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The Role of Vitamin D and Micronutrient Supplementation in Preventing Osteoporosis in Postmenopausal Women

Hanna Rzepka 1 ORCID: https://orcid.org/0009-0008-2501-7235
E-mail: haniarzepka2000@gmail.com
1. Municipial Hospital in Gliwice Zygmunta Starego 20, 44-100 Gliwice

Paweł Stępowski 2 ORCID: https://orcid.org/0009-0007-9444-4292
E-mail: pawel.stepowski@gmail.com
2. Municipial Hospital in Gliwice Zygmunta Starego 20, 44-100 Gliwice

Mateusz Tajster 3 ORCID: https://orcid.org/0009-0006-3833-6433
E-mail: mateusztajster@gmail.com
3. Municipial Hospital in Gliwice Zygmunta Starego 20, 44-100 Gliwice

Abstract

Osteoporosis is a major skeletal disorder characterised by reduced bone mineral density and deteriorating microarchitecture, imposing a considerable burden of fragility fractures on postmenopausal women worldwide (Compston, McClung and Leslie, 2019). The estrogen withdrawal that accompanies menopause accelerates bone resorption, tipping the remodelling balance toward net bone loss and increasing fracture vulnerability within the first decade after the final menstrual period (Cummings and Melton, 2002). Vitamin D, calcium, and a growing number of accessory micronutrients—including vitamin K2 and magnesium—play interrelated and mechanistically distinct roles in maintaining skeletal integrity (Capozzi, Scambia and Lello, 2020). This narrative review synthesises current evidence on the biology of bone loss after menopause, the contributions of individual micronutrients, clinical data on supplementation efficacy, diagnostic standards, management strategies, and the integration of nutritional support with pharmacologic therapy. Evidence indicates that vitamin D and calcium together modestly reduce fracture incidence and preserve bone mineral density, though benefits depend heavily on baseline nutritional status, dosing regimen, and patient adherence (Liu et al., 2020). Vitamin K2 and magnesium represent emerging adjuncts whose mechanistic rationale is compelling, although large randomised controlled trial data remain incomplete (Ma et al., 2022; Rondanelli et al., 2021). The review concludes that micronutrient optimisation is a necessary but insufficient sole strategy; it must be embedded within broader preventive and pharmacologic frameworks to achieve meaningful reductions in postmenopausal fracture risk.

Keywords: osteoporosis; postmenopausal; vitamin D; calcium; vitamin K2; magnesium; bone mineral density; fracture prevention; supplementation; micronutrients

Aim of the Work

This paper aims to provide a comprehensive, evidence-based review of the role of vitamin D and micronutrient supplementation in preventing osteoporosis among postmenopausal women. The review addresses the biological mechanisms underlying postmenopausal bone loss, the metabolic and skeletal functions of key micronutrients, the clinical evidence supporting supplementation strategies, and the diagnostic tools available to clinicians. Special attention is given to the integration of nutritional interventions with pharmacologic therapy, population-level prevention, and areas requiring further research.

Methods and Materials

This review was conducted using a structured narrative methodology consistent with PRISMA guidelines for non-systematic reviews. A comprehensive literature search was performed in PubMed, Scopus, and Web of Science for the years 2000 to 2024, supplemented by landmark studies from earlier decades where foundational. Search terms included postmenopausal osteoporosis, vitamin D supplementation, calcium and bone health, vitamin K2 and fracture, magnesium and bone mineral density, DXA and diagnosis, bisphosphonates, denosumab, teriparatide, and FRAX. Peer-reviewed original articles, systematic reviews, meta-analyses, and international clinical guidelines were included. Sources were prioritised based on methodological quality, recency, and relevance to postmenopausal populations. Data were organised thematically across biological, clinical, and public-health dimensions. Ethical approval was not required as no primary data were collected.

Introduction

Osteoporosis is a systemic skeletal disease defined by low bone mass and microarchitectural deterioration of bone tissue, resulting in enhanced bone fragility and susceptibility to fracture. It is among the most prevalent chronic conditions affecting older women globally: estimates from the International Osteoporosis Foundation suggest that one in three women over the age of fifty will sustain an osteoporotic fracture during her lifetime (International Osteoporosis Foundation, 2021). Hip fractures in particular carry substantial morbidity, with mortality rates in the twelve months following injury reaching fifteen to twenty percent, and a large proportion of survivors experiencing permanent functional limitation (Cauley, 2015).

Postmenopausal women constitute the highest-risk group for primary osteoporosis. The abrupt decline in circulating estrogen that follows the cessation of ovarian function destabilises the coupling between osteoblast-mediated bone formation and osteoclast-mediated resorption, favouring a prolonged period of net bone loss (Black and Rosen, 2016). In the first five to seven years after menopause, annual losses at the lumbar spine and femoral neck may reach two to three percent, compared with approximately 0.5 to 1.0 percent in premenopausal women (Compston, McClung and Leslie, 2019). This accelerated phase is superimposed on the slower, age-related cortical and trabecular decline that continues throughout later life (Cummings and Melton, 2002).

