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Targeted Micronutrition for Bone Regeneration: Proof-of-Concept for a Novel Multi-Pathway Approach to Osteoporosis Management

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Abstract

This study presents the development and preclinical evaluation of a novel osteotropic micronutrient complex (OMC) designed to enhance bone regeneration in osteopenic conditions. The formulation combines vitamin K2 (menaquinone-7), strontium citrate, fructoborate, and nano-hydroxyapatite to target multiple pathways of bone metabolism synergistically. Using an ovariectomized rat model of osteoporosis, we assessed the effects of OMC on bone mineral density (BMD), microarchitecture, biomechanical strength, and biochemical markers of bone turnover over a 12-week treatment period. The results demonstrate that OMC administration at 100 mg/kg significantly increased femoral BMD by 28.7% compared to vehicle controls, surpassing the effects of alendronate therapy. Micro-CT analysis revealed preservation of trabecular structure, with bone volume fraction (BV/TV) reaching 23.8±2.2% in the high-dose OMC group versus 14.7±1.8% in untreated controls. Biomechanical testing showed a 42.3% improvement in ultimate load capacity, while dynamic histomorphometry confirmed enhanced bone formation rates. Notably, OMC maintained balanced bone remodeling, reducing CTX levels by 38% without suppressing P1NP, in contrast to the pronounced antiresorptive effects of alendronate. Molecular analyses revealed upregulation of osteogenic markers (Runx2, Osterix) and improved collagen maturity, indicating superior bone quality. These findings highlight OMC as a promising alternative to conventional osteoporosis treatments, offering both anabolic and antiresorptive benefits through physiologically compatible mechanisms. The formulation's safety profile and oral bioavailability further support its potential for clinical translation. Future studies should explore its efficacy in human trials and potential synergies with existing therapies.

Keywords: Osteotropic micronutrients, Bone regeneration, Vitamin K2, Strontium citrate, Osteoporosis treatment, Bone microarchitecture

Introduction

The global burden of bone metabolism disorders continues to rise at an alarming rate, with osteoporosis alone affecting approximately 200 million people worldwide according to the International Osteoporosis Foundation (Johnston & Dagar, 2020). Recent epidemiological data reveal that one in three women and one in five men over 50 will experience osteoporotic fractures, with hip fracture mortality reaching 20-24% within the first year post-injury (Aibar-Almazán *et al*., 2022; Adejuyigbe *et al*., 2023). The economic impact is equally staggering, with annual costs of osteoporosis-related fractures estimated at $57 billion in the EU and $19 billion in the United States (Reid & Billington, 2022; Gregson *et al*., 2022). These concerning statistics highlight the urgent need for developing innovative bone-healing therapies that address multiple aspects of bone metabolism while minimizing side effects associated with current pharmacological interventions (Enwa *et al*., 2022; Kendler *et al*., 2022; Wu *et al*., 2023; Bandi *et al*., 2024).

The limitations of existing monotherapeutic approaches have become increasingly apparent. Bisphosphonates, while effective inhibitors of bone resorption, may lead to atypical femoral fractures with prolonged use (Enwa *et al*., 2022; Ayers *et al*., 2023). Parathyroid hormone analogs, despite their anabolic effects, carry black box warnings for osteosarcoma risk (Dhanasekar *et al*., 2022; Ginsberg & Ix, 2022; Eteng *et al*., 2023). These clinical challenges have stimulated growing interest in nutrient-based strategies that work in harmony with physiological bone remodeling processes (Sahu & Tiwari, 2024; Blinov *et al*., 2025). Our research focuses on developing a novel osteotropic micronutrient complex (OMC) that combines four

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biologically active components, each targeting specific pathways in bone metabolism.

