Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/z9drvn04

BONE & BONE MATRIX BUILDERS: KEY FRONTIERS IN OSTEOPOROSIS MANAGEMENT

Dr. Nitin Kimmatkar[1*]

[1*]Associate Professor, Orthopedics, Indira Gandhi Government Medical College, Nagpur, Maharashtra.

***Corresponding author:** Dr. Nitin Kimmatkar
*Associate Professor, Orthopedics, Indira Gandhi Government Medical College, Nagpur, Maharashtra. **Email:** kimmatkarnitin@gmail.com

Abstract
Osteoporosis remains a critical global health concern. While conventional therapies have predominantly focused on calcium and vitamin D supplementation alongside anti-resorptive agents, recent advances have emphasized the importance of enhancing not only mineral density but also the quality and functionality of the bone matrix. Particular focus is given to the utility of mineral transporters, such as calcium aspartate and calcium orotate, which exhibit superior bioavailability and enhanced cellular uptake compared to traditional calcium salts, including carbonate and citrate. These organo-mineral compounds facilitate targeted intracellular mineral delivery, stimulate osteoblastic activity, and contribute to matrix remodeling, resulting in promising outcomes that include increased bone mineral density and a reduction in fracture incidence. Emerging evidence suggests that such formulations support better absorption kinetics and minimize adverse systemic effects commonly associated with conventional supplementation. This review explored the mechanistic basis of these mineral transporters and their integration into contemporary osteoporosis management protocols. The evolving paradigm advocates for a shift towards bone health strategies that are not merely density-driven but matrix-conscious and bioavailability-optimized. Future studies should prioritize high-quality clinical trials to substantiate these promising therapeutic agents.

Keywords: Bone Remodeling, Bone Matrix, Calcium Aspartate, Calcium Orotate, Osteoporosis, Mineral Transporters

1. Introduction

Osteoporosis is a significant public health issue characterized by a systemic loss of bone mass and microarchitectural deterioration. Globally, it affects approximately 200 million individuals and contributes to over 8.9 million fractures annually, resulting in considerable morbidity and escalating healthcare costs.(1,2) The burden of osteoporosis is particularly pronounced among older populations. In the United States, prevalence rates have been reported at approximately 14% in older women and 4% in older men, with even higher figures observed when multiple skeletal sites are assessed.(3) In India, the incidence of hip fractures demonstrates wide variability, with estimates ranging from 8% to 62% in women over the age of 50 and from 8.5% to 24.6% in men, with an associated mortality rate of 15–20%.(4)

Osteoporosis results from an imbalance between bone formation and resorption, driven by estrogen deficiency, poor nutrition, a sedentary lifestyle, inflammation, and genetic or epigenetic influences.(5)

The impact of osteoporosis extends beyond statistical data, posing a serious threat to both bone health and overall quality of life. They are associated with chronic pain, reduced mobility, loss of independence, and elevated mortality risk. Furthermore, the economic burden is projected to increase sharply in parallel with population aging, particularly in resource-constrained healthcare systems.(1) Thus, practical prevention and management strategies are critical, empowering, and proactive.

Contrary to the common perception that osteoporosis is an inevitable consequence of aging, the literature underscores the importance of early preventive strategies. These include an adequate intake of bone-supporting nutrients, such as calcium and vitamin D, regular weight-bearing physical activity, and avoidance of modifiable risk factors, including smoking and excessive alcohol consumption.(6,7) Public education and targeted health programs for adolescents and adults are critical for fostering lifelong skeletal health.(8)

Current osteoporosis management strategies primarily involve supplementation and anti-resorptive agents, such as bisphosphonates. However, these methods have drawbacks, including poor long-term adherence, gastrointestinal issues, and cardiovascular risks from high-dose calcium.(9,10) Additionally, conventional calcium supplements may not sufficiently enhance the quality and functionality of the bone matrix.(11)

In recent years, there has been growing interest in mineral transporters as a novel approach to osteoporosis management. Unlike conventional calcium supplements, mineral transporters, such as calcium aspartate and calcium orotate, offer superior bioavailability, enhanced cellular uptake, and targeted delivery to bone tissue.(12) Despite their potential advantages, there is a significant paucity of research on these compounds, particularly regarding their mechanisms of action and clinical efficacy. This review aims to address the research gap by exploring the role of mineral transporters, specifically calcium aspartate and calcium orotate, in bone health and the management of osteoporosis. We will examine the mechanistic basis of these compounds, their interactions with matrix vesicle-mediated mineralization processes, and their potential advantages over conventional calcium supplements.

2. Methodology

A non-systematic literature search was conducted using multiple databases, including PubMed, Google Scholar, and Scopus, to identify relevant studies, reviews, and clinical guidelines published between 2000 and 2025. The following keywords and Boolean combinations were used: "osteoporosis," "bone matrix," "bone remodeling," "calcium supplementation," "mineral transporters," "sclerostin inhibitors," "bone mineral density," "calcium aspartate," "calcium orotate," "fracture risk," "hydroxyapatite," "matrix vesicles," and "osteoblast activation."

Articles were selected based on their relevance to the central themes of bone metabolism, mineral transporters, treatment efficacy, matrix biology, and the inclusion of clinical data or mechanistic insights. Preferences were given to peer-reviewed studies, meta-analyses, randomized controlled trials, and authoritative guidelines. Although this review did not adhere to the structured protocol of a systematic review, efforts were made to maintain rigor by cross-referencing multiple sources and ensuring consistency across findings.

Given the limited literature addressing mineral transporters in bone health, particularly calcium orotate, we supplemented our search with chemical and structural analyses to develop theoretical models despite the limited empirical evidence. This approach allowed us to propose the mechanisms of action based on the known properties of these compounds and their analogous structures.