Nutritional factors represent modifiable determinants of bone health that operate throughout the life course. Vitamin D, the key regulator of calcium homeostasis, has long been the cornerstone

of both preventive and adjunctive therapeutic strategies (Holick et al., 2011). Calcium provides the principal mineral substrate for bone matrix mineralisation. More recently, vitamin K2 and magnesium have attracted scientific attention as important cofactors that influence bone quality beyond simple mineral content (Capozzi, Scambia and Lello, 2020). Yet despite decades of research, considerable uncertainty persists regarding optimal dosing, the conditions under which supplementation confers measurable benefit, and the extent to which nutritional intervention can substitute for or potentiate pharmacologic therapy (Bolland et al., 2015).

This review synthesises the current understanding of bone biology, the pathophysiology of postmenopausal bone loss, the roles and clinical evidence for key micronutrients, and the practical framework for assessment and management in postmenopausal women. The overarching objective is to provide clinicians and researchers with an integrated perspective on micronutrient supplementation as a component of comprehensive osteoporosis prevention (Kanis et al., 2019).

Chapter 1 – Bone Biology and Pathophysiology of Postmenopausal Osteoporosis

Bone is a metabolically active connective tissue that undergoes continuous renewal through a process of remodelling. This cycle involves the coordinated activity of osteoclasts, which resorb aged or damaged bone, and osteoblasts, which synthesise new matrix and facilitate its mineralisation. The process is tightly regulated by the RANK/RANKL/osteoprotegerin (OPG) signalling axis: RANKL, produced by osteoblasts and osteocytes, binds to its receptor RANK on osteoclast precursors, promoting their differentiation and activation. OPG, a decoy receptor secreted by osteoblasts, competes with RANK for RANKL binding, thereby limiting resorption (Khosla and Hofbauer, 2017). Under physiological conditions these forces remain in approximate balance, maintaining skeletal mass and architecture throughout adulthood (Gallagher and Sai, 2010).

The composition of bone reflects this dual activity. The organic matrix, principally type I collagen, provides tensile strength and flexibility, while the mineral phase, predominantly hydroxyapatite, confers compressive rigidity. Cortical bone, which constitutes approximately eighty percent of skeletal mass and forms the outer shell of long bones, provides structural support. Trabecular bone, concentrated in vertebral bodies, the femoral neck, and the distal radius, has a much higher surface-to-volume ratio and undergoes more rapid turnover, making it particularly vulnerable to accelerated remodelling (Compston, McClung and Leslie, 2019).

Estrogen plays a central inhibitory role in osteoclastogenesis. It suppresses RANKL expression, promotes OPG secretion, and induces apoptosis in mature osteoclasts. The precipitous fall in

estrogen at menopause removes this restraint, causing a disproportionate increase in resorption depth and resorption frequency that outpaces formation capacity (Black and Rosen, 2016). Bone turnover markers—serum carboxy-terminal collagen crosslinks (CTX) for resorption and procollagen type I N-terminal propeptide (P1NP) for formation—rise sharply in the perimenopause and remain elevated for several years before declining to a new, post-menopausal steady state (Compston, McClung and Leslie, 2019). Simultaneously, the absolute number of active osteoblasts diminishes with age, reducing the skeletal capacity for repair (Gallagher and Sai, 2010).

The architectural consequences are clinically significant. In trabecular bone, resorption leads to thinning and eventual perforation of individual trabeculae, permanently disrupting the plate-and-strut network that distributes mechanical load. Once trabecular connectivity is lost it cannot be fully restored by antiresorptive therapy, underscoring the importance of early intervention (Khosla and Hofbauer, 2017). Cortical bone loses porosity through expanded remodelling at the endosteal surface, reducing wall thickness and increasing fracture susceptibility independently of mineral density. These qualitative changes explain why fracture risk, though correlated with bone mineral density, extends well beyond what density measurements alone can predict (Cummings and Melton, 2002).

Table 1. Key Cellular and Hormonal Determinants of Bone Remodeling in Postmenopausal Women

Factor	**Cell Type / Origin**	**Effect on Bone Remodeling**	**Change at Menopause**
Estrogen	Ovarian follicles	Inhibits RANKL; promotes OPG; induces osteoclast apoptosis	Marked decrease → net resorption
RANKL	Osteoblasts / osteocytes	Drives osteoclast differentiation and activation	Relative increase after estrogen loss
OPG (osteoprotegerin)	Osteoblasts	Decoy receptor; limits osteoclastogenesis	Decreased production

PTH (parathyroid hormone)	Parathyroid glands	Mobilises calcium; stimulates resorption; anabolic at low pulsatile doses	Secondary elevation if calcium/vitamin D insufficient
IGF-1	Liver / bone	Promotes osteoblast proliferation and matrix synthesis	Declines with age
Sclerostin	Osteocytes	Inhibits Wnt signaling; suppresses bone formation	Increases with age and immobility

Chapter 2 – Assessment and Diagnosis of Osteoporosis

The clinical identification of osteoporosis relies on the integration of bone mineral density measurement, fracture history, and validated fracture risk algorithms. The World Health Organization defined osteoporosis in postmenopausal women in 1994 as bone mineral density at or below 2.5 standard deviations from the mean of a young adult reference population, expressed as a T-score of −2.5 or lower (World Health Organization, 1994). Low bone mass, or osteopenia, corresponds to T-scores between −1.0 and −2.5, representing a clinically important intermediate category that requires monitoring and lifestyle intervention even in the absence of pharmacologic treatment (Kanis et al., 2019).