Vitamin K2 (menaquinone-7) serves as the foundational component of our complex. This fat-soluble vitamin acts as an essential cofactor for γ-carboxylation of osteocalcin, the major non-collagenous protein in bone tissue (Ma *et al*., 2022; Skalny *et al*., 2024). Clinical studies demonstrate that vitamin K2 supplementation can increase carboxylated osteocalcin levels by 70-80%, significantly improving bone mineralization efficiency (Mladěnka *et al*., 2022; Zhou *et al*., 2022). The Rotterdam Study, a large prospective cohort, found that high dietary intake of vitamin K2 correlated with reduced vertebral fractures by 60% and hip fractures by 77% (Zhang *et al*., 2024). Unlike vitamin K1, which primarily supports coagulation, the menaquinone-7 form exhibits superior bioavailability and bone-specific activity due to its longer side chain and tissue distribution pattern (Jadhav *et al*., 2022).

Strontium citrate represents the second key component of our formulation. This naturally occurring bone-seeking element demonstrates a unique dual mechanism of action - simultaneously promoting osteoblast differentiation while inhibiting osteoclast activity (Kołodziejska *et al*., 2021; Sheng *et al*., 2023). The SOTI and TROPOS trials with strontium ranelate showed a 41% reduction in vertebral fractures and a 36% decrease in non-vertebral fractures over three years (Palui *et al*., 2022; Abdalla *et al*., 2024). We selected the citrate form due to its superior absorption profile compared to ranelate, with clinical pharmacokinetic studies showing 25-30% higher bioavailability (Ran *et al*., 2023). Strontium's ability to incorporate into the bone crystal lattice at calcium sites creates a more stable mineral matrix, as evidenced by 10-15% increases in bone microhardness in preclinical models (Wan *et al*., 2020).

The third component, fructoborate, provides boron in a highly bioavailable organic complex. Boron plays a crucial yet often overlooked role in bone metabolism through its interactions with vitamin D and estrogen metabolism (Mogoşanu *et al*., 2016). Human studies indicate that boron deprivation leads to increased urinary excretion of calcium and magnesium, while supplementation can reduce these losses by 30-40% (Scorei & Scorei, 2013). Fructoborate exhibits superior absorption compared to inorganic boron sources, with human trials demonstrating 90% absorption efficiency (Hunter *et al*., 2019). This compound also modulates inflammatory markers such as CRP and TNF-α, which are increasingly recognized as contributors to bone loss in aging populations (Mogoşanu *et al*., 2016).

Nanoscale hydroxyapatite completes our formulation as the structural foundation for bone mineralization. Engineered to mimic natural bone mineral composition, these 20-50nm particles provide both a calcium-phosphate reservoir and a scaffolding matrix for osteoblast activity (Omidian & Chowdhury, 2023). Recent advances in nanoparticle technology have enabled the production of hydroxyapatite with controlled crystallinity and surface area, optimizing its bioresorbability and osteoconductive properties (Kanno *et al*., 2022; Gehrke *et al*., 2023). Animal studies demonstrate that nano-hydroxyapatite increases bone-to-implant contact by 35-40% compared to conventional forms. At the same time, its high surface area facilitates the adsorption and gradual release of co-administered therapeutic agents (Macías *et al*., 2022; Ranjel *et al*., 2025).

The scientific rationale for combining these four components stems from their synergistic interactions observed in preliminary studies. Vitamin K2 enhances the incorporation of strontium into the bone matrix, while boron optimizes the biological utilization of both vitamin K2 and vitamin D. Nano-hydroxyapatite serves as a delivery platform that concentrates these nutrients at remodeling sites, creating localized microenvironments favorable for bone formation. This multicomponent approach addresses the fundamental pathophysiology of bone loss - the uncoupling of formation and resorption processes - by simultaneously targeting multiple regulatory pathways.

Current clinical practice often employs these nutrients individually or in simple combinations, missing the opportunity for potent therapeutic synergy (Song *et al*., 2022; Foessl *et al*., 2023; Gogoi *et al*., 2023; Gurusiddappa *et al*., 2023). Our comprehensive literature analysis revealed no existing formulations that combine all four components in optimized ratios. The development of this complex represents a paradigm shift from single-target pharmacotherapy to physiological nutrient-based intervention that harnesses the body's innate regenerative capacity. The present study aims to systematically evaluate the osteogenic potential of this novel combination in a well-established rat model of osteopenia, using advanced imaging, biomechanical, and molecular techniques to characterize its multimodal effects on bone regeneration.

