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Calcium, Vitamin D, and Prebiotic Components: Evidence on Bone Mineralization and Bone Mineral Density

Nour-Eddine Ziraoui, Hafiz Rahman, Nurul Hidayah
World Food Supplement Association

Abstract: Background: Bone mineral density (BMD) reflects the long-term balance between mineral intake, bone turnover, age, hormonal status, vitamin D status, and habitual nutrient intake. The NVTIA® formulation examined in this article contains calcium citrate malate, calcium L-lactate, casein phosphopeptide (CPP), inulin, resistant dextrin, and microencapsulated vitamin D3. Objective: To assess whether the rationale for this formulation is consistent with human evidence on calcium supplementation, bone mineralization, and BMD. Methods: The formulation composition and technical characteristics were considered together with a focused review of human clinical evidence available through 14 August 2026. Randomized trials of calcium salts, calcium with vitamin D, and prebiotic-assisted calcium interventions were considered, together with meta-analytic evidence on bone loss. Results: The clinical response to calcium supplementation was not uniform. Greater effects were generally reported in older adults, women with vitamin D deficiency, women later after menopause, and individuals with lower calcium intake. Controlled studies support calcium citrate and CCM as calcium sources with effects on BMD or bone loss in selected populations. Calcium combined with vitamin D also improved BMD at several skeletal sites in some older populations. In adolescents, inulin-type fructans increased calcium absorption and whole-body mineral accrual. In contrast, the 2026 RENEW trial did not show an additional BMD benefit from adding inulin to a calcium-rich permeate regimen in vitamin-D-supplemented postmenopausal women. A meta-analysis in adults aged 50 years and older found modest preservation of hip and spine BMD with calcium, with or without vitamin D. Conclusion: The available evidence provides a reasonable basis for evaluating the formulation as a bone-health intervention, but the expected response is likely to depend on age, baseline calcium and vitamin D status, and adherence. A clinical study of the finished tablet should therefore define elemental-calcium intake and vitamin D exposure and include standardized measures such as serum 25(OH)D, bone-turnover markers, and site-specific DXA.

Keywords: bone mineral density; bone mineralization; calcium citrate malate; calcium; vitamin D; inulin; postmenopause; DXA

Introduction

Bone mineral density (BMD) reflects the balance between bone formation and bone loss over time. It is influenced by calcium intake, vitamin D status, parathyroid hormone (PTH), bone turnover, sex hormones, mechanical loading, renal function, and adherence to supplementation. For this reason, BMD is a useful long-term outcome, but responses to calcium supplementation can differ substantially between populations.

The NVTIA® ingredient platform evaluated in this study is represented by a formulation containing

50.0% calcium citrate malate and 15.0% calcium L-lactate by total tablet mass, together with CPP, inulin, resistant dextrin, and microencapsulated vitamin D3. NVTIA® refers to the branded ingredient platform evaluated through the formulation described in this article.Earlier formulation testing showed greater calcium release and soluble-calcium retention under simulated gastrointestinal conditions. The present analysis examines these formulation characteristics in relation to human evidence on calcium supplementation, bone mineralization, and BMD.

This topic is also relevant to the broader scientific scope of the World Food Supplement Association, where the first author, Nour-Eddine Ziraoui, is affiliated, because calcium–vitamin D combinations provide a useful context for examining nutrient interactions, dose equivalence, and differences between target populations.