The quality of the evidence was assessed based on study design, sample size, methodology, and potential biases. Where direct evidence is limited, we have indicated the theoretical nature of the proposed mechanisms and highlighted the need for further research. Given the narrative nature of the synthesis, no formal quality appraisal tools were applied. However, a critical judgment was used to prioritize higher evidence sources where applicable.

3. Understanding the Role of Bone and Bone Matrix in Skeletal Integrity

Bone Physiology and Remodeling

Skeletal integrity is maintained through the dynamic interplay between bone cells and the extracellular matrix (ECM). Bone functions as a structural framework and metabolically active tissue that adapts to mechanical loading. Continuous remodeling by osteoblasts and osteoclasts is central to this process. (13) Osteocytes, which are terminally differentiated osteoblasts embedded in the bone matrix, serve as mechanosensors and mediate communication between cells, and they are involved in the process of bone remodeling.(14) Periostin, secreted by mesenchymal stem cells, supports osteogenesis and matrix stability.(15) Bone adapts to mechanical loading through mechanotransduction, a process that integrates biochemical signals and cellular responses to maintain skeletal integrity.(16) Disruption of these mechanisms, particularly when resorption exceeds formation, leads to osteoporosis and compromised bone integrity.(17) The cycle comprises the activation, resorption, reversion, formation, and mineralization phases (Figure 1).

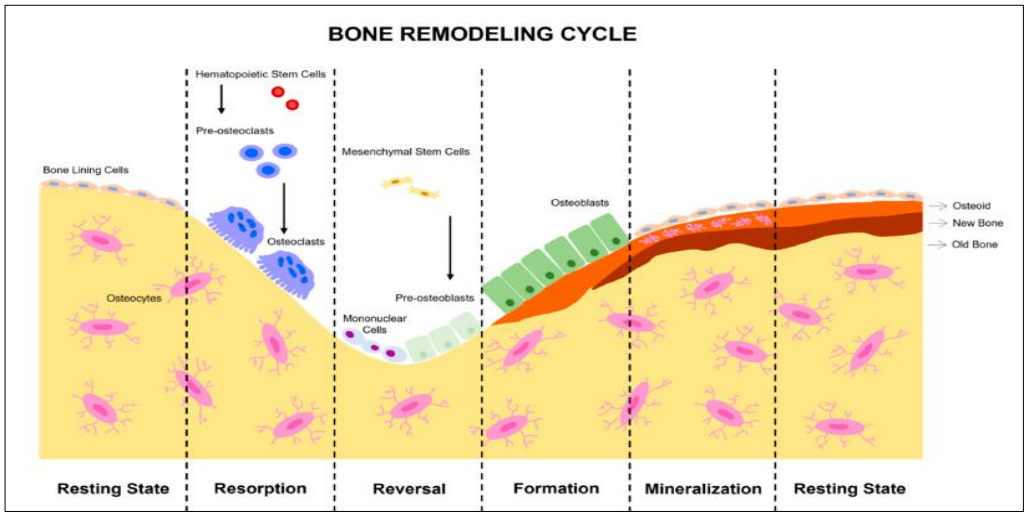


Figure 1: Remodelling process stages

Bone Matrix Composition and Function

Bone is a hierarchically structured nanocomposite consisting of a mineral (hydroxyapatite) and an organic matrix. The organic matrix comprises fibrillar proteins (primarily collagen I) and various non-fibrillar proteins. Table 1 summarizes the critical functions of the bone matrix components.

Table 1: Critical Functions of Bone Matrix Components

Component	Function	Role in Bone Health
Type I Collagen	Provides tensile strength and scaffold for mineralization	Forms 90% of organic matrix; defects lead to osteogenesis imperfecta
Proteoglycans	Regulate collagen fibrillogenesis and mineral deposition	Modulate hydration and viscoelasticity of bone
Osteocalcin	Regulates hydroxyapatite crystal growth	Biomarker of bone formation; regulates mineralization
Osteopontin	Cell attachment and signaling	Inhibits crystal growth; facilitates osteoclast attachment
Bone Sialoprotein	Initiates mineralization	Nucleates hydroxyapatite formation
Matrix Gla Protein	Inhibits inappropriate mineralization	Prevents vascular calcification; regulates matrix mineralization
Periostin	Supports collagen cross-linking	Enhances bone strength and quality
Decorin	Regulates collagen fibrillogenesis	Contributes to bone matrix organization
Biglycan	Binds TGF-β and enhances osteoblast differentiation	Modulates bone formation and remodeling
Fibronectin	Cell adhesion and migration	Facilitates osteoblast attachment to matrix

Aging-Related Changes in Bone Matrix

Age-related changes in the bone matrix result in a deterioration of its mechanical properties. Contrary to earlier beliefs, the increased brittleness observed with aging is not solely due to heightened mineralization or reduced mineral heterogeneity. Instead, it stems from alterations in collagen and the interactions between collagen and minerals. Key changes in the bone matrix due to aging and osteoporosis include a decrease in collagen content and quality, modifications in collagen cross-linking patterns, and the accumulation of advanced glycation end-products (AGEs).(18) Additionally, there is a reduction in water content at the collagen-mineral interface, shifts in the carbonate-to-phosphate ratio, and a decrease in non-collagenous proteins. The accumulation of AGEs leads to increased brittleness while reducing loosely bound water diminishes the older bone's ability to dissipate energy and resist fractures.(18) These findings underscore the necessity of focusing not only on bone mineral density but also on the quality of the bone matrix in strategies for managing osteoporosis.