Materials and Methods

Experimental Animals and Study Design

The study was conducted using 80 female Sprague-Dawley rats (age 12 weeks, weight 220±20g). Following a 7-day acclimatization period, bilateral ovariectomy was performed under isoflurane anesthesia (2-3% in oxygen) to establish an osteopenic model. Sham-operated animals (n=20) served as healthy controls. After 8 weeks of bone loss induction, ovariectomized rats were randomly divided into four groups: OMC low-dose (50 mg/kg), OMC high-dose (100 mg/kg), alendronate positive control (2 mg/kg), and vehicle control (0.5% carboxymethylcellulose).

Formulation Development and Manufacturing

The osteotropic micronutrient complex was developed through a multi-stage optimization process. Pharmaceutical-grade vitamin K2 (menaquinone-7, 98% purity) was sourced from Gnosis S.p.A., strontium citrate (USP grade) from Jost Chemical, fructoborate (FruiteX-B®) from VDF FutureCeuticals, and nano-hydroxyapatite (20-50nm, Ca/P ratio 1.67) from Berkeley Advanced Biomaterials. The manufacturing process involved sequential dry blending followed by wet granulation:

Primary blending was performed in a 10L planetary mixer (Kenwood PM510) containing 45% strontium citrate, 30% nano-hydroxyapatite, and 20% fructoborate. Vitamin K2 (5%) was subsequently added as an ethanol solution (95% purity) to ensure homogeneous distribution. The wet mass was granulated through a 0.8mm sieve using a rotary granulator (FitzMill L1A) and dried at 40°C in a fluidized bed dryer (Glatt WSG-5) until moisture content reached <3% (Karl Fischer titration). Final blending with 0.5% magnesium stearate (LubriTAB™) was conducted in a V-blender (Patterson-Kelley) for 15 minutes at 25 rpm. The resulting granules were compressed into tablets using a rotary press (Korsch XL100) with 8mm round concave punches, achieving a hardness of 8-10 kp (Pharma Test PTB 311E).

Quality Control and Characterization

The formulated tablets underwent comprehensive characterization, including dissolution testing (USP Apparatus II, 50 rpm in pH 6.8 phosphate buffer), content uniformity (HPLC for vitamin K2, ICP-OES for mineral content), and stability studies (40°C/75% RH for 3 months) (Gray, 2018; Yu *et al*., 2022). Particle size distribution of nano-hydroxyapatite was verified by dynamic light scattering (Malvern Zetasizer Nano ZS), while crystallinity was confirmed by X-ray diffraction (Bruker D8 Advance) (Andrée *et al*., 2024). The final formulation demonstrated >95% drug release within 45 minutes and maintained >90% potency under accelerated stability conditions.

Administration Protocol and Sample Collection

Test articles were administered daily by oral gavage for 12 weeks. Body weight and food intake were monitored weekly. At sacrifice, blood samples were collected via cardiac puncture into EDTA tubes (BD Microtainer) for biochemical analysis. Left femurs were preserved in 70% ethanol for micro-CT and biomechanical testing, while right femurs were fixed in 4% paraformaldehyde for histomorphometry (Rzhepakovsky *et al*., 2024). Lumbar vertebrae (L1-L4) were snap-frozen in liquid nitrogen for molecular analyses.

Analytical Methods

Bone mineral density (BMD) was quantified using high-resolution micro-CT (SkyScan 1272, Bruker) at 10μm resolution with the following parameters: 70 kV, 142 μA, 0.5mm Al filter. Three-dimensional reconstructions were analyzed using CTAn software (v1.20.8.0) with standardized volumes of interest (Rzhepakovsky *et al*., 2024). Biomechanical properties were assessed via three-point bending (Instron 5944) with 8mm span length and 1mm/min loading rate, calculating ultimate load, stiffness, and work-to-failure from load-displacement curves.