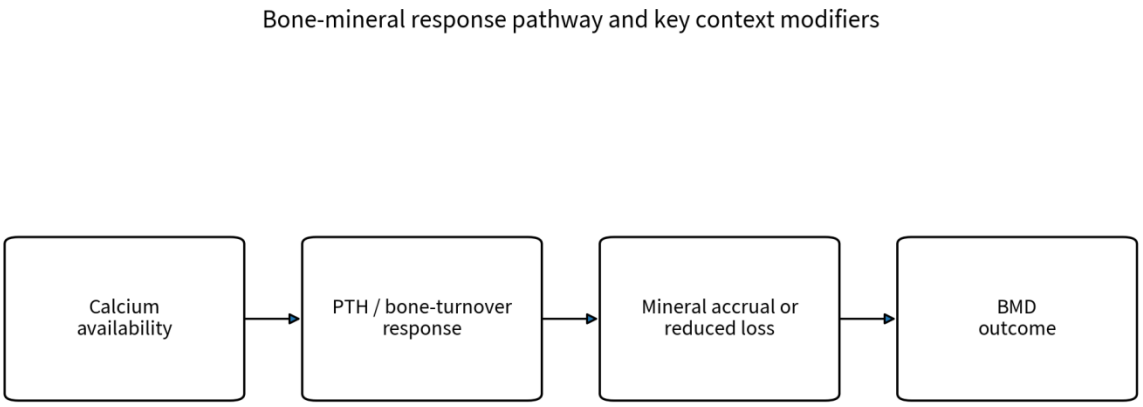


Figure 1. Simplified pathway linking calcium availability to BMD. Age, baseline calcium intake, vitamin D status, menopausal stage, adherence and concurrent therapies can modify each step.

Materials and Methods

2.1 Formulation composition and dosing context.The NVTIA®-based formulation contains 50.000% calcium citrate malate (CCM), 15.000% calcium L-lactate, 2.500% casein phosphopeptide (CPP), 5.000% inulin, 2.000% resistant dextrin, and 0.200% microencapsulated vitamin D3 powder, together with standard tableting excipients. The microencapsulated vitamin D3 powder has a specified potency of 90,000–110,000 IU/g. For clinical dose matching, the elemental calcium and vitamin D3 content should be analytically verified on a per-tablet basis and expressed relative to the intended daily intake.

2.2 Clinical evidence identification.A targeted search of primary randomized controlled trials and relevant systematic reviews and meta-analyses was conducted up to 14 August 2026. The search was designed as a targeted evidence appraisal rather than a systematic review or formal de novo meta-analysis. Priority was given to studies reporting bone mineral density (BMD) assessed by dual-energy X-ray absorptiometry (DXA) or equivalent densitometric methods, bone mineral content (BMC), or validated markers of bone turnover in populations relevant to calcium supplementation. Evidence was selected to cover organic calcium salts, calcium combined with vitamin D, relevant age and menopausal strata, prebiotic co-intervention, and recent developments in calcium formulation research. Because the present work is an evidence synthesis rather than a de novo quantitative meta-analysis, effect estimates were retained and reported according to the metrics used in the original publications.

2.3 Interpretive framework.The evidence was interpreted according to baseline calcium and vitamin D status, age, menopausal stage, intervention dose, intervention duration, and skeletal site. Particular attention was given to whether these factors could modify the observed effects of calcium-containing interventions. Importantly, evidence derived from individual ingredients or related calcium formulations was not considered equivalent to direct clinical evidence for the complete formulation. Accordingly, formulation-specific clinical development should be evaluated

through a randomized controlled study using standardized elemental-calcium exposure, with prespecified BMD outcomes and clearly defined target populations. Such a study would allow the clinical effect of the complete formulation to be distinguished from evidence derived from its individual components.

Table 1. Components of the preferred formulation most relevant to bone-mineral interpretation

Component	Mass fraction	Bone-health evidence role
Calcium citrate malate	50.000%	Principal organic calcium source; quantify elemental calcium per tablet for clinical dose matching
Calcium L-lactate	15.000%	Second organic calcium source
Casein phosphopeptide (CPP)	2.500%	Co-granulated calcium-binding peptide ingredient; human absorption evidence is mixed/neutral
Inulin	5.000%	Prebiotic fiber; ingredient-level trials support calcium absorption in selected populations
Resistant dextrin	2.000%	Dietary-fiber co-ingredient; evaluate its contribution within complete-formulation clinical studies
Microencapsulated vitamin D3 powder	0.200%	Potency 90,000–110,000 IU/g; define exposure from assayed tablet content and daily intake

Evidence Synthesis

1. Calcium alone and menopausal context.Dawson-Hughes et al. conducted a two-year controlled trial in 301 healthy postmenopausal women who were randomized to placebo, calcium carbonate, or calcium citrate malate (CCM) [1]. The effect of calcium was most apparent among women who were more than five years postmenopause and had dietary calcium intakes below 400 mg/day. In contrast, supplementation did not prevent the relatively rapid loss of spinal bone during the early postmenopausal period. Thus, the skeletal response to calcium cannot be considered independent of menopausal stage or habitual calcium intake.