4. Changing Paradigm in Osteoporosis Management

Limitations of the Mineral Density-Focused Approach

While bone mineral density (BMD) has long been the focus of osteoporosis assessment, recent evidence highlights the essential role of organic matrix components in bone strength.(19) Age-related degradation of the collagen network and accumulation of AGEs compromise bone toughness and increase fracture risk. (20) Moreover, treatments such as teriparatide have demonstrated improvements in bone matrix quality, even without significant gains in BMD, emphasizing the need for matrix-centric therapeutic strategies.(21) A holistic view of bone metabolism must consider the cellular interplay and the mineral and organic components of bone. This paradigm shift advocates comprehensive assessment strategies that combine BMD with biochemical markers of bone quality.(22) Recent studies have highlighted the limitations of relying solely on DEXA scans for assessing bone health, which can result in an underestimation of total bone quality due to diminished bone mineralization or structural irregularities.(23) To overcome these challenges, emerging diagnostic tools such as biomarker-based monitoring and advanced imaging techniques—like high-resolution peripheral quantitative computed tomography and magnetic resonance imaging—enhance the evaluation of bone microarchitecture and treatment precision.(24)

This evolving understanding of bone biology necessitates re-evaluating current approaches with increased attention to therapies that enhance mineral density and matrix quality, particularly in vulnerable populations, which should be integral to any comprehensive osteoporosis management plan.(25)

Limitations of Conventional Calcium Supplementation

The hydroxyapatite-centered approach has addressed calcium and vitamin D deficiencies in osteoporosis, highlighting the role of hydroxyapatite as a crucial contributor to BMD. However, emerging evidence suggests that general calcium supplementation may not be effective in preventing or slowing the progression of osteoporosis. Some studies suggest that calcium supplementation, particularly in forms such as calcium citrate, can increase serum calcium levels above physiological needs, potentially leading to adverse effects. (26) Literature reports a rise in BMD from calcium carbonate is 1% in 6 months. (27) Moreover, a growing body of literature has challenged the protective effects of calcium supplementation against fractures.

Furthermore, double-blind, placebo-controlled trials involving older adults have shown that calcium supplements do not significantly reduce the incidence of fractures.(26) In a five-year, double-blind, placebo-controlled study of 1,460 women aged over 70, the findings revealed that supplementation with calcium carbonate tablets at 1,200 mg/day is ineffective as a public health intervention in preventing clinical fractures due to poor long-term compliance. Still, it is effective in those patients who are compliant.(28) Similar findings were reported in a systematic review, which demonstrated that calcium supplementation does not significantly reduce the risk of hip fractures.(29) Calcium

salts are relatively water-insoluble; gastric acid secretion plays a vital role in their absorption, as a lower pH enhances their solubility and hence reduces their precipitation. (30)
Concerns have also been raised regarding poor bioavailability, gastrointestinal side effects, drug and food interactions, insolubility in the small intestine, and cardiovascular risks associated with long-term calcium supplementation. (30). A randomized, placebo-controlled trial conducted in a population of 1,471 postmenopausal, healthy women, with a 5-year follow-up, revealed that 1,000 mg/day elemental calcium supplements increased the incidence of cardiovascular events and the risk of hospitalization in the presence of other comorbidities.(31) Calcium supplementation may increase the incidence of constipation, severe diarrhea, and abdominal pain.(32) Defining the optimal dosages for calcium supplementation remains uncertain, especially considering the potential adverse health impacts in vulnerable populations, such as those with pre-existing cardiovascular issues.(33) The focus on enhancing hydroxyapatite density through calcium supplementation overlooks the complexities of the bone remodeling processes and the structural integrity of the bone matrix, which are essential for maintaining bone strength and fracture resistance.(34)

5. Mineral Transporters: A New Approach to Osteoporosis Management

Concept of Mineral Transporters

Optimizing therapeutic response in osteoporosis requires replenishing calcium and vitamin D to strengthen hydroxyapatite and address matrix degradation. This includes stimulating osteoblasts to enhance collagen synthesis, restore the triple-helix structure, reduce carbonate-phosphate exchange, and minimize AGE formation. (18) Improving the synthesis of proteoglycans and glycosaminoglycans to support matrix integrity. Innovative approaches now focus on mineral transporter formulations to enhance calcium bioavailability and cellular uptake. These transporters enhance mineral delivery at the cellular level by overcoming the membrane permeability challenges inherent to positively charged ions and their limited solubility across a wide range of pH levels, from 4 to 11.(35) The administration emphasizes restoring nutrient balance at the cellular level and supports the integration of calcium aspartate and calcium orotate as next-generation supplements.(35) Current research highlights the potential of specialized mineral transporter formulations, such as calcium aspartate and calcium orotate, showing promise compared to traditional calcium sources.(36)
A mineral transport substance releases an ion at a particular cell site, which involves complex biochemical systems within all body cells. Positively charged mineral ions, such as calcium, magnesium, and potassium, may have considerable difficulty passing through the positively charged surfaces of membranes.(37) There are three types of mineral transport mechanisms: passive diffusion, which permits fat-soluble substances without a transport carrier; Facilitated diffusion, which requires a special transport to serve as a carrier of water-soluble substances; and active transport, which requires the input of adenosine triphosphate. Current research highlights the potential of specialized mineral transporter formulations, such as calcium aspartate and calcium orotate, which show promise compared to traditional calcium sources.