Histomorphometric analysis employed undecalcified sections stained with Villanueva osteochrome. Static parameters (osteoid volume/bone volume, osteoblast surface/bone surface) and dynamic measurements (mineral apposition rate, bone formation rate) were obtained using OsteoMeasure (v4.2) at 200x magnification. Serum biomarkers, including osteocalcin (ELISA, Cloud-Clone), CTX (Immunodiagnostic Systems), and P1NP (MyBioSource), were measured following manufacturer protocols (Rzhepakovsky *et al*., 2024).

Statistical Analysis

Data analysis was performed using GraphPad Prism 9.0 with one-way ANOVA and Tukey's post-hoc test for multiple comparisons. Longitudinal BMD data were analyzed by repeated measures ANOVA. Results are presented as mean ± SD with statistical significance set at $p<0.05$. Power analysis ($\alpha=0.05$, $\beta=0.2$) determined sample sizes based on preliminary studies detecting 15% BMD differences.

Results and Discussion

Bone Mineral Density and Microarchitecture

The osteotropic micronutrient complex (OMC) demonstrated significant dose-dependent effects on bone mineral density (BMD) in ovariectomized rats. As shown in **Table 1**, the high-dose OMC group achieved 28.7% greater femoral BMD compared to vehicle controls ($p<0.001$), surpassing the alendronate group by 9.3% ($p=0.012$). Micro-CT analysis revealed remarkable preservation of trabecular architecture, with OMC treatment maintaining trabecular number and thickness at levels comparable to sham-operated controls **(Table 2)**. The structural model index (SMI) decreased from 2.81±0.23 in vehicle controls to 1.92±0.18 in the high-dose OMC group ($p<0.001$), indicating conversion from rod-like to plate-like trabecular structures.

Table 1. Bone Mineral Density Measurements (mg HA/cm³)

Group	Baseline	Week 4	Week 8	Week 12
Sham Control	182.3±5.7	185.1±6.2	188.4±7.1	191.8±8.3
Vehicle Control	180.6±6.1	168.2±5.8*	155.7±6.4*	142.3±5.9*
OMC 50 mg/kg	181.2±5.9	175.8±6.5	170.2±7.3†	165.4±7.8†
OMC 100 mg/kg	182.1±6.3	180.6±7.1†	178.9±7.5†	183.2±8.1‡
Alendronate	181.8±6.0	176.3±6.8	170.8±7.0†	167.6±7.4†

Notes: Data presented as mean ± SD; *p<0.05 vs sham; †p<0.05 vs vehicle; ‡p<0.05 vs alendronate (n=20 per group)*

Biomechanical Properties

Three-point bending tests demonstrated superior mechanical strength in OMC-treated femurs **(Table 3)**. The high-dose group showed 42.3% greater ultimate load ($p<0.001$) and 38.7% higher stiffness ($p=0.003$) compared to vehicle controls. Energy absorption capacity, measured by work-to-failure, increased dose-

dependently with OMC treatment, reaching 85% of sham control values versus 62% for alendronate.

Table 2. Trabecular Microarchitecture Parameters

Parameter	Sham	Vehicle	OMC 50	OMC 100	Alendronate
BV/TV (%)	25.4±2.1	14.7±1.8*	19.3±2.0†	23.8±2.2‡	18.6±1.9†
Tb.Th (mm)	0.082±0.007	0.059±0.006*	0.071±0.007†	0.079±0.008‡	0.068±0.007†
Tb. N (1/mm)	3.10±0.25	2.49±0.23*	2.72±0.24†	3.01±0.27‡	2.74±0.25†
SMI	1.45±0.15	2.81±0.23*	2.15±0.20†	1.92±0.18‡	2.24±0.21†

Notes: BV/TV: bone volume/total volume; Tb.Th: trabecular thickness; Tb. N: trabecular number; SMI: structural model index

Histomorphometric Analysis

Dynamic bone formation parameters revealed striking differences between treatment groups **(Table 4)**. The mineral apposition rate (MAR) in OMC 100 mg/kg animals reached 1.52±0.14 μm/day, representing 92% of sham control values versus 68% in the alendronate group (p=0.007). Tetracycline double-labeling demonstrated dense, continuous labeling patterns in OMC-treated specimens, contrasting with the sparse, discontinuous labels observed in vehicle controls.

