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# MOLECULAR MECHANISMS OF OSTEOTROPIC MICRONUTRIENTS IN BONE HEALING: SIGNALING PATHWAYS, REDOX HOMEOSTASIS, AND MATRIX MATURATION

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**ABSTRACT**
Delayed union and non-union complicate a substantial minority of fractures and are strongly associated with ageing and metabolic comorbidity, motivating close scrutiny of the biological factors that determine repair. Micronutrients have traditionally been regarded as passive structural raw materials, yet accumulating evidence shows that they act as direct molecular modulators of the healing cascade. This review reframes osteotropic micronutrients as regulators positioned along the four phases of bone repair (inflammation, soft callus, hard callus, and remodelling) and interprets their actions through a unifying three-axis framework: regulation of osteogenic and osteoclastic signalling, enzymatic support of collagen matrix synthesis and cross-linking, and preservation of redox homeostasis. Within this framework we examine the macrominerals (Ca, P, Mg), essential trace metals (Zn, Cu, Mn, Fe), redox-active and structural trace elements (Se, Sr, B, Si, F), and osteotropic vitamins (D, K, C), mapping each onto specific molecular targets, from RUNX2 and lysyl oxidase to the glutathione peroxidases and γ-glutamyl carboxylase. We then analyse the synergies, antagonisms, and characteristic deficiency signatures that arise as these nutrients converge on shared enzymatic and redox hubs, underscoring that their effects are dose-dependent, ratio-sensitive, and phase-specific rather than simply additive. Finally, we consider the translational implications for bioavailability and for phase-matched, multi-element delivery systems, including biopolymer-stabilised nanocarriers, that may convert this mechanistic understanding into nutrition-based adjuncts to fracture management.

**KEYWORDS:** Bone regeneration; Trace elements; Osteogenic signalling; Redox homeostasis; Collagen cross-linking; Osteoblast differentiation; Ion delivery systems

## 1. INTRODUCTION

Bone possesses a remarkable and largely unique capacity for self-repair, yet this capacity is neither unconditional nor uniform across patients. A substantial minority of fractures fail to consolidate: pooled data place the prevalence of tibial non-union near 7 % [1], and for long-bone fractures the figure rises to an estimated 10–15 % [2]. The risk increases sharply with age and metabolic comorbidity, with older age and type 2 diabetes among the most consistently reported patient-level predictors of non-union [3]. Impaired healing carries a disproportionate clinical and economic cost, driving repeated interventions, prolonged immobilisation, and loss of function. Against this background, the biological determinants that tip the balance between successful and failed repair have attracted intense mechanistic scrutiny.

Bone healing is not a single event but an orchestrated, temporally staged cascade, haematoma and inflammation, soft (cartilaginous) callus formation, hard (bony) callus formation, and remodeling, each governed by discrete molecular programmes [4]. Canonical Wnt/β-catenin and BMP/Smad signalling drive osteoprogenitor commitment, while parallel FGF, VEGF, and Notch inputs coordinate progenitor recruitment and vascular ingrowth [5]; suppression of BMP signalling and dysregulation of Wnt and matrix metalloproteinase pathways are, correspondingly, molecular hallmarks of non-union [2]. Superimposed on these pathways are two pervasive requirements that are easily overlooked: the enzymatic machinery of matrix synthesis and cross-linking, and the maintenance of redox homeostasis in a microenvironment in which excess reactive oxygen species disrupt the osteoblast–osteoclast balance and delay repair [6].

It is precisely at these three intersections, signalling, matrix maturation, and redox balance, that micronutrients exert their influence. Traditionally, elements such as calcium and phosphorus have been framed as passive

structural raw materials, and trace elements and vitamins as ancillary "supporting actors," yet minerals are increasingly recognised as active regulators of skeletal physiology whose deficiency directly impairs bone formation and wound healing [7]. Zinc, for example, is a structural cofactor for numerous zinc-finger transcription factors and metalloenzymes central to osteoblast function [8,9]; vitamin K γ-carboxylates osteocalcin and matrix Gla protein, the calcium-binding proteins that couple mineral deposition to matrix quality [10]; and a broader set of trace elements, copper, iron, and selenium among them, serve as obligatory cofactors for collagen cross-linking, matrix hydroxylation, and antioxidant defence [11]. Far from being inert, osteotropic micronutrients are direct molecular modulators of the healing programme [12].