A similar pattern was reported by Reid et al. in 122 postmenopausal women receiving 1000 mg/day calcium for two years [2]. The annual change in total-body BMD was −0.0055±0.0010 g/cm² in the calcium group and −0.0097±0.0010 g/cm² in the placebo group, representing a 43% lower rate of bone loss (P=0.005). Differences were also reported at the leg, trunk, lumbar spine, and Ward triangle. These findings are more consistent with preservation of existing bone than with stimulation of new bone formation.

Studies of other calcium salts provide related evidence. In early- and mid-postmenopausal women, 800 mg/day calcium citrate was associated with a two-year lumbar BMD change of +1.03%, compared with −2.38% with placebo (P<0.001) [5]. CCM also produced a favorable response in the subgroup of later-postmenopausal women with low calcium intake in the Dawson-Hughes study [1]. The available trials do not allow direct equivalence to be assumed between citrate, CCM, and calcium L-lactate, but they provide clinical evidence that calcium delivery is not restricted to calcium carbonate formulations.

2. Calcium plus vitamin D in older and deficient populations.The magnitude of the response appears to be greater in populations with a more pronounced nutritional deficit. Grados et al. studied older women with marked vitamin D deficiency and reported a 12-month increase in L2–L4 BMD of 2.98% with 1000 mg calcium plus 800 IU vitamin D daily, compared with a decrease of 0.21% in the placebo group (P=0.0009) [3]. Femoral-neck BMD increased by 1.19% versus a decrease of 0.83%, respectively (P=0.015). In a separate study of adults aged 65 years or older, Dawson-Hughes et al. found smaller but statistically significant improvements in femoral-neck, spinal, and total-body BMD after three years of supplementation with 500 mg calcium and 700 IU vitamin D3 daily [4].

Other populations have shown more site-specific responses. Following a recent low-energy fracture, Hitz et al. reported higher lumbar-spine BMD after one year of high-dose calcium carbonate plus vitamin D than with placebo containing a small amount of vitamin D, whereas the difference at the hip did not reach statistical significance [7]. Daly et al. also reported reduced bone loss at clinically relevant skeletal sites among men over 50 years of age who consumed calcium- and vitamin-D3-fortified milk [8]. Taken together, these studies indicate that the response to combined calcium and vitamin D varies across skeletal sites and according to the characteristics of the population studied.

3. Prebiotics, calcium absorption and mineral accrual.Evidence for a role of prebiotics in calcium-related skeletal outcomes has been obtained in younger populations. In growing adolescents, 8 g/day of mixed inulin-type fructans increased calcium absorption. After one year, whole-body BMC was 35±16 g higher than in the control group (P=0.03), while the corresponding BMD difference was 0.015±0.004 g/cm² (P=0.01) [6]. The study therefore provides a link between increased calcium absorption and measurable changes in skeletal mineral accrual during a period of active bone growth.

The findings in postmenopausal women are less straightforward. The 2026 RENEW randomized trial included 417 postmenopausal females assigned to placebo, calcium carbonate, calcium-rich dairy permeate, or calcium-rich permeate plus inulin, with vitamin D supplied across the intervention groups [9]. After 12 months, lumbar-spine BMD was higher than placebo in both the calcium carbonate group (adjusted β=0.0158 g/cm²; 95% CI 0.0066–0.0251; P=0.0009) and the permeate-plus-inulin group (β=0.0142 g/cm²; 95% CI 0.0046–0.0238; P=0.0040). At the femoral neck, a significant difference was observed with calcium-rich permeate (β=0.0116 g/cm²; 95% CI 0.0042–0.0190; P=0.0022). Adding inulin did not produce a measurable additional BMD benefit in this study. This contrasts with the adolescent findings and suggests that the skeletal consequences of prebiotic supplementation may depend on the population and the calcium formulation with which it is combined.