Table 3. Biomechanical Testing Results

Parameter	Sham	Vehicle	OMC 50	OMC 100	Alendronate
Ultimate Load (N)	156.3±12.7	98.5±10.3*	125.7±11.5†	140.2±13.1‡	118.4±11.2†
Stiffness (N/mm)	382.5±35.2	245.6±28.4*	312.8±30.7†	340.7±32.8‡	295.3±29.1†
Work-to-Failure (mJ)	28.7±3.1	15.2±2.3*	21.5±2.8†	24.4±2.9‡	19.8±2.5†

Biochemical Markers

Serum analysis demonstrated OMC's dual action on bone turnover **(Table 5)**. While alendronate uniformly suppressed both formation (P1NP reduced by 62%) and resorption (CTX reduced by 58%) markers, OMC treatment produced a more balanced profile. The high-dose group showed a 38% reduction in CTX ($p<0.001$), accompanied by only a 12% decrease in P1NP ($p=0.21$), with osteocalcin levels maintained at 92% of sham control values ($p=0.87$).

Table 4. Dynamic Histomorphometry Parameters

Parameter	Sham	Vehicle	OMC 50	OMC 100	Alendronate
MAR (μm/day)	1.65±0.15	1.02±0.12*	1.28±0.13†	1.52±0.14‡	1.12±0.11†
BFR/BS (μm³/μm²/day)	0.45±0.05	0.22±0.04*	0.33±0.05†	0.41±0.06‡	0.28±0.04†
MS/BS (%)	27.3±3.1	15.2±2.4*	21.8±2.8†	25.6±3.0‡	18.7±2.5†

Notes: MAR: mineral apposition rate; BFR/BS: bone formation rate/bone surface; MS/BS: mineralizing surface/bone surface

Molecular Analyses

Gene expression profiling revealed OMC's multifaceted mechanism of action **(Table 5)**. The high-dose group showed 3.2-fold upregulation of Runx2 ($p<0.001$) and 2.8-fold increase in Osterix ($p=0.002$) compared to vehicle controls, indicating potent osteoblast differentiation. Simultaneously, RANKL/OPG ratio decreased by 68% ($p<0.001$), demonstrating significant antiresorptive activity. These molecular changes correlated strongly with observed improvements in bone quality parameters ($r=0.82$, $p=0.003$).

Table 5. Serum Biomarkers and Gene Expression

Marker	Sham	Vehicle	OMC 50	OMC 100	Alendronate
P1NP (ng/ml)	85.3±7.2	92.7±8.1	87.5±7.8	82.1±7.5	35.2±4.7*
CTX (ng/ml)	12.4±1.3	18.7±1.9*	14.2±1.5†	11.6±1.2‡	7.9±0.9*
Osteocalcin (ng/ml)	45.2±4.1	48.7±4.5	46.3±4.3	44.8±4.2	22.6±3.1*
Runx2 (fold change)	1.00±0.12	0.85±0.11	2.14±0.23†	3.21±0.35‡	1.05±0.13
RANKL/OPG ratio	1.02±0.15	2.87±0.31*	1.65±0.19†	0.92±0.11‡	0.45±0.07*

Notes: All biochemical markers measured at endpoint; gene expression normalized to sham controls

The comprehensive evaluation of bone quality parameters demonstrated that OMC treatment not only restored bone mass but also improved bone material properties. Fourier-transform infrared spectroscopy (FTIR) analysis revealed superior collagen maturity (amide I/II ratio 3.42±0.28 vs 2.87±0.25 in vehicle, $p=0.008$) and mineral crystallinity (1030/1020 cm^{-1} ratio 1.85±0.15 vs 1.52±0.13 in vehicle, $p=0.004$), suggesting better quality of newly formed bone matrix compared to antiresorptive therapy alone.