Despite a substantial literature, existing reviews are predominantly organised element-by-element and centred on systemic deficiency or dietary intake, and the evidence base for nutrition in fracture repair remains heterogeneous and largely preclinical [11]. How individual nutrients map onto specific phases and nodes of the repair cascade, how their actions converge on shared enzymatic and redox hubs, and how these insights might be translated through bioavailability-oriented delivery strategies remain fragmented across disciplines.

This review addresses that gap by reframing osteotropic micronutrients not as a catalogue of elements but as modulators positioned along the healing cascade. We adopt a unifying three-axis framework, (i) regulation of osteogenic and osteoclastogenic signalling, (ii) enzymatic support of collagen matrix synthesis and cross-linking, and (iii) preservation of redox homeostasis, and use it to interpret the macrominerals (Ca, P, Mg), essential trace metals (Zn, Cu, Mn, Fe), redox-active and structural trace elements (Se, Sr, B, Si, F), and osteotropic vitamins (D, K, C) (Table 1). We then examine the cross-talk, synergies, and deficiency signatures that arise when these nutrients converge on common molecular targets, and close with a translational perspective on chemical speciation, bioavailability, and emerging biopolymer-stabilised delivery systems.

**Table 1. Classification of osteotropic micronutrients: reference intakes, principal dietary sources, and bone-specific functions**

| Micronutrient | Category | Adult reference intake (RDA/AI)† | Principal dietary sources | Bone-specific function |
|---|---|---|---|---|
| Calcium (Ca) | Macromineral | 1000 mg (1200 mg if >70 y) | Dairy, leafy greens, fortified foods | Hydroxyapatite substrate; CaSR signalling |
| Phosphorus (P) | Macromineral | 700 mg | Meat, dairy, whole grains, nuts | Hydroxyapatite ($PO_4^{3-}$); ALP-liberated Pi trigger |
| Magnesium (Mg) | Macromineral | 310–420 mg | Green vegetables, legumes, nuts, whole grains | Apatite-lattice substitution; osteoblast adhesion; PTH modulation |
| Zinc (Zn) | Essential trace metal | 8–11 mg | Meat, shellfish, legumes, seeds | RUNX2 co-factors, ALP; inhibits osteoclastogenesis |
| Copper (Cu) | Essential trace metal | 900 µg | Shellfish, organ meats, nuts, seeds | Lysyl oxidase cross-linking; HIF/VEGF angiogenesis |
| Manganese (Mn) | Essential trace metal | 1.8–2.3 mg | Whole grains, nuts, leafy greens, tea | Glycosyltransferases (proteoglycans); Mn-SOD |
| Iron (Fe) | Essential trace metal | 8 mg (18 mg, women 19–50 y) | Red meat, legumes, fortified cereals, greens | Prolyl/lysyl & HIF hydroxylases; ferroptosis in excess |
| Selenium (Se) | Redox-active trace element | 55 µg | Brazil nuts, seafood, organ meats, cereals | Selenoproteins (GPx, TrxR); antioxidant defence |
| Strontium (Sr) | Structural trace element | No formal RDA (~1–5 mg intake) | Seafood, whole grains, root vegetables, dairy | Dual action: ↑ osteoblasts, ↓ osteoclasts (CaSR) |
| Boron (B) | Structural trace element | No formal RDA (~1–3 mg; UL 20 mg) | Fruits (apple, pear), nuts, legumes, greens | Modulates vitamin D & steroid-hormone metabolism |
| Silicon (Si) | Structural trace element | No formal RDA (~20–50 mg intake) | Whole grains, cereals, some vegetables, beer | Collagen synthesis/cross-linking; early calcification |
| Fluoride (F) | Structural trace element | 3–4 mg (AI) | Fluoridated water, tea, marine fish | Fluorapatite formation; brittle bone in excess |

| | | | | |
|---|---|---|---|---|
| Vitamin D | Osteotropic vitamin | 15 µg / 600 IU (20 µg if >70 y) | Fatty fish, egg yolk, fortified foods, sunlight | VDR-directed osteoblast differentiation & mineralisation |
| Vitamin K | Osteotropic vitamin | 90–120 µg (AI) | Leafy greens (K1); fermented foods/natto (K2) | γ-carboxylation of osteocalcin & matrix Gla protein |
| Vitamin C | Osteotropic vitamin | 75–90 mg | Citrus, berries, peppers, leafy vegetables | Collagen hydroxylation; epigenetic osteogenic priming; antioxidant |