4. Meta-analytic perspective.The broader evidence base is consistent with the individual trials described above. Tang et al. combined data from 29 randomized trials involving 63,897 adults aged 50 years or older [10]. Calcium supplementation, either alone or together with vitamin D, was associated with approximately 0.54% less bone loss at the hip (95% CI 0.35–0.73) and 1.19% less bone loss at the spine (95% CI 0.76–1.61), with P<0.0001 for both outcomes. The size of these effects was modest at the population level, although the direction of the findings was generally consistent with the controlled trials. Differences in baseline calcium and vitamin D status, age, menopausal stage, and other population characteristics may partly explain the variation in response across studies.

Table 2. Representative randomized evidence for bone mineralization and BMD

Study	Population/duration	Intervention	Outcome	Key result	Interpretation
Dawson-Hughes 1990 [1]	301 healthy postmenopausal women; 2 y	Placebo, 500 mg Ca/d as carbonate, or 500 mg Ca/d as CCM	BMD by menopausal stage and baseline Ca intake	Benefit concentrated in later postmenopause with low dietary Ca; early rapid spinal loss was not prevented	Strong evidence that baseline intake and menopausal timing modify response.
Reid 1993 [2]	122 postmenopausal women; 2 y	1000 mg Ca/d vs placebo	Total-body and regional BMD	Total-body loss −0.0055 vs −0.0097 g/cm²/y; 43% reduction, P=0.005	Demonstrates attenuation of bone loss with calcium in a defined postmenopausal population.
Grados 2003 [3]	192 elderly women; vitamin D deficient; 12 mo	1000 mg Ca + 800 IU vitamin D/d vs placebo	Lumbar, femoral neck, trochanter, whole-body BMD	L2–L4 +2.98% vs −0.21% (P=0.0009); femoral neck +1.19% vs −0.83% (P=0.015)	Large response in a deficiency-enriched older population.
Dawson-Hughes 1997 [4]	389 adults ≥65 y; 3 y	500 mg Ca + 700 IU vitamin D3/d vs placebo	Femoral neck, spine, total-body BMD	Femoral neck +0.50% vs −0.70% (P=0.02); total body +0.06% vs −1.09% (P<0.001)	Supports modest multi-site BMD preservation in older adults.
Ruml 1999 [5]	63 early/mid-postmenopausal women; 1–2 y	800 mg Ca/d as calcium citrate vs placebo	Lumbar and radial BMD	At 2 y L2–L4 +1.03% vs −2.38% (P<0.001)	Relevant organic-calcium evidence, although not the same salt as CCM.
Abrams 2005 [6]	100 adolescents; 1 y	8 g/d inulin-type fructans vs maltodextrin	Whole-body BMC/BMD	BMC +35±16 g (P=0.03); BMD +0.015±0.004 g/cm² (P=0.01)	Links enhanced Ca absorption to mineral accrual in growth.
RENEW 2026 [9]	417 randomized postmenopausal females; 316 completed; 12 mo	Placebo, Ca carbonate, Ca-rich milk permeate, or permeate+inulin; all received vitamin D	CTX and BMD	Lumbar BMD higher vs placebo with Ca carbonate β=0.0158 g/cm² and permeate+inulin β=0.0142; no additional inulin advantage	Current evidence: calcium strategy matters; inulin did not independently improve BMD in this setting.