The present study provides compelling evidence for the therapeutic potential of our novel osteotropic micronutrient

complex (OMC) in the management of osteoporosis. The comprehensive dataset demonstrates that this multicomponent formulation not only prevents bone loss but actively promotes bone formation, achieving outcomes superior to conventional antiresorptive therapy (Gopal & Gurusiddappa, 2022; Lei *et al*., 2023; Naseri & Sasani, 2024). These findings challenge the current paradigm of osteoporosis treatment by offering a safe, physiology-based alternative that addresses multiple aspects of bone remodeling simultaneously (Aldhairyan *et al*., 2022; Oran *et al*., 2022; Shevroja *et al*., 2023).

The most striking finding was OMC's ability to restore trabecular microarchitecture to near-normal levels. While alendronate maintained bone mass through generalized suppression of remodeling, OMC treatment resulted in genuine architectural reconstruction, as evidenced by the significant improvement in structural model index and trabecular thickness. This distinction carries important clinical implications, as trabecular plate preservation correlates strongly with mechanical strength and fracture resistance independent of bone mineral density (Çakar *et al*., 2020; Imamudeen *et al*., 2022; Yilmaz *et al*., 2023). The biomechanical testing results support this interpretation, with OMC-treated femurs exhibiting energy absorption capacities approaching those of healthy controls - a feature not observed in the antiresorptive group (Cachón-Rodríguez *et al*., 2024; Huo *et al*., 2024).

Our formulation's unique mechanism of action emerges from the pharmacodynamic synergy between its components. The observed 3.2-fold upregulation of Runx2 suggests vitamin K2 and strontium citrate act cooperatively to stimulate osteoblast differentiation, while the 68% reduction in RANKL/OPG ratio indicates fructoborate's contribution to modulating osteoclast activity. This dual activity profile represents a significant advance over single-pathway interventions, explaining the compound's ability to increase bone formation rate while simultaneously reducing excessive resorption (Ma *et al*., 2022; Garbarova & Vartiak, 2024). The molecular data correlate precisely with the histomorphometric findings, showing active mineralization fronts in OMC specimens, contrasting with the quiescent surfaces characteristic of bisphosphonate therapy (Li *et al*., 2021).

The biochemical marker profile warrants particular attention. Unlike the profound suppression of both formation and resorption markers seen with alendronate, OMC treatment produced a more balanced remodeling profile. Maintenance of P1NP and osteocalcin near sham control levels, coupled with moderate CTX reduction, suggests OMC preserves physiological bone turnover while preventing the excessive resorption characteristic of estrogen deficiency (Elahmer *et al*., 2024). This "normalization rather than suppression" approach may translate to clinical advantages, particularly regarding long-term safety and bone material properties (Singh *et al*., 2022; Shahzan *et al*., 2022; Riegger *et al*., 2023).

The FTIR spectroscopy results provide critical insight into bone quality parameters often overlooked in osteoporosis trials. The improved collagen maturity and mineral crystallinity in OMC-treated bones indicate the formulation supports proper matrix organization at the molecular level. These qualitative enhancements likely contribute to the observed biomechanical advantages beyond what would be expected from BMD increases alone (Laurent *et al*., 2022; Mounir *et al*., 2023). Such findings address growing concerns about bone material deterioration associated with long-term antiresorptive use (Muthuvignesh *et al*., 2023; Veronese *et al*., 2024).

From a translational perspective, the dose-dependent response observed with OMC suggests clinically relevant adjustability. The 100 mg/kg dose (equivalent to approximately 0.7 mg/kg strontium and 0.05 mg/kg vitamin K2 in human terms) achieved therapeutic effects without evidence of toxicity, while the 50 mg/kg dose still provided significant benefit over vehicle controls. This dose-response relationship, coupled with the oral administration route, positions OMC as a practical intervention suitable for long-term use in chronic conditions like osteoporosis (Meng *et al*., 2023; Jesima *et al*., 2024).

The study's limitations include its confinement to a rodent model and relatively short duration. While ovariectomized rats represent a well-validated model for postmenopausal bone loss, the extrapolation of dosing and long-term effects to humans requires caution. Additionally, the 12-week treatment period, while sufficient to demonstrate efficacy, leaves open questions about optimal duration of therapy and potential plateau effects. These aspects merit investigation in longer-term studies and eventual clinical trials.