**Notes**. † Adult values; ranges reflect sex-specific RDA (or AI where an RDA is not established), per standard dietary reference intakes. Strontium, boron, and silicon have no formal RDA and are given as typical dietary intakes.

**2. The bone healing cascade: a molecular primer**

Postnatal bone repair is a regenerative rather than reparative process that partly recapitulates embryonic skeletogenesis, proceeding through two ossification routes, intramembranous ossification adjacent to rigidly stabilised cortices and endochondral ossification within the mobile callus, and unfolding across four overlapping phases: haematoma/inflammation, soft (cartilaginous) callus, hard (bony) callus, and remodelling [4,5]. The same developmental signalling modules, Wnt, TGF-β/BMP, FGF, VEGF, and Notch, are redeployed at each phase, which is why perturbation of any single module can derail the entire trajectory [5].

The inflammatory phase begins with haematoma formation and a burst of pro-inflammatory cytokines, including interleukin-1, interleukin-6, and tumour necrosis factor-α, which recruit neutrophils and monocyte-derived macrophages. This early inflammation is indispensable for initiating repair, yet its role is strictly biphasic: a timely switch from pro-inflammatory (M1) to reparative (M2) macrophage phenotypes is required, and failure to resolve inflammation shifts the balance toward osteoclastic bone loss and delayed union [13].

As inflammation resolves, mesenchymal progenitors are recruited and commit along chondrogenic or osteogenic lineages. In the endochondral route, a SOX9-driven cartilaginous template is progressively replaced by bone. Osteogenic commitment is governed by the master transcription factors RUNX2 and Osterix, acting downstream of canonical Wnt/β-catenin and BMP/Smad signalling; Wnt/β-catenin activity simultaneously couples osteoblast differentiation to vascular ingrowth [14], whereas suppression of BMP signalling and elevation of its antagonists Noggin and Gremlin are molecular signatures of failed healing [2]. Osteoblasts then deposit a type I collagen matrix and express alkaline phosphatase, priming the scaffold for mineralisation.

Mineralisation and callus maturation are critically dependent on vascularisation. A specialised capillary subtype, type H vessels, physically and molecularly couples angiogenesis to osteogenesis through HIF-1α, VEGF, PDGF-BB, and Notch signalling, delivering oxygen, minerals, and osteoprogenitors to the mineralising front [15]. Hypoxia-driven HIF-1α stabilisation is thus a central sensor linking the vascular and skeletal compartments.

The final remodelling phase reshapes woven bone into mechanically competent lamellar bone through coordinated osteoclast resorption and osteoblast formation. This coupling is governed by the RANKL/RANK/OPG axis, in which the RANKL-to-OPG ratio sets the tempo of resorption, and is further tuned by systemic regulators such as parathyroid hormone acting through Wnt and RANKL/RANK/OPG pathways [16]. Together these four phases define the molecular map onto which osteotropic micronutrients are superimposed in the sections that follow (Fig. 1), acting at three recurring intersections: osteogenic/osteoclastic signalling, collagen matrix maturation, and redox balance.