Dual-energy X-ray absorptiometry (DXA) of the lumbar spine and proximal femur remains the reference standard for clinical bone densitometry. DXA delivers a low radiation dose, provides reproducible measurements, and has been validated against fracture outcomes in large epidemiological cohorts (Cooper et al., 2011). The sites measured—lumbar spine L1–L4, femoral neck, and total hip—reflect regions of high clinical relevance for vertebral and hip fractures respectively. In patients with pronounced degenerative changes at the spine, femoral neck DXA provides a more reliable estimate, as osteophytes and aortic calcification may artificially elevate lumbar readings. The distal third of the radius is assessed in specific situations, such as primary hyperparathyroidism, where cortical sites are preferentially affected (National Osteoporosis Guideline Group, 2024).

Because most fragility fractures occur in individuals whose T-score does not reach the −2.5 threshold, risk stratification tools have become indispensable. The FRAX algorithm, developed by the World Health Organization Collaborating Centre in Sheffield, integrates femoral neck BMD with ten independent clinical risk factors—including age, sex, prior fracture, parental hip fracture history, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, smoking, excessive alcohol consumption, and body mass index—to estimate the ten-year probability of major osteoporotic fracture and hip fracture (Harvey et al., 2017). Treatment thresholds vary by country and guideline, but in many settings a ten-year major fracture probability of twenty percent or above, or a hip fracture probability of three percent or above, triggers pharmacologic intervention independent of BMD classification (Kanis et al., 2019).

Laboratory evaluation complements densitometry by identifying secondary causes of bone loss and guiding treatment planning. Minimum investigations include serum calcium, phosphate, albumin, creatinine, thyroid-stimulating hormone, 25-hydroxyvitamin D, and alkaline phosphatase. Additional markers—including parathyroid hormone, serum protein electrophoresis, and urinary calcium excretion—are assessed when clinical suspicion warrants (National Osteoporosis Guideline Group, 2024). Bone turnover markers, particularly serum CTX and P1NP, are not diagnostic but provide information on the rate of skeletal remodelling and can assist in monitoring treatment response, with significant suppression of CTX observed within three months of bisphosphonate initiation (Compston, McClung and Leslie, 2019).

Table 2. WHO Diagnostic Classification of Bone Mineral Density by DXA T-Score

Category	**T-Score Range**	**Clinical Implication**
Normal	$T \geq -1.0$	Standard lifestyle measures; reassess in 5–10 years if risk factors absent
Osteopenia (low bone mass)	$-2.5 < T < -1.0$	Lifestyle and nutritional optimisation; consider FRAX; serial BMD monitoring
Osteoporosis	$T \leq -2.5$	Pharmacologic therapy indicated in conjunction with supplementation

Severe osteoporosis	T ≤ −2.5 with fragility fracture	Urgent pharmacologic treatment; anabolic agents may be first-line

Chapter 3 – Vitamin D: Metabolism and Mechanisms of Action

Vitamin D is a fat-soluble secosteroid that functions as a prohormone, requiring sequential hydroxylation steps to achieve biological activity. Cutaneous synthesis from 7-dehydrocholesterol upon ultraviolet B irradiation is the predominant source in most populations, with dietary intake—from fatty fish, fortified dairy products, and supplements—constituting a secondary but important contribution (Holick et al., 2011). The first hydroxylation occurs in the liver, converting vitamin D3 (cholecalciferol) or D2 (ergocalciferol) to 25-hydroxyvitamin D [25(OH)D], the major circulating form and the accepted measure of vitamin D status (Makris, Sempos and Cavalier, 2020). The second, rate-limiting hydroxylation takes place predominantly in the renal proximal tubule, yielding 1,25-dihydroxyvitamin D [1,25(OH)2D], or calcitriol, the hormonally active metabolite. This step is stimulated by parathyroid hormone, hypocalcemia, and hypophosphatemia, and is suppressed by fibroblast growth factor 23 (FGF-23) and high calcium and phosphate concentrations (Rosen, 2011).

Calcitriol exerts its principal genomic effects through the vitamin D receptor (VDR), a nuclear transcription factor expressed in intestinal epithelium, renal tubules, bone cells, parathyroid glands, and numerous non-skeletal tissues. In the small intestine, calcitriol upregulates calbindin and the epithelial calcium channel TRPV6, increasing transcellular calcium absorption from approximately ten to fifteen percent under deficiency conditions to thirty to forty percent under sufficiency (Holick et al., 2011). Simultaneously, it promotes intestinal phosphate transport, ensuring adequate substrate delivery for hydroxyapatite synthesis. In the kidney, calcitriol reduces urinary calcium and phosphate losses, further reinforcing positive mineral balance (Rosen, 2011).

In bone, calcitriol has biphasic and context-dependent effects. At physiological concentrations it supports osteoblast differentiation and mineralisation through induction of osteocalcin, osteopontin, and alkaline phosphatase expression. At supraphysiological concentrations, or when serum calcium falls, it can stimulate RANKL expression and osteoclastic resorption as a mechanism to mobilise skeletal calcium stores. This duality underscores the importance of

maintaining calcitriol within an optimal range rather than simply maximising its concentration (Tella and Gallagher, 2014). Vitamin D also modulates parathyroid gland function by suppressing PTH gene transcription, thus attenuating the secondary hyperparathyroidism that accelerates bone turnover in deficient individuals (Holick et al., 2011).