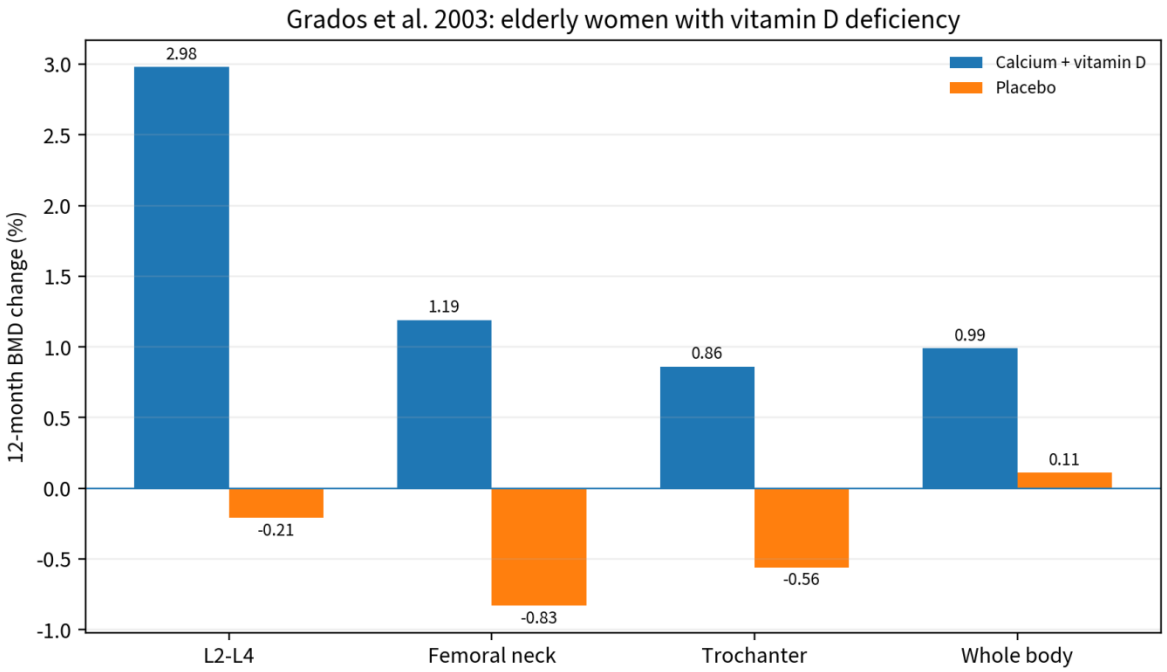


Figure 2. Site-specific 12-month BMD changes in vitamin-D-deficient elderly women reported by Grados et al. [3]. Values are trial-specific and are not extrapolated to the present formulation.

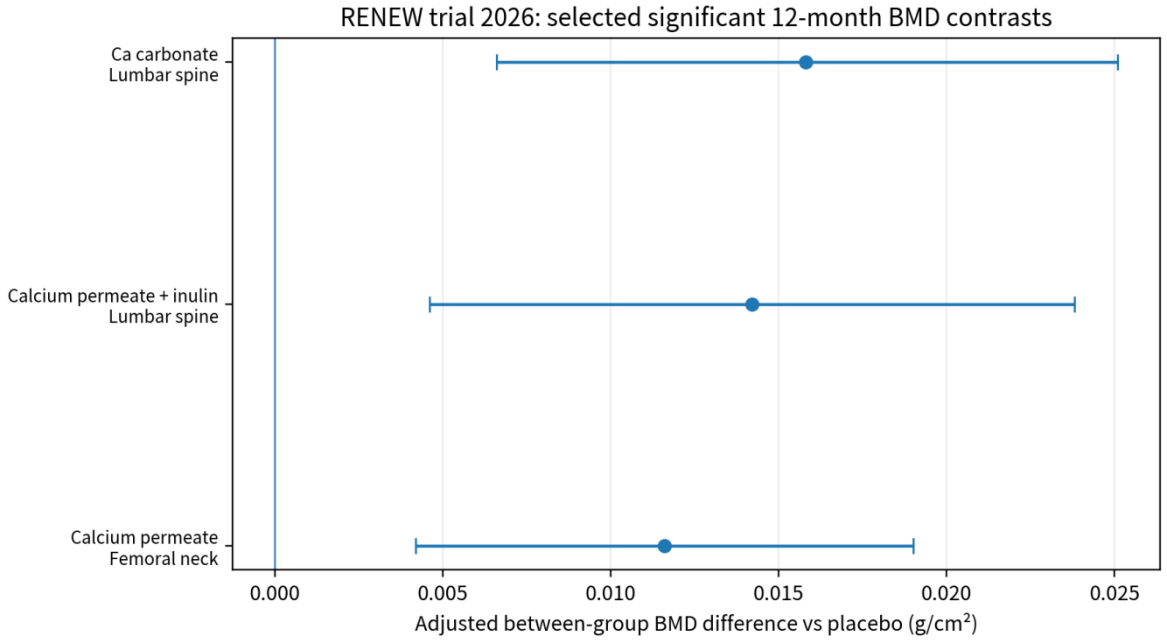


Figure 3. Selected significant adjusted BMD contrasts from the 2026 RENEW trial [9]. The trial did not demonstrate an additional BMD advantage attributable to inulin.