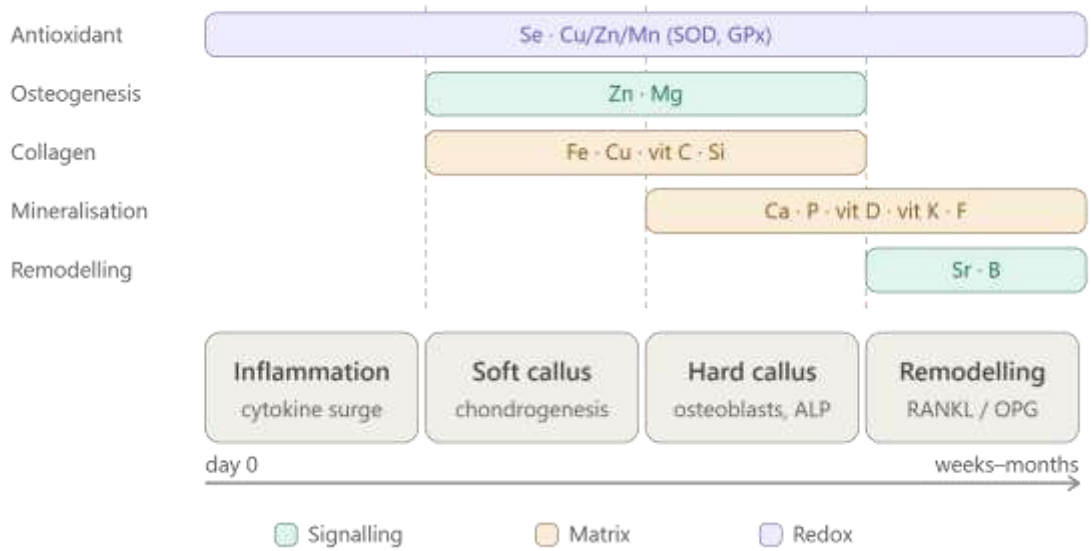


**Figure 1. The temporal map that anchors: the four healing phases along the bottom, with each nutrient group drawn as a lane spanning the phases where it is molecularly most active, colour-keyed to the three axes.**

**3. Macrominerals: calcium, phosphorus, and magnesium**

The macrominerals constitute the bulk of the bone mineral phase, yet their contribution to healing extends well beyond bulk supply. Calcium and inorganic phosphate co-precipitate as carbonated hydroxyapatite on the collagen scaffold laid down during hard-callus formation, and the local ionic product of $Ca^{2+}$ and Pi is a direct determinant of the rate and quality of mineral nucleation [18]. Calcium additionally acts as a signalling ion: extracellular $Ca^{2+}$ sensed through the calcium-sensing receptor modulates osteoblast proliferation, chemotaxis, and survival, coupling mineral availability to the anabolic activity of the mineralising front, while systemic $Ca^{2+}$ homeostasis governed by parathyroid hormone and 1,25-dihydroxyvitamin D ensures that resorption and formation remain balanced during remodelling [7,18].

Phosphorus is equally bifunctional. As orthophosphate it is a stoichiometric constituent of hydroxyapatite, and alkaline phosphatase-liberated Pi at the osteoblast surface is a proximal trigger of matrix mineralisation. At the systemic level, phosphate balance is maintained by the gut–bone–parathyroid–kidney axis, in which the bone-derived phosphatonin FGF23, acting with its co-receptor α-Klotho, suppresses renal sodium-dependent phosphate cotransporters (NaPi-2a/2c) and 1,25-dihydroxyvitamin D synthesis; dysregulation of this axis produces the mineralisation defects of hypophosphataemic rickets and osteomalacia [19]. Phosphate is, however, not innocuous in excess: elevated extracellular Pi drives abnormal cell signalling and oxidative stress that are cytotoxic to bone and vascular cells, underscoring that a physiological, not maximal, Ca/Pi supply supports optimal repair [20].

Magnesium, the fourth most abundant cation in the body, occupies a distinct mechanistic niche. Roughly half of total body magnesium resides in bone, where $Mg^{2+}$ substitutes into the hydroxyapatite lattice and modulates crystal size, maturation, and solubility; adequate magnesium yields smaller, more soluble, biologically remodellable crystals, whereas deficiency produces larger, more brittle mineral [21]. Beyond its structural role, $Mg^{2+}$ is a cofactor for ATP-dependent reactions, influences integrin-mediated osteoblast adhesion, and participates in PTH secretion and action, so that magnesium deficiency impairs both mineralisation and the hormonal control of bone turnover [7,18]. These properties make magnesium a recurring design element in degradable Mg-based fixation implants, whose controlled ion release can locally stimulate osteogenesis.

Together, the macrominerals illustrate the central theme of this review: even the classical "building-block" elements act simultaneously as matrix constituents and as signalling agents, and their effects on healing are dose-dependent and homeostatically constrained rather than simply additive (Table 2).