Among postmenopausal women, vitamin D insufficiency is highly prevalent and compounded by multiple age-related factors: reduced cutaneous synthesis due to decreased 7-dehydrocholesterol in ageing skin, limited sun exposure due to mobility restriction or geographical latitude, decreased intestinal absorption, and impaired renal 1-alpha hydroxylation (Rosen, 2011). Serum 25(OH)D below 50 nmol/L (20 ng/mL) is conventionally classified as deficiency, while insufficiency spans 50–75 nmol/L (20–30 ng/mL). Most guidelines recommend targeting concentrations above 75 nmol/L (30 ng/mL) for optimal skeletal benefit in older adults, though some evidence suggests concentrations above 100 nmol/L may be required for full suppression of PTH-mediated bone resorption (Holick et al., 2011; Makris, Sempos and Cavalier, 2020).

Chapter 4 – Micronutrients in Bone Health: Calcium, Vitamin K2, Magnesium, and Others

Calcium is the most abundant mineral in the human body, with approximately ninety-nine percent residing in the skeleton as hydroxyapatite. It is the principal mineral substrate of bone matrix and also plays critical roles in neuromuscular transmission, vascular tone, and intracellular signalling. Adequate calcium intake throughout life is a prerequisite for achieving peak bone mass during adolescence and for limiting bone loss after menopause (Capozzi, Scambia and Lello, 2020). Current guidelines recommend 1,000–1,200 mg per day of elemental calcium for postmenopausal women, ideally from dietary sources—including dairy products, fortified plant milks, leafy green vegetables, and legumes—supplemented as necessary to close dietary gaps (Kanis et al., 2019). Calcium absorption is saturable and inversely related to dose; doses of 500 mg or less are absorbed more efficiently than larger single doses, which has practical implications for supplement scheduling (Tella and Gallagher, 2014).

The relationship between calcium supplementation and cardiovascular safety has generated considerable debate since a widely-publicised meta-analysis raised concerns about increased myocardial infarction risk with calcium supplements used independently of vitamin D (Bolland et al., 2015). Subsequent analyses, including data from the Women's Health Initiative, have not consistently replicated this signal, and most major guidelines continue to endorse calcium supplementation as safe within recommended ranges, particularly when taken with food and

alongside vitamin D (Rossouw et al., 2002). Calcium supplementation alone, however, is no longer recommended as a fracture prevention strategy in the general postmenopausal population; its primary utility is as an adjunct to pharmacologic therapy or to correct frank dietary deficiency (National Osteoporosis Guideline Group, 2024).

Vitamin K2, comprising the menaquinone family (notably MK-4 and MK-7), is an essential cofactor for the gamma-carboxylation of osteocalcin, a bone matrix protein synthesised by osteoblasts. Carboxylated osteocalcin binds hydroxyapatite with high affinity, regulating crystal growth and contributing to bone matrix quality (Shearer and Newman, 2014). Undercarboxylated osteocalcin (ucOC), an accepted marker of vitamin K insufficiency, is elevated in postmenopausal women and correlates with increased fracture risk in prospective cohort data. Mechanistically, vitamin K2 also activates matrix Gla protein (MGP), which inhibits vascular and soft tissue calcification, and may attenuate RANKL-mediated osteoclastogenesis through nuclear steroid receptor pathways (Shearer and Newman, 2014). A systematic review and meta-analysis of nine randomised controlled trials found that vitamin K2 supplementation was associated with significantly increased lumbar spine and forearm BMD percentage change in postmenopausal women with osteoporosis, with MK-7 showing particularly sustained effects over three-year follow-up periods (Ma et al., 2022). The clinical use of menaquinone-4 (menatetrenone) as an approved anti-osteoporotic drug in Japan, at a dose of 45 mg daily, represents the most established pharmacological application of vitamin K2 in osteoporosis management.

Magnesium constitutes approximately fifty to sixty percent of bone mineral content, residing partly within the hydroxyapatite lattice and partly on crystal surfaces. It regulates hydroxyapatite crystal formation, and deficiency reduces bone stiffness by altering crystal structure. Magnesium also participates indirectly in vitamin D metabolism: it is a required cofactor for vitamin D hydroxylation enzymes in both the liver and kidney, and for PTH secretion and end-organ responsiveness. Magnesium deficiency can therefore impair the activation of vitamin D even when intake is adequate, creating a functional state of vitamin D resistance (Rondanelli et al., 2021). Epidemiological studies consistently associate higher dietary magnesium intake with greater bone mineral density, and clinical data, though limited by small sample sizes, suggest that magnesium supplementation may partially attenuate postmenopausal bone loss (Rondanelli et al., 2021; Capozzi, Scambia and Lello, 2020).

Additional micronutrients of emerging interest include zinc, which supports osteoblast function and collagen synthesis; silicon, implicated in the formation of the collagen matrix; and vitamin C, essential for hydroxylation of proline and lysine residues in collagen cross-linking (Capozzi,

Scambia and Lello, 2020). Protein intake, while not a micronutrient per se, warrants mention: adequate dietary protein is necessary for bone matrix synthesis and muscle mass preservation, with observational data linking higher protein intake to reduced hip fracture risk in older women. The skeletal benefit of physical activity—particularly weight-bearing and resistance exercise—complements micronutrient sufficiency by providing the mechanical loading signals that stimulate osteoblast activity through mechanotransduction pathways (Uusi-Rasi et al., 2015).

Chapter 5 – Clinical Evidence on Supplementation

The clinical evidence base for vitamin D and calcium supplementation in postmenopausal osteoporosis is extensive but heterogeneous, with results varying according to baseline nutritional status, supplemental doses, outcome measures, and population characteristics. The Women's Health Initiative (WHI) Calcium and Vitamin D trial, which randomised over 36,000 postmenopausal women to 1,000 mg calcium carbonate plus 400 IU vitamin D3 daily or placebo, demonstrated a modest but statistically significant improvement in hip BMD at seven years, with a borderline non-significant reduction in hip fracture incidence (Jackson et al., 2006). Post-hoc analyses showed greater benefit in women who were vitamin D-insufficient at baseline and in those over sixty-five years of age, suggesting that supplementation is most effective in the presence of underlying deficiency (Jackson et al., 2006).

A systematic review and meta-analysis by Liu et al. (2020), pooling randomised controlled trials in postmenopausal women, reported that combined calcium and vitamin D supplementation significantly increased total BMD (standardised mean difference 0.54; 95% CI 0.23–0.85), lumbar spine BMD, and arm BMD, and significantly reduced the incidence of hip fracture (relative risk 0.86; 95% CI 0.76–0.98). Notably, the benefit for hip fracture was observed primarily in trials using dairy products fortified with both nutrients rather than isolated supplements, suggesting that food matrix effects may modulate absorption and efficacy. Conversely, a large meta-analysis of 33 randomised trials in community-dwelling older adults found no significant fracture reduction with calcium, vitamin D, or their combination versus placebo across overall populations (Bolland et al., 2015), reinforcing that supplementation benefits are most evident in deficient or institutionalised individuals rather than in generally healthy, well-nourished cohorts.

The dose and formulation of vitamin D supplementation significantly influence outcomes. Daily doses of 800–2,000 IU of cholecalciferol (vitamin D3) are generally recommended for postmenopausal women at risk of deficiency, with higher doses—up to 4,000 IU—considered

for those with documented deficiency or malabsorption syndromes (Holick et al., 2011). Vitamin D3 is consistently more effective than D2 (ergocalciferol) at raising and sustaining 25(OH)D concentrations (Makris, Sempos and Cavalier, 2020). Intermittent high-dose supplementation—such as single annual doses of 300,000–500,000 IU—has yielded paradoxical increases in fall and fracture risk in some trials, possibly due to VDR downregulation or transient suppression of active metabolites, and is no longer recommended. Regular daily or weekly dosing is preferred (Bischoff-Ferrari et al., 2009).

For vitamin K2, clinical trial evidence is most robust in Japanese populations receiving menatetrenone (MK-4, 45 mg/day), where randomised data demonstrate reductions in vertebral fracture incidence and modest preservation of lumbar BMD in postmenopausal women with osteoporosis. A three-year European trial using low-dose MK-7 (180 mcg/day) in healthy postmenopausal women showed that, while BMD differences were marginal in the first year, significant attenuation of bone loss relative to placebo emerged by year three, with improvements in age-adjusted vertebral bone strength indices (Knapen et al., 2013). A 2022 meta-analysis confirmed that vitamin K2 supplementation significantly increased lumbar spine and forearm BMD percentage change and reduced undercarboxylated osteocalcin levels in postmenopausal women with osteoporosis, supporting its role as an adjunctive supplement, though fracture reduction data outside Japan remain insufficient to establish it as a first-line preventive intervention (Ma et al., 2022).

The evidence for magnesium supplementation on fracture outcomes is largely observational and mechanistic rather than based on well-powered randomised trials. Available data suggest that supplementation may improve BMD modestly in women with low magnesium intake and that it potentiates vitamin D activation (Rondanelli et al., 2021). Combination supplementation trials incorporating calcium, vitamin D, and magnesium report synergistic effects on bone turnover markers, though definitive fracture endpoint data are lacking. In the interim, ensuring dietary magnesium adequacy (320 mg/day recommended for women over fifty) represents a reasonable clinical goal, achievable through dietary sources—nuts, seeds, whole grains, and dark leafy vegetables—with supplementation reserved for documented deficiency or high-risk groups (Capozzi, Scambia and Lello, 2020).

Chapter 6 – Clinical Management and Supplementation Strategies in Postmenopausal Women

Effective clinical management of osteoporosis in postmenopausal women requires a stratified approach that matches intervention intensity to fracture risk while ensuring fundamental

nutritional adequacy across all risk categories. For all postmenopausal women, regardless of bone density status, baseline recommendations encompass sufficient calcium intake (1,000–1,200 mg daily from diet and supplements combined), vitamin D sufficiency (targeting serum 25(OH)D above 75 nmol/L), regular weight-bearing and resistance exercise, avoidance of smoking, and moderation of alcohol intake (Kanis et al., 2019; National Osteoporosis Guideline Group, 2024). These measures provide the skeletal and muscular foundation upon which pharmacologic interventions, where required, can operate most effectively.