Matrix Vesicle-Mediated Mineralization

Bone mineralization involves two phases: primary and secondary mineralization. Matrix vesicles MVs are specialized extracellular vesicles (30-300 nm in diameter) that are initial sites for mineral nucleation in the bone and cartilage.(38) Primary mineralization begins with the secretion of matrix vesicles (MV) by osteoblasts and chondrocytes, which are equipped with specialized enzymes and transporters, such as tissue-nonspecific alkaline phosphatase, nucleotide pyrophosphatase /phosphodiesterase 1, and PHOSPHO1, that play pivotal roles in regulating phosphate metabolism. The membrane of the MVs contains annexins that create calcium channels, facilitating calcium entry into the vesicles. Within the inner leaflet of the MV membrane, phosphatidylserine acts as a nucleation site for the formation of calcium phosphate crystals. (37) As the levels rise within the MVs, they form amorphous calcium phosphate, eventually transforming into hydroxyapatite crystals.(39) These crystals grow until they breach the MV membrane, extending into the surrounding extracellular matrix. They then serve as templates for further mineralization, especially along collagen fibrils.

Recent research has identified the specific enzymes and transporters involved, like phospholipase A2 (PLA2) and ectonucleotide pyrophosphatase/phosphodiesterase 6, which generate the phosphate required for mineralization within MVs.(40) Understanding the complex interplay between these enzymes and transporters in MV-mediated mineralization provides a foundation for developing targeted therapies that enhance bone mineralization in osteoporosis.

Types of Mineral Transporters for Bone Health

Active mineral transporters have emerged as key components in the management of osteoporosis, particularly considering their role in transporting essential minerals into osteogenic cells while mitigating the risks of elevated serum calcium levels and associated cardiovascular complications. Among these transporters, 2-aminoethylphosphonic acid (AEP), aspartic acid, and Orotic acid have attracted attention due to their unique mechanisms of action.

1. AEP (2-aminoethylphosphoric acid) is a constituent of cell membranes and a mineral complexing agent. It allows its uptake through the outer membrane, where it decomposes to release ions within the cell.(39)
2. Aspartic acid, particularly its L-form, forms complexes with minerals that facilitate their traversal through the cell membrane, ultimately releasing them in an ionic form upon metabolization.(39)
3. Orotic acid forms a highly complex salt with any mineral and has no affinity for the outer cell membrane but penetrates the outer cell membrane even in the form of a complex salt. It is metabolized only at the membrane sites of the mitochondria and structures found in the cell plasma. Only here will the mineral be released in the form of ions.(35)

The emerging interest in calcium orotate, an organo-mineral compound, stems from its potential to support bone remodeling and anti-inflammatory properties, although more robust clinical evidence is required.(41) The targeted delivery mechanisms of these active mineral transporters align with the objectives of osteoporosis management by enhancing mineral bioavailability to osteoblasts and minimizing systemic absorption, thereby reducing potential complications.(41) Overall, integrating calcium aspartate, orotate, and calcitriol within treatment protocols for osteoporosis reflects a well-established understanding of their roles in improving bone density and minimizing fracture risk. Calcium Orotate and Calcium aspartate have proven to be valuable compounds in traumatic and inflammatory conditions where bone cells are damaged.(42) This approach aligns with guidelines that recommend dietary supplementation for individuals at high risk of osteoporosis, particularly those over 50 years old. (43)

Clinical Evidence Supporting Calcium Aspartate as a Mineral Transporter

Calcium aspartate is recognized for its organic nature and superior bioavailability, with evidence supporting its ability to stimulate osteoblastic activity and significantly increase BMD in postmenopausal women.(10) As a chelated form of calcium, calcium aspartate offers several theoretical advantages over conventional calcium salts in maintaining bone health and calcium absorption. Firstly, as an amino acid, it enhances calcium transport across intestinal membranes, leading to improved cellular uptake and facilitating the effective transport of calcium. Additionally, its organic nature reduces gastrointestinal side effects, such as constipation and other digestive complaints. (Figure 2) Furthermore, emerging evidence suggests it may directly stimulate osteoblast function, promoting bone formation and overall bone health.(44) The absorption of calcium aspartate is not affected by food, allowing it to effectively reach the inner layer of the outer cell membrane of osteoblasts, with an absorption rate of 92.06%. Once inside, it is metabolized to release calcium ions. This process increases bone density by stimulating osteoblast activity, ensuring the conversion of calcium into bone mass, and promoting collagen production. (42)

Calcium aspartate is effective for the recalcification of bone tissue in osteoporosis. A study conducted by Indian clinicians in 2022 highlighted the greater acceptance of chelated calcium as a preferred option owing to its superior absorbability, better bioavailability, organic nature, and ability to stimulate osteoblastic activity. This makes it a more effective choice for managing osteoporosis than conventional calcium forms such as calcium carbonate and calcium citrate.(45) Additionally, a study