**Table 2. Molecular targets of osteotropic macro-, and micronutrients across the healing cascade**

| Element | Main healing phase | Molecular target / pathway | Effect | Axis | Key refs |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| $Ca^{2+}$ | Hard callus, remodelling | Hydroxyapatite nucleation; calcium-sensing receptor; PTH/1,25-D homeostasis | ↑ mineralisation; ↑ osteoblast proliferation & survival | Matrix, signalling | [18,7] |
| Pi (P) | Hard callus | Hydroxyapatite ($PO_4^{3-}$); ALP-liberated Pi; FGF23–α-Klotho / NaPi-2a/2c | ↑ physiological mineralisation; ↓ osteogenesis & ↑ oxidative stress when in excess | Matrix, signalling | [19,20] |
| $Mg^{2+}$ | Soft → hard callus | Hydroxyapatite lattice substitution; integrin-mediated adhesion; ATP cofactor; PTH modulation | ↑ crystal quality & remodellability; ↑ osteoblast activity (deficiency → brittle mineral) | Matrix, signalling | [18,7] |
| $Zn^{2+}$ | Hard callus, remodelling | Zinc-finger TFs (RUNX2 co-factors); ALP; MMPs; RANKL–NFATc1 | ↑ osteoblast differentiation & collagen; ↓ osteoclastogenesis | Signalling, matrix | [22,8] |
| $Cu^{2+}$ | Soft → hard callus | Lysyl oxidase (collagen/elastin cross-linking); HIF-1α/VEGF | ↑ matrix tensile strength; ↑ angiogenesis-coupled osteogenesis | Matrix, signalling | [25,22] |
| $Mn^{2+}$ | Soft callus | Glycosyltransferases (proteoglycan/GAG); integrin activation; Mn-SOD (SOD2) | ↑ cartilage template & adhesion; antioxidant protection (dose-dependent) | Matrix, redox | [25,7] |
| $Fe^{2+}$ | Soft → hard callus; angiogenesis | Prolyl/lysyl hydroxylases (collagen); HIF prolyl hydroxylases; BMP–iron cross-talk | ↑ collagen maturation & HIF tuning; ↓ osteogenesis via ferroptosis when in excess | Matrix, signalling, redox | [28,29] |
| Se | Inflammation → remodelling | Selenoproteins: GPx, thioredoxin reductase; RANKL redox signalling | ↑ antioxidant protection of osteoblasts; ↓ osteoclastogenesis; ↑ BMD | Redox | [7,32] |
| $Sr^{2+}$ | Hard callus, remodelling | Calcium-sensing receptor/Wnt; OPG↑/RANKL↓; apatite substitution | ↑ osteoblast activity; ↓ osteoclast resorption (dual action) | Signalling, matrix | [22] |
| B | Remodelling (systemic) | 25-OH-vitamin D & steroid hormone metabolism; Ca/Mg handling | ↑ BMD at low-dose supplementation (toxic in excess) | Signalling | [33] |
| Si | Soft → hard callus | Type I collagen synthesis/cross-linking; osteoblast differentiation | ↑ mineralisation & matrix maturation | Matrix | [25,34] |
| $F^-$ | Hard callus | Fluorapatite formation ($OH^-$ substitution); osteoblast proliferation | ↑ crystal stability at low dose; brittle, poorly remodelled bone in excess | Matrix | [18] |
| Vitamin D | Hard callus, remodelling | VDR (nuclear); CYP27B1 autocrine 1,25-D; intestinal Ca/Pi absorption | ↑ mineral substrate; ↑ stage-dependent osteoblast differentiation & mineralisation | Signalling, matrix | [25] |
| Vitamin K | Hard callus, remodelling | γ-glutamyl carboxylase → osteocalcin, MGP; SXR (MK-4) | ↑ mineral–matrix coupling & osteoblastogenesis; ↓ osteoclast formation & ectopic calcification | Matrix, signalling | [9] |
| Vitamin C | Soft → hard callus | Prolyl/lysyl hydroxylases; TET & | ↑ collagen maturation; epigenetic priming of | Matrix, signalling, redox | [26] |

| | | | | | |
|---|---|---|---|---|---|
| | | Jumonji demethylases; antