality and optimises calcium utilisation, thereby improving treatment outcomes [7]. This is further supported by meta-analytic evidence, which demonstrated that combined vitamin K and vitamin D supplementation significantly increases total bone mineral density compared with either nutrient alone [8].

The current study reflects that dietary modifications were the most frequently recommended lifestyle measure alongside calcium and vitamin D supplementation, while a substantial proportion of physicians endorsed a comprehensive approach including diet, sunlight, and exercise. This aligns with evidence demonstrating that regular weight-bearing exercise combined with a balanced diet and adequate calcium and vitamin D intake synergistically enhances bone mass and reduces fracture risk, with stronger support for diet and exercise than for other lifestyle interventions [9,10]. Evidence from prior research shows that comorbidities and adherence are key determinants of response to calcium and vitamin D therapy. A study by Sanfélix-Genovés et al. reported that patients with poorer adherence often had multiple concurrent pathologies, highlighting the influence of comorbidities on treatment outcomes [11]. Furthermore, another study showed that adherence to calcium/vitamin D supplementation remained low, with only about one-third of persistent patients demonstrating adequate compliance [12]. In line with this, the present study found that physicians most frequently identified comorbidities as the primary factor influencing treatment response, followed by patient adherence to supplementation.

A study by Cortney Bosworth et al. reported that patients with moderate chronic kidney disease benefit from calcium and vitamin D_3 supplementation, with consistent treatment effects across eGFR groups despite CKD-related challenges in bone metabolism. This evidence underscores the clinical relevance of targeted supplementation in populations with impaired renal function [13]. Aligning with these findings, the present study observed chronic kidney disease as the most common comorbidity among patients receiving calcium and vitamin D, followed by osteoarthritis and hypertension. In addition, most physicians reported that patients with recurrent fractures respond particularly well to high-dose vitamin D, reflecting the established role of vitamin D in improving bone turnover and preventing further skeletal fragility.

Evidence shows that when taken with food, calcium carbonate and calcium citrate have minimal differences in absorption, as demonstrated by Heaney et al., indicating that the choice between the two should be guided more by

patient characteristics than by intrinsic pharmacokinetic superiority [14]. In line with this, the present study found that physicians most commonly preferred calcium carbonate, followed by calcium citrate. Furthermore, this preference likely reflects practical considerations such as cost, tolerability, and patient-specific factors, supported by the observation that both forms offer comparable efficacy under typical clinical conditions.

The literature suggests that combined calcium and vitamin D usually yields only modest gains in bone density. For example, a 2025 meta-analysis of trials in osteoporotic postmenopausal women found a small but statistically significant increase in pelvic BMD (standardized mean difference ≈0.20) with Ca+D supplementation [15]. This is consistent with physicians' observations of mostly "moderate" (vs. large) improvements. Likewise, clinical guidelines generally recommend fixed supplement doses- e.g., on the order of 800-1000 IU vitamin D (plus ≈1000-1200 mg calcium) daily for older adults while noting that needs may be adjusted based on diet and risk profile [16]. Thus, the predominance of standard dosing in this study aligns with prevailing guidance, even as some practitioners tailor doses to individual intake and risk factors.

Physicians in the present study reported persistent patient misconceptions, including the belief that supplementation is only required in older adults and that higher doses lead to faster bone strengthening. Evidence from Orces et al. shows that vitamin D supplementation is relevant across multiple demographic groups, not limited to the elderly [17]. Furthermore, another study warns that high-dose vitamin D may be unsafe, underscoring the need for individualized, evidence-based dosing rather than dose escalation based on patient assumptions [18]. Evidence indicates that calcium and vitamin D supplementation reduces fracture risk, as shown in classic trials reporting fewer hip and nonvertebral fractures with combined therapy [19]. Supplementation has also been associated with modest improvements in muscle function and reduced fall risk, particularly in vitamin D–deficient or high-risk individuals [20]. These findings align with the present study, where physicians commonly used fracture reduction or a combination of fracture risk, BMD changes, and symptom improvement to assess long-term effectiveness. The predominance of moderate improvements in muscle strength reported by physicians similarly reflects the modest yet clinically meaningful benefits observed in prior research.

Previous studies show that dietary fiber can reduce calcium absorption by binding minerals in the gut, while proton pump inhibitors impair calcium uptake by lowering gastric acidity [21,22]. These findings align with the present study, where physicians most frequently identified high fiber intake and PPI use as key absorption-limiting factors. Moreover, vitamin D deficiency is well documented to worsen musculoskeletal pain and increase fracture susceptibility in individuals with diabetes [23], consistent with physician observations.

Limitations

This study is limited by its modest sample size and reliance on physician-reported experiences, which may introduce recall bias and restrict the generalisability of findings. The cross-sectional design prevents assessment of causal relationships, and the absence of direct patient-level clinical or biochemical data limit's objective evaluation of treatment outcomes. Additionally, variability in physician practice patterns and regional representation may influence response patterns. Future studies incorporating larger, more diverse cohorts with longitudinal follow-up and objective clinical measures are needed to validate and extend these real-world observations.

5. Conclusion

The findings from this physician-based study highlight that treatment response to calcium and vitamin D supplementation is shaped by multiple determinants, including comorbidities, adherence, nutrient synergy, and absorption-related factors. Vitamin K_2 emerged as the most preferred adjunct, consistent with evidence supporting its role in enhancing calcium utilisation and bone quality. Physicians commonly observed moderate improvements in bone mineral density and muscle strength, with dietary habits, PPI use, and low dietary fat identified as major barriers to optimal absorption. Misconceptions regarding dosing and age-related need for supplementation remain prevalent, underscoring the importance of patient education. These insights provide a practical understanding of real-world prescribing patterns and factors influencing therapeutic outcomes, supporting more individualised and evidence-aligned supplementation strategies in routine clinical practice.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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