Discussion

The available clinical literature is broadly consistent with the nutritional rationale of the formulation, although the expected benefit is likely to vary across populations. Calcium supplementation appears more relevant to bone preservation when habitual calcium intake is low, vitamin D status is inadequate, age-related secondary hyperparathyroidism contributes to increased bone turnover, or the demand for replacement mineral is relatively high. Calcium alone, however, does not appear sufficient to fully counter the rapid estrogen-associated bone loss that occurs during early postmenopause [1].

The use of two organic calcium sources in the NVTIA® formulation is consistent with the broader calcium literature, but the proportions of calcium salts should not be interpreted as equivalent to the elemental calcium dose. The current composition is expressed as mass fractions of the individual calcium ingredients rather than as elemental calcium delivered per tablet. For a clinical study, therefore, elemental calcium and vitamin D3 should be measured analytically for each production batch, with the intervention dose subsequently defined in terms of mg elemental calcium/day and IU or µg vitamin D3/day.

CPP and the prebiotic components should likewise be regarded as potential modifiers of calcium handling rather than established BMD-active ingredients. The clearest clinical evidence for inulin-type fructans comes from adolescents undergoing skeletal growth [6]. By comparison, the RENEW trial found no additional BMD benefit from inulin when it was added to a calcium-containing intervention in vitamin-D-supplemented postmenopausal women [9]. The difference between these populations is relevant to interpretation of the present formulation, since the effect of a prebiotic may depend on the host population and the calcium matrix rather than occurring as a uniform ingredient-specific response.

Clinical evaluation of the finished formulation would therefore be most informative in adults with low-to-moderate habitual calcium intake, with baseline 25(OH)D status and menopausal status recorded as prespecified stratification factors. A 12- to 24-month randomized study could assess BMD at the lumbar spine, total hip, and femoral neck by DXA, while serum P1NP, CTX, PTH, and calcium could provide complementary information on bone remodeling and mineral homeostasis. Prospective assessment of adherence and total dietary calcium intake would also be important, as differences in either factor could substantially influence the observed treatment effect.

Limitations

The studies considered in this review cover different life stages because age, menopausal status, baseline calcium intake, and vitamin D status can influence the response to calcium supplementation. The results should therefore not be interpreted as representing a single effect size applicable to all populations. Formulation studies provide information on properties such as calcium release and stability, whereas the clinical studies provide evidence on skeletal outcomes including BMD. These evidence streams are complementary but do not constitute direct clinical evidence for the complete formulation. A formulation-specific clinical study should consequently standardize elemental-calcium and vitamin D3 exposure, document habitual calcium intake, and prespecify relevant population subgroups to facilitate interpretation of the resulting BMD data.

Conclusion

Randomized clinical evidence indicates that calcium supplementation can help preserve or improve BMD in selected populations, with responses influenced by factors such as age, baseline calcium intake, and vitamin D status. Controlled studies of organic calcium salts provide supportive evidence, while combined calcium and vitamin D supplementation has produced site-specific BMD benefits in several populations. Evidence for prebiotic enhancement is more variable and does not indicate a consistent additional BMD effect across different age groups or calcium matrices.

The available evidence therefore provides a reasonable nutritional and biological basis for further evaluation of the NVTIA® formulation, but it does not establish clinical efficacy of the finished formulation itself. Direct evaluation of the complete formulation remains necessary. A randomized controlled study using analytically verified elemental-calcium and vitamin D3 exposure, DXA-based BMD measurements, and appropriate bone-turnover markers would provide a more direct assessment of its effects on bone mineralization and skeletal outcomes.

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