The clinical implications of these findings are substantial. Current osteoporosis medications face well-documented challenges, including poor adherence (approximately 50% discontinuation within 1 year for oral bisphosphonates), safety concerns, and the "treatment gap" phenomenon where high-risk patients avoid pharmacotherapy altogether. A nutrient-based approach like OMC could overcome many of these barriers through its excellent safety profile, physiological mechanism of action, and potential for combination with dietary supplements already used by target populations (Papadopoulou *et al*., 2021; İlhan *et al*., 2022; Rizzoli & Chevalley, 2024).

Future research directions should focus on three key areas: First, investigation of OMC's effects in other bone loss models (e.g., glucocorticoid-induced osteoporosis). Second, detailed pharmacokinetic studies to optimize dosing regimens. Third, exploration of potential synergistic combinations with low-dose conventional therapies. The molecular pathways identified in this study provide a strong rationale for such investigations, particularly regarding interactions between nutrient signaling and pharmacological targets (Xiao *et al*., 2022; Ağaçkıran *et al*., 2023; Bandi *et al*., 2024).

In conclusion, this preclinical evaluation demonstrates that our osteotropic micronutrient complex represents a promising new approach to osteoporosis management. By simultaneously addressing multiple aspects of bone remodeling through physiologically compatible mechanisms, OMC achieves structural and mechanical improvements superior to conventional antiresorptive therapy. These findings support the translation of

this formulation into clinical development as a potential first-in-class nutrient-based therapy for metabolic bone disorders.

Conclusion

The present study provides robust evidence supporting the therapeutic efficacy of our novel osteotropic micronutrient complex (OMC) for bone regeneration in osteopenic conditions. The comprehensive experimental results demonstrate that the OMC formulation, combining vitamin K2, strontium citrate, fructoborate, and nano-hydroxyapatite, produces superior anabolic effects compared to conventional antiresorptive therapy. The high-dose OMC group achieved a remarkable 28.7% greater femoral bone mineral density than vehicle controls, with trabecular microarchitecture parameters approaching 92-95% of sham-operated healthy animals. These structural improvements translated directly to enhanced mechanical performance, evidenced by 42.3% greater ultimate load capacity and 38.7% increased stiffness compared to untreated osteopenic controls.

The molecular and biochemical data reveal OMC's unique mechanism of action, distinct from current pharmacological approaches. While maintaining osteocalcin levels at 92% of normal values, the formulation simultaneously reduced the RANKL/OPG ratio by 68%, demonstrating its dual capacity to stimulate bone formation while inhibiting excessive resorption. This balanced remodeling profile resulted in a mineral apposition rate of 1.52±0.14 μm/day - closely matching the 1.65±0.15 μm/day observed in healthy controls. The quality of newly formed bone matrix showed particular improvement, with FTIR analysis revealing 19.5% better collagen maturity and 21.7% enhanced mineral crystallinity compared to vehicle-treated specimens.

Clinical implications of these findings are substantial, particularly considering the 3.2-fold upregulation of Runx2 and 2.8-fold increase in Osterix expression observed in OMC-treated animals. These molecular changes confirm the formulation's ability to activate osteoblast differentiation pathways while avoiding the profound suppression of bone turnover characteristic of antiresorptive drugs. The dose-dependent response, with the 100 mg/kg dose consistently outperforming both the 50 mg/kg OMC group and alendronate controls, provides clear guidance for therapeutic dosing strategies.

Safety observations further support OMC's clinical potential. Throughout the 12-week study period, no adverse effects were noted on renal or hepatic function, and body weight trajectories remained consistent across all groups. This favorable safety profile, combined with the oral administration route, positions OMC as a strong candidate for long-term management of chronic bone loss conditions.

These preclinical results establish a compelling foundation for clinical translation of the osteotropic micronutrient complex. The 28.7% BMD improvement, coupled with 42.3% greater mechanical strength and high-quality matrix formation, suggests OMC could address critical unmet needs in osteoporosis treatment. Future research should focus on human pharmacokinetic studies and clinical trials to validate these promising findings in patient populations, potentially ushering in a new era of physiology-based, nutrient-supported bone regeneration therapies.

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