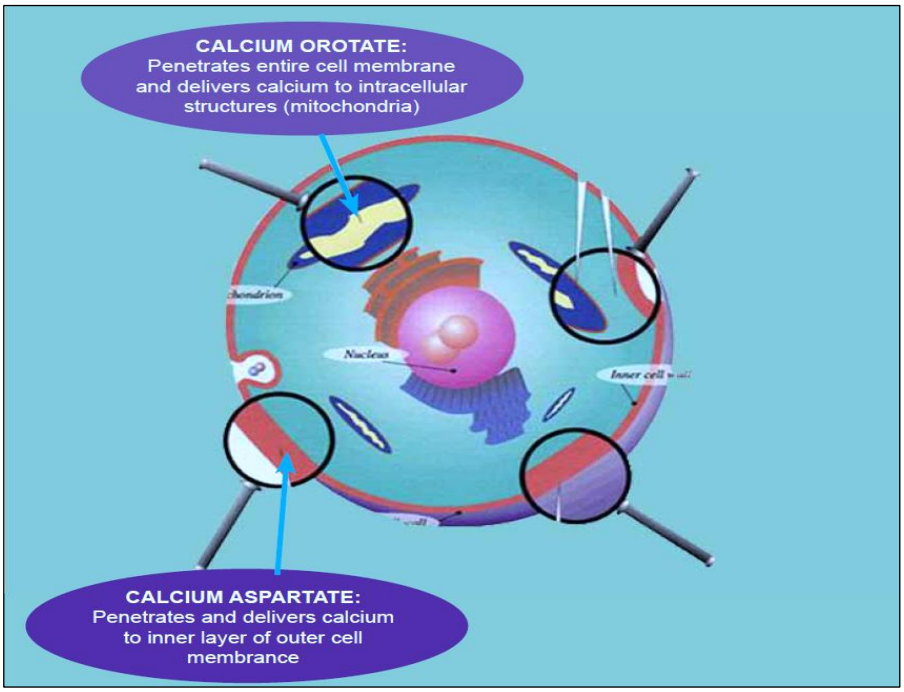
by Tang et al. involving 1,306 individuals with an initial T-score of -1.5 or lower investigated the effects of anhydrous calcium aspartate compared to a placebo, calcium citrate, vitamin D, or two placebos. The findings indicated that within 3–12 months, the administration of anhydrous calcium aspartate led to a significant increase in BMD (Table 2).(46) Previous research has shown the superior efficacy of calcium aspartate in improving bone mineral density across multiple skeletal sites compared to calcium citrate and a placebo. The consistent increase in BMD over the 12 months provided compelling evidence for the use of calcium aspartate in osteoporosis management. Despite these promising findings, further research is needed to fully elucidate how calcium aspartate enhances bone health and its long-term efficacy in preventing fractures.(46)

Table 2: Improvement in Bone Mineral Density (G/cm²) with Different Calcium Formulations

Parameter	Drug	Base Line	3 months	12 months
Left Femoral Neck	Calcium Aspartate	0.631±0.12	0.647±0.14	0.653±0.16
	Calcium Citrate	0.628±0.14	0.633±0.12	0.630±0.17
	Placebo	0.637±0.15	0.640±0.12	0.634±0.15
Lumbar Spine (L1-L4)	Calcium Aspartate	0.778±0.16	0.811±0.19	0.822±0.18
	Calcium Citrate	0.785±0.15	0.790±0.16	0.781±0.13
	Placebo	0.797±0.17	0.795±0.14	0.791±0.17
Total Hip	Calcium Aspartate	0.682±0.17	0.705±0.17	0.710±0.20
	Calcium Citrate	0.637±0.15	0.689±0.17	0.688±0.21
	Placebo	0.685±0.16	0.680±0.13	0.677±0.16

Clinical Evidence Supporting Calcium Orotate as a Mineral Transporter

Calcium orotate has shown positive effects on bone recalcification and anti-inflammatory properties, positioning it as a favorable option for individuals with compromised bone health. (41,45) Orotic acid, a pyrimidine carboxylic acid, forms a chelate with calcium, presenting several unique advantages, including enhanced mineral delivery, efficient calcium transport, and reduced inflammatory bone resorption, with an absorption rate of up to 90%. Furthermore, it also enhances osteoblast function and promotes bone matrix formation. Electron microscopic findings revealed its direct delivery of calcium to the interior of the cell, where it is readily utilized across the membrane. (Figure 2)



(Adapted from: Medical Progress January 2011)

Figure 2: Role of calcium orotate and calcium Aspartate

The long-term clinical tolerance of calcium orotate is superior to that of other therapeutic calcium substances. Calcium orotate use has demonstrated significant improvement in various diseases associated with decalcification and bone injury.(47) This concept is crucial in bone formation as cell membranes control the process, and the microgranules of hydroxyapatite must be formed within the osteoblast and then released through the cell membrane.(48)

In a double-blind, placebo-controlled randomized study conducted on 80 postmenopausal women with a T-score < -2.5 at ESIC Hospital, Warangal, for 2 months, treatment with calcium orotate resulted in a more than two-fold increase in serum calcium levels in women with postmenopausal osteoporosis compared to treatment with calcium carbonate + vitamin D3, which was highly significant.(48) The assessment parameters in the Oswestry Disability Index showed a highly significant increase in the activity and symptomatic relief of osteoporotic patients. (Table 3) The calcium orotate group reported almost twice the improvement in assessment with no adverse effect parameters. Therefore, it is prudent to conclude that supplementation with mineral transporters, such as calcium orotate and calcium aspartate, should be considered the preferred choice in the management of osteoporosis due to its more significant improvement in calcium status and bone mineral density and better tolerability. It suggests a potential shift towards using chelated and organo-mineral compounds as effective therapeutic agents in osteoporosis management.(46) However, these findings require further validation in larger, well-designed clinical trials. Much of the proposed mechanism of action is theoretical and based on chemical structure analysis rather than robust empirical evidence. This represents a significant research gap that should be addressed in future studies.