Vitamin D supplementation doses should be individualised based on baseline serum 25(OH)D. Women with documented deficiency (below 50 nmol/L) may require loading doses of 50,000 IU weekly for eight to twelve weeks, followed by maintenance doses of 1,500–2,000 IU daily. In women with insufficiency (50–75 nmol/L) or those at high risk due to limited sun exposure, polypharmacy, or malabsorption, maintenance doses of 800–1,500 IU daily are appropriate (Holick et al., 2011). Monitoring of serum 25(OH)D three to four months after initiating supplementation confirms adequate response and guides dose adjustment. Cholecalciferol (D3) is preferred over ergocalciferol (D2) given its superior efficacy in maintaining circulating levels. Upper tolerable intake levels of 4,000 IU daily are generally well tolerated, with toxicity (hypercalcaemia, nephrolithiasis) associated with prolonged intake exceeding 10,000 IU daily (Bischoff-Ferrari et al., 2009).

Calcium supplementation should be targeted to close the gap between dietary intake and recommended levels rather than administered uniformly. Women consuming adequate dairy and fortified foods may require little or no supplemental calcium, whereas those with restricted diets, lactose intolerance, or malabsorption may need 500–1,000 mg of supplemental elemental calcium daily. Calcium carbonate is most economical but requires gastric acid for optimal dissolution and should be taken with meals; calcium citrate is preferred in women using proton pump inhibitors or with achlorhydria, as it does not depend on acid for absorption (Tella and Gallagher, 2014). Doses exceeding 500 mg should be divided to maximise absorption efficiency.

Vitamin K2 supplementation at doses of 180 mcg/day (MK-7 form) may be considered as an adjunct in postmenopausal women with low dietary vitamin K intake, particularly those consuming limited green leafy vegetables or fermented soy products (Knapen et al., 2013; Ma et al., 2022). The principal contraindication is concurrent warfarin anticoagulation, as vitamin K directly opposes the drug's mechanism of action. For women on anticoagulants, any consideration of vitamin K2 supplementation requires haematological review and dose adjustment. Magnesium supplementation, typically as magnesium citrate or glycinate at 250–

400 mg daily, may be beneficial in women with serum magnesium below 0.75 mmol/L or with diets low in whole grains, nuts, and seeds (Rondanelli et al., 2021).

Patient education is an integral but often underutilised component of supplementation management. Many postmenopausal women associate osteoporosis exclusively with pharmacologic treatment, unaware that sub-optimal vitamin D and calcium status substantially diminishes the efficacy of antiresorptive agents (Siris et al., 2014). Structured consultations that address dietary sources, correct supplement timing, and the rationale for combined nutritional and pharmacologic approaches improve adherence and long-term outcomes. Follow-up DXA scanning at one to three years and periodic reassessment of serum 25(OH)D, calcium, and bone turnover markers enable treatment adjustment and provide objective evidence of treatment response that reinforces patient engagement (National Osteoporosis Guideline Group, 2024).

Table 3. Summary of Recommended Micronutrient Supplementation Strategies in Postmenopausal Women

Micronutrient	**Daily Target Intake**	**Preferred Form**	**Key Clinical Notes**
Vitamin D	800–2,000 IU (maintenance) Up to 4,000 IU if deficient	Cholecalciferol (D3)	Monitor serum 25(OH)D; avoid bolus high-dose regimens; target >75 nmol/L
Calcium	1,000–1,200 mg total (diet + supplement)	Carbonate (with meals) or Citrate (with PPIs)	Fill dietary gap only; divide doses ≤500 mg; reassess if renal stones or CVD risk
Vitamin K2	180 mcg (MK-7 form)	Menaquinone-7 (MK-7)	Contraindicated with warfarin; consult haematology if anticoagulated
Magnesium	320 mg (dietary target) 250–400 mg	Magnesium citrate or glycinate	Supports vitamin D activation; check serum levels if symptomatic

	supplemental if deficient		

Chapter 7 – Integration with Pharmacologic Therapy

Micronutrient supplementation and pharmacologic osteoporosis therapy are not competing alternatives but complementary components of a unified treatment strategy. All major clinical guidelines—including the European guidance from ESCEO and the IOF, as well as the NOGG—explicitly recommend that calcium and vitamin D be used as adjuncts to all pharmacologic osteoporosis therapies, as adequate nutritional status is a prerequisite for optimal drug efficacy and safety (Kanis et al., 2019; National Osteoporosis Guideline Group, 2024).

Bisphosphonates—including alendronate, risedronate, and zoledronic acid—are the first-line pharmacologic therapy for most postmenopausal women with osteoporosis requiring treatment across European healthcare systems, including Poland. They inhibit farnesyl pyrophosphate synthase within osteoclasts, disrupting the mevalonate pathway, inducing osteoclast apoptosis, and substantially reducing bone resorption (Khosla and Hofbauer, 2017). Oral alendronate (70 mg weekly) and risedronate (35 mg weekly) are widely reimbursed and remain the most commonly prescribed agents. Intravenous zoledronic acid (5 mg annually) offers equivalent efficacy with superior adherence in patients intolerant of oral preparations. Pivotal trials demonstrate thirty to fifty percent reductions in vertebral fracture risk and twenty to forty percent reductions in hip fracture risk (Compston, McClung and Leslie, 2019). Vitamin D and calcium adequacy is essential during bisphosphonate therapy: hypocalcaemia is a recognised complication of intravenous zoledronic acid in vitamin D-deficient patients, and inadequate calcium availability limits the mineralisation of newly formed bone matrix (Kanis et al., 2019).

Denosumab, a fully human monoclonal antibody targeting RANKL, represents an important alternative for patients intolerant of bisphosphonates and for those with chronic kidney disease. By directly inhibiting RANKL, it prevents osteoclast formation and function across all skeletal sites, producing larger and more consistent BMD gains over three to ten years (Khosla and Hofbauer, 2017). Its principal limitation is the rebound increase in bone turnover that follows discontinuation, which can produce rapid BMD loss and an elevated risk of multiple vertebral fractures; transition to a bisphosphonate is therefore mandatory when denosumab is stopped (Compston, McClung and Leslie, 2019). Vitamin D and calcium supplementation during

denosumab therapy are universally recommended and reduce the risk of symptomatic hypocalcaemia, particularly in the weeks following each injection (Kanis et al., 2019).

Raloxifene, a selective oestrogen receptor modulator (SERM), merits mention in the European and Polish context as it is reimbursed and widely used in postmenopausal women who cannot tolerate bisphosphonates or for whom they are contraindicated. It reduces vertebral fracture risk by approximately thirty percent and carries the additional benefit of reducing invasive breast cancer risk. Its use is limited by an increased risk of venous thromboembolism and the absence of proven hip fracture reduction, making patient selection important (Black and Rosen, 2016). As with all pharmacologic agents, calcium and vitamin D sufficiency is required for optimal effect (Kanis et al., 2019).

Anabolic agents—teriparatide (recombinant PTH 1-34) and romosozumab (a monoclonal antibody against sclerostin with dual anabolic and antiresorptive action)—are reserved for women at very high fracture risk, including those with multiple vertebral fractures or those who have failed antiresorptive therapy. Teriparatide demonstrated a sixty-five percent reduction in vertebral fracture risk and a fifty-three percent reduction in non-vertebral fracture risk in a landmark randomised trial in postmenopausal women with osteoporosis (Neer et al., 2001). Per ESCEO-IOF recommendations, patients at very high fracture risk are increasingly directed to anabolic therapy first, as it produces larger and more rapid BMD gains than antiresorptives, which can then be used in consolidation (Kanis et al., 2019). Adequate vitamin D and calcium status is particularly important during anabolic therapy, as the accelerated bone formation stimulated by these agents places heightened demands on circulating calcium and mineralisation processes (Holick et al., 2011).

The concept of sequential therapy has gained prominence as understanding of long-term pharmacologic management has evolved. Anabolic agents are most effective when administered before antiresorptive therapy, as the rapid BMD gains they produce are consolidated and maintained by subsequent bisphosphonate use (Khosla and Hofbauer, 2017). Patient adherence to long-term pharmacologic regimens remains a major clinical challenge: studies show that up to fifty percent of patients discontinue bisphosphonate therapy within the first year, substantially increasing fracture risk (Siris et al., 2014). Regardless of the sequence or agent chosen, micronutrient optimisation remains a constant requirement and represents the one component of osteoporosis management that carries no risk of serious adverse events when appropriately dosed.

Chapter 8 – Prevention, Public Health, and Future Research Directions

The public health burden of postmenopausal osteoporosis is immense and growing as populations age. Globally, osteoporosis-related fractures affect an estimated 8.9 million people annually, with vertebral and hip fractures carrying the highest costs in terms of mortality, disability, and healthcare utilisation (Cauley, 2015). Despite available preventive and therapeutic tools, a substantial treatment gap persists: fewer than twenty-five percent of postmenopausal women diagnosed with osteoporosis after a fragility fracture receive appropriate pharmacologic treatment within twelve months of fracture, a phenomenon known as the secondary fracture prevention gap (Siris et al., 2014).

Prevention must begin before clinical osteoporosis develops. Maximising peak bone mass during adolescence and early adulthood through adequate calcium, vitamin D, and protein intake, combined with regular weight-bearing physical activity, creates the largest possible skeletal reserve against which menopausal and age-related bone loss operates (Cooper et al., 2011). Public health initiatives targeting adolescent nutrition, particularly in populations with low dairy consumption or limited sun exposure, represent cost-effective long-term investments in skeletal health. During the perimenopause, proactive screening of vitamin D and calcium status—and correction of deficiencies identified—can attenuate the accelerated bone loss of the early postmenopausal years (Kanis et al., 2019).

Population-level screening strategies for osteoporosis remain inconsistently implemented across healthcare systems. Most guidelines recommend DXA screening beginning at age sixty-five for all women, with earlier screening recommended for postmenopausal women under sixty-five who have additional risk factors as determined by validated tools such as FRAX or the Osteoporosis Self-Assessment Tool (Harvey et al., 2017; National Osteoporosis Guideline Group, 2024). Fracture Liaison Services (FLS), which systematically identify and manage patients presenting with fragility fractures, have demonstrated reductions of up to forty percent in secondary fracture rates and represent one of the most evidence-supported models of organised osteoporosis care (Cauley, 2015).

Food fortification represents a scalable approach to improving population vitamin D and calcium status. Mandatory fortification of staple foods—flour, milk, and breakfast cereals—has substantially reduced vitamin D deficiency in countries such as Finland, Canada, and the United States, with measurable effects on fracture rates at the population level (Bischoff-Ferrari et al., 2009). Extending fortification to a broader range of foods, and expanding mandatory

fortification to regions with high burden of vitamin D insufficiency, represents an important and underutilised public health lever (Rosen, 2011).

Several areas require further research to optimise micronutrient strategies in postmenopausal osteoporosis. First, the optimal threshold for serum 25(OH)D in relation to skeletal outcomes remains debated, with some evidence suggesting benefits plateau beyond 75 nmol/L while others support higher targets (Holick et al., 2011). Well-powered randomised trials correlating specific serum levels with fracture endpoints—rather than BMD surrogates—are needed. Second, vitamin K2 fracture reduction data outside the Japanese population are insufficient to support universal recommendation; large multicentre European and North American trials are required (Ma et al., 2022). Third, the interaction between gut microbiome composition and nutrient absorption, including calcium, magnesium, and vitamin K, represents an emerging frontier: microbiome modulation through diet or probiotics may offer novel approaches to improving micronutrient bioavailability. Fourth, personalised supplementation guided by genetic polymorphisms in the VDR, CYP2R1, and GC genes may explain inter-individual variability in response to vitamin D supplementation and could allow more precise targeting of dosing (Watts et al., 2012).

From a pharmacoeconomic perspective, the cost-effectiveness of vitamin D and calcium supplementation as adjuncts to pharmacologic therapy in high-risk postmenopausal women is well established. Studies consistently demonstrate favourable cost-benefit ratios compared with no supplementation, driven principally by reductions in hip fracture hospitalisation costs (Cauley, 2015). Extending cost-effectiveness analyses to include broader micronutrient combinations—particularly vitamin K2 and magnesium—as integral components of supplementation regimens would inform the development of evidence-based combination products and prescribing frameworks.

Conclusion

Postmenopausal osteoporosis represents one of the most prevalent and clinically consequential chronic diseases of older women, arising from the intersection of estrogen withdrawal, ageing skeletal biology, and modifiable nutritional and lifestyle factors (Cummings and Melton, 2002; Compston, McClung and Leslie, 2019). Vitamin D and calcium have occupied the centre of nutritional management for decades, supported by a substantial evidence base demonstrating their roles in preserving bone mineral density and, under conditions of deficiency, reducing fracture incidence (Jackson et al., 2006; Liu et al., 2020). Their efficacy is greatest when used

to correct genuine nutritional gaps and as adjuncts to pharmacologic therapy, rather than as standalone interventions in nutritionally replete populations (Bolland et al., 2015).

Vitamin K2 and magnesium represent mechanistically credible and clinically promising adjuncts whose routine incorporation into supplementation regimens is supported by emerging data, even as definitive large-scale fracture endpoint trials remain incomplete (Ma et al., 2022; Rondanelli et al., 2021). Together with adequate protein intake, physical activity, and avoidance of tobacco and excess alcohol, these micronutrients form the nutritional scaffold upon which pharmacologic osteoporosis therapy achieves its full potential (Uusi-Rasi et al., 2015).

Diagnosis rests on DXA-based BMD measurement interpreted within the WHO T-score framework and contextualised by FRAX-derived absolute fracture risk (World Health Organization, 1994; Harvey et al., 2017). Pharmacologic therapy—led by bisphosphonates and, in selected patients, denosumab, teriparatide, or romosozumab—substantially reduces fracture risk and should be initiated without delay in women who meet treatment thresholds (Neer et al., 2001; Khosla and Hofbauer, 2017). Micronutrient sufficiency must be assured in all patients receiving pharmacologic therapy, as it is a prerequisite for treatment safety and efficacy rather than an optional add-on (Kanis et al., 2019).

The persistent gap between diagnosis and treatment, and between current population-level vitamin D status and target concentrations in most parts of the world, represents the primary obstacle to reducing the global burden of osteoporotic fractures (Cauley, 2015; Siris et al., 2014). Addressing this gap requires coordinated action across clinical practice, public health policy, food fortification programmes, and patient education. Future research into personalised supplementation strategies, microbiome-nutrient interactions, and the long-term skeletal effects of combination micronutrient regimens will refine the precision with which nutritional interventions can be deployed. Recognising micronutrient optimisation not as a peripheral concern but as a fundamental pillar of postmenopausal skeletal health is essential to achieving meaningful progress in fracture prevention

Author’s Contribution:

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AI

Artificial intelligence tools were used in this study in two main capacities. First, they supported the analysis of clinical reasoning narratives by identifying recurring linguistic patterns associated with specific logical fallacies, while also assisting in the organization and preprocessing of the dataset to streamline the analytical workflow. Second, they contributed to refining the manuscript's academic language, improving clarity, precision, and adherence to established standards of scientific writing.

Throughout the study, AI functioned exclusively as a supportive instrument under continuous human supervision. The interpretation of results, the classification of reasoning errors, and the formulation of conclusions were carried out solely by experts in clinical medicine and formal logic. AI was employed only to enhance efficiency in tasks such as data handling, pattern recognition, and language editing, and it did not replace human judgment at any stage of the research process.

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