Table 3: Comparison of Calcium Orotate vs. Calcium Carbonate + Vitamin D3 in Postmenopausal Osteoporosis

Drug	Parameter	Baseline	After treatment	Change	% Change	95% CI	P Value
C	Disability Index	68.06 ± 16.06	58.41±14.61	9.65 ± 7.90	14.2	62.92-73.19, 53.74-63.08	<0.0001
O		69.85 ± 17.89	43.69 ± 12.85	26.17 ± 15.67	37.5	64.13-75.58, 39.58-47.79	<0.0001
C	Neck Disability Index	76.62 ± 21.89	65.38 ± 14.88	11.24 ± 10.54	14.7	69.61-83.62, 60.62-70.14	<0.0001
O		67.97 ± 21.11	46.06 ± 14.84	26.17 ± 15.67	38.5	61.22-74.72, 41.32-50.81	<0.0001
C	Functional Strength of Cervical Spine	8.05 ± 2.38	5.58 ± 2.01	2.48 ± 1.55	30.8	7.29-8.81, 4.91-6.25	<0.0001
O		8.30 ± 2.67	3.92 ± 1.36	4.38 ± 1.72	52.8	7.45-9.15, 3.27-4.58	<0.0001

C: Calcium carbonate + Vitamin D3, O: Calcium orotate

Calcium Aspartate and Calcium Orotate interaction with drugs

Patients on long-term proton pump inhibitor (PPI) therapy have been reported to have higher risks for osteoporotic fractures. Emerging evidence suggests that PPIs lead to deficiencies in essential nutrients, including calcium, due to their effects on gastric acid secretion. Conventional calcium supplements, such as calcium carbonate, have been reported to have limited bioavailability when used in conjunction with PPIs. This is primarily attributed to the hypochlorhydria induced, which can reduce the solubility of calcium supplements and hinder their absorption in the gastrointestinal tract. Calcium aspartate and calcium orotate, however, may offer a more favorable profile in this regard, as they are considered more bioavailable and soluble over a wider pH range compared to traditional calcium salts, suggesting a reduced likelihood of interaction with the acid-reducing effects of PPIs. Therefore, integrating calcium aspartate and/or orotate into therapeutic regimens may mitigate some of these risks. (49,50)

Safety Profile Comparison

One of the significant advantages of mineral transporters is their favorable safety profile compared to conventional calcium supplements. Although calcium carbonate and citrate have been associated with gastrointestinal side effects, cardiovascular concerns, and kidney stone formation, studies on calcium aspartate and orotate have reported minimal adverse events due to the absence of ionization during gastrointestinal transit, as well as a lack of food interaction with these mineral transporters preventing formation of magma precipitation.(51)

In a double-blind, placebo-controlled study at the ESIC hospital, no adverse or serious events were reported with calcium orotate, establishing its comparable safety and tolerability to calcium carbonate.(46) This favorable safety profile and enhanced efficacy position mineral transporters as the preferred option for long-term osteoporosis management.

6. Future Directions and Challenges

Future research in osteoporosis prevention should focus on enhancing the bioavailability of calcium and vitamin D through the use of advanced mineral transporter formulations. Personalized supplementation strategies, tailored to individual genetic and metabolic profiles, could improve efficacy by adapting to specific risk factors, such as age and hormonal status. Clinical trials are necessary to evaluate the long-term safety and efficacy of mineral transporters, such as calcium aspartate and calcium orotate, which have shown promise in enhancing bone mineral density with fewer side effects.

Exploring different vitamin D metabolites, such as calcitriol, may reveal ways to enhance calcium transport. Additionally, the synergy between vitamin D and mineral transporters should be examined to optimize bone health. Innovative delivery systems, such as nanocarriers, can enhance calcium uptake by osteoblasts and mitigate the risks associated with excessive serum calcium levels. Additionally, the gut microbiome's influence on calcium absorption warrants further investigation, particularly regarding the effects of probiotics and dietary interventions. Long-term safety concerns, particularly cardiovascular risks associated with calcium supplementation, must be addressed, including the establishment of safe intake levels. Combining mineral transporters with anabolic treatments could enhance bone regeneration. By focusing on these areas, osteoporosis prevention can become safer and more effective, potentially transforming bone health management and reducing the risk of fractures.

7. Conclusion

Osteoporosis management is evolving beyond conventional calcium and vitamin D supplementation toward a more comprehensive approach prioritizing BMD and bone matrix integrity. Emerging evidence highlights the superior bioavailability and cellular uptake of mineral transporters such as calcium aspartate and calcium orotate compared to traditional calcium salts, offering enhanced therapeutic efficacy and osteoblastic activation. Calcium aspartate and calcium orotate have high bioavailability, site specificity, good tolerability, no risk of kidney stones, and no food interactions and, therefore, better compliance. These organo-mineral compounds represent a promising frontier in osteoporosis care, aligning with treat-to-target strategies and personalized interventions. By integrating advanced mineral formulations with matrix-focused therapies, lifestyle modifications, and multidisciplinary care models, this evolving paradigm holds the potential to improve clinical outcomes and reduce fracture risk more effectively. Future research should further validate these approaches through robust clinical trials to optimize their implementation in routine practice.

Disclosure Statement: The author reported no potential conflict of interest.

Funding: This research initiative was supported by Overseas Health Care Pvt Ltd.

Acknowledgement: The author would like to acknowledge Mr. Dileep Kumar for his assistance in collating research materials and providing editorial support during the preparation of this manuscript.

8. References

1. Laskou F, Patel HP, Cooper C, Dennison E. A pas de deux of osteoporosis and sarcopenia: osteosarcopenia. Climacteric. 2022 Feb;25(1):88–95.
2. Qi G, Jiang Z, Lu W, Li D, Chen W, Yang X, et al. Berbamine inhibits RANKL- and M-CSF-mediated osteoclastogenesis and alleviates ovariectomy-induced bone loss. Front Pharmacol. 2022;13:1032866.
3. Looker AC, Melton LJ, Borrud LG, Shepherd JA. Lumbar spine bone mineral density in US adults: demographic patterns and relationship with femur neck skeletal status. Osteoporos Int. 2012 Apr;23(4):1351–60.
4. Rinonapoli G, Ruggiero C, Meccariello L, Bisaccia M, Ceccarini P, Caraffa A. Osteoporosis in Men: A Review of an Underestimated Bone Condition. Int J Mol Sci. 2021 Feb 20;22(4):2105.
5. Cha Y, Seo SH, Kim JT, Kim JW, Lee SY, Yoo JI. Osteoporosis Feature Selection and Risk Prediction Model by Machine Learning Using a Cross-Sectional Database. J Bone Metab. 2023 Aug;30(3):263–73.
6. Sheng B, Li X, Nussler AK, Zhu S. The relationship between healthy lifestyles and bone health: A narrative review. Medicine (Baltimore). 2021 Feb 26;100(8):e24684.
7. Albrecht BM, Stalling I, Foettinger L, Recke C, Bammann K. Adherence to Lifestyle Recommendations for Bone Health in Older Adults with and without Osteoporosis: Cross-Sectional Results of the OUTDOOR ACTIVE Study. Nutrients. 2022 Jun 14;14(12):2463.
8. Chan CY, Mohamed N, Ima-Nirwana S, Chin KY. A Review of Knowledge, Belief and Practice Regarding Osteoporosis among Adolescents and Young Adults. Int J Environ Res Public Health. 2018 Aug 12;15(8):1727.
9. Reid CE. Invited Perspective: What Do We Know about Fetal–Maternal Health and Health Care Needs after Wildfires? Not Nearly Enough. Environ Health Perspect [Internet]. 2022;130(8). Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2017901526&from=export
10. Karpouzos A, Diamantis E, Farmaki P, Savvanis S, Troupis T. Nutritional Aspects of Bone Health and Fracture Healing. J Osteoporos. 2017;2017:4218472.
11. Szulc P, Boutroy S, Chapurlat R. Prediction of Fractures in Men Using Bone Microarchitectural Parameters Assessed by High-Resolution Peripheral Quantitative Computed Tomography-The Prospective STRAMBO Study. J Bone Miner Res. 2018 Aug;33(8):1470–9.
12. Weaver CM, Bischoff-Ferrari HA, Shanahan CJ. Cost-benefit analysis of calcium and vitamin D supplements. Arch Osteoporos. 2019 Apr 30;14(1):50.
13. Adejuyigbe B, Kallini J, Chiou D, Kallini JR. Osteoporosis: Molecular Pathology, Diagnostics, and Therapeutics. Int J Mol Sci. 2023 Sep 26;24(19):14583.
14. Zhang C, Bakker AD, Klein-Nulend J, Bravenboer N. Studies on Osteocytes in Their 3D Native Matrix Versus 2D In Vitro Models. Curr Osteoporos Rep. 2019 Aug;17(4):207–16.
15. Bonnet N, Garnero P, Ferrari S. Periostin action in bone. Mol Cell Endocrinol. 2016 Sep 5;432:75–82.
16. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos. 2013;8(1):136.
17. Liu C, Cyphert EL, Stephen SJ, Wang B, Morales AL, Nixon JC, et al. Microbiome-induced increases and decreases in bone matrix strength can be initiated after skeletal maturity. J Bone Miner Res. 2024 Oct 29;39(11):1621–32.
18. Burr DB. Changes in bone matrix properties with aging. Bone. 2019 Mar;120:85–93.
19. Paschalis E, Krege J, Gamsjaeger S, Eriksen E, Burr D, Disch D, et al. Teriparatide Treatment Increases Mineral Content and Volume in Cortical and Trabecular Bone of Iliac Crest: A Comparison of Infrared Imaging With X-Ray–Based Bone Assessment Techniques. Journal of Bone and Mineral Research [Internet]. 2018 [cited 2025 Mar 21]; Available from:

https://www.semanticscholar.org/paper/Teriparatide-Treatment-Increases-Mineral-Content-in-Paschalis-Krege/138b245f5dd49aba15b38e4f10b53d499dc4f9a3
20. Kegelman CD, Coulombe JC, Jordan KM, Horan DJ, Qin L, Robling AG, et al. YAP and TAZ Mediate Osteocyte Perilacunar/Canalicular Remodeling. J Bone Miner Res. 2020 Jan;35(1):196–210.
21. Henriksen. Degradation of the Organic Phase of Bone by Osteoclasts: A Secondary Role for Lysosomal Acidification. Journal of Bone and Mineral Research. 2006;
22. Seabra O, Pereira VG, Espindula AP, Cardoso FAG, Volpon JB, Pereira SAL, et al. Even without changing the bone mineral density, alcohol consumption decreases the percentage of collagen, the thickness of bone trabeculae, and increases bone fragility. An Acad Bras Ciênc. 2022;94(suppl 3):e20210661.
23. Kim JM, Lin C, Stavre Z, Greenblatt MB, Shim JH. Osteoblast-Osteoclast Communication and Bone Homeostasis. Cells. 2020 Sep 10;9(9):2073.
24. Blake GM, Fogelman I. The role of DXA bone density scans in the diagnosis and treatment of osteoporosis. Postgrad Med J. 2007 Aug;83(982):509–17.
25. Wang L, Xu X, Zhang Y, Hao H, Chen L, Su T, et al. A model of health education and management for osteoporosis prevention. Exp Ther Med. 2016 Dec;12(6):3797–805.
26. US Preventive Services Task Force, Grossman DC, Curry SJ, Owens DK, Barry MJ, Caughey AB, et al. Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2018 Apr 17;319(15):1592–9.
27. Tai V, Leung W, Grey A, Reid IR, Bolland MJ. Calcium intake and bone mineral density: systematic review and meta-analysis. BMJ. 2015 Sep 29;351:h4183.
28. Prince RL, Devine A, Dhaliwal SS, Dick IM. Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. Arch Intern Med. 2006 Apr 24;166(8):869–75.
29. Fan T, Nocea G, Modi A, Stokes L, Sen SS. Calcium and vitamin D intake by postmenopausal women with osteoporosis in Spain: an observational calcium and vitamin D intake (CaVIT) study. Clin Interv Aging. 2013 Jan 1;8:689–96.
30. Kamath SU. Mineral transporters: A new dimension for bone health. Med Prog 2011 Jan;1(1):10-15.
31. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ. 2011 Apr 19;342:d2040.
32. Li K, Wang XF, Li DY, Chen YC, Zhao LJ, Liu XG, et al. The good, the bad, and the ugly of calcium supplementation: a review of calcium intake on human health. Clin Interv Aging. 2018;13:2443–52.
33. Yao P, Bennett D, Mafham M, Lin X, Chen Z, Armitage J, et al. Vitamin D and Calcium for the Prevention of Fracture: A Systematic Review and Meta-analysis. JAMA Netw Open. 2019 Dec 2;2(12):e1917789.
34. Lyu H, Zhao SS, Yoshida K, Tedeschi SK, Xu C, Nigwekar SU, et al. Delayed Denosumab Injections and Bone Mineral Density Response: An Electronic Health Record-based Study. J Clin Endocrinol Metab. 2020 May 1;105(5):1435–44.
35. Vranken L, Wyers CE, Van der Velde RY, Janzing HM, Kaarsemaker S, Geusens PP, et al. Comorbidities and medication use in patients with a recent clinical fracture at the Fracture Liaison Service. Osteoporos Int. 2018 Feb;29(2):397–407.
36. Tang Y, Peng B, Liu J, Liu Z, Xia Y, Geng B. Systemic immune-inflammation index and bone mineral density in postmenopausal women: A cross-sectional study of the national health and nutrition examination survey (NHANES) 2007-2018. Front Immunol. 2022;13:975400.
37. Gillette JM, Nielsen-Preiss SM. The role of annexin 2 in osteoblastic mineralization. J Cell Sci. 2004 Jan 26;117(Pt 3):441–9.

38. Bottini M, Mebarek S, Anderson KL, Strzelecka-Kiliszek A, Bozycki L, Simão AMS, et al. Matrix vesicles from chondrocytes and osteoblasts: Their biogenesis, properties, functions and biomimetic models. Biochim Biophys Acta Gen Subj. 2018 Mar;1862(3):532–46.
39. Zhao Y, Ren Y, Han J, Li K, Deng J, Zhu X, et al. T. The effect of aspartic acid surface-modified mg-zn-zr alloy on adhesion, proliferation, and osteogenic differentiation of human bone mesenchymal stem cells. Int J Mol Sci 2021;22(5):2535.
40. Wu LNY, Genge BR, Kang MW, Arsenault AL, Wuthier RE. Changes in Phospholipid Extractability and Composition Accompany Mineralization of Chicken Growth Plate Cartilage Matrix Vesicles. Journal of Biological Chemistry. 2002 Feb;277(7):5126–33.
41. The Anti-Inflammatory and Immune-Inhibiting Effects of Calcium Orotate on Bradythrophic Tissues-CM14.pdf - Mineral Transporters Packet [Internet]. [cited 2025 Mar 21]. Available from: https://brewersciencelibrary.com/proddetail.php?prod=The Anti-Inflammatory and Immune-Inhibiting Effects of Calcium Orotate on Bradythrophic Tissues-CM14.pdf
42. Muhammad MV, Singh R, Malhotra R. Mineral transporters- The novel approach in management of bone health and osteoporosis. Orthopedics today 2010 Jan-Mar;12(1)1-6.
43. Mohr W, Görz E, Hilbert P, Gerlach U. The influence of calcium-orotate on experimental artificial calcification. arzneimittel-forschung/drug research 1975;25(7):1135-1140.
44. Beck-Cormier S, Lelliott CJ, Logan JG, Lafont DT, Merametdjian L, Leitch VD, et al. Slc20a2, Encoding the Phosphate Transporter PiT2, Is an Important Genetic Determinant of Bone Quality and Strength. Journal of Bone and Mineral Research. 2019 Jun 1;34(6):1101–14.
45. Shantaram M, Manjula K. Expert opinion on the clinical use of calcium and vitamin d supplements in osteoporosis in indian settings. Int J Res Orthop 2024;10(2):364-8.
46. Manjula S, Krishna K. Expert opinions on the prevalence, diagnosis, and treatment choice for osteoarthritis management in Indian settings. IP International Journal of Orthopaedic Rheumatology. 2024 Feb 13;9(2):74–8.
47. Makowiec-Dabrowska T, Radwan-Wlodarczyk Z, Koszada-Wlodarczyk W, Siedlecka J, Wilczynski J. [The influence of chemical and physical factors in the work environment on the amount of risk for abnormal pregnancy outcome]. Med Pr. 1997;48(3):239–59.
48. International Conference on Medical, Biological and Pharmaceutical Sciences (ICMBPS) [Internet]. [cited 2025 Mar 21]. Available from: https://waset.org/medical-biological-and-pharmaceutical-sciences-conference
49. Hansen KE, Jones AN, Lindstrom MJ, Davis LA, Ziegler TE, Penniston KL, et al. Do proton pump inhibitors decrease calcium absorption? J Bone Miner Res. 2010 Dec;25(12):2786–95.
50. Fitzpatrick D, Lannon R, Laird E, Ward M, Hoey L, Hughes CF, et al. The association between proton pump inhibitors and hyperparathyroidism: a potential mechanism for increased fracture-results of a large observational cohort study. Osteoporos Int. 2023 Nov;34(11):1917–26.
51. Kalra S. pH solubility and mineral transporters. Orthopedics Med Prog 2010 Jul;1(7):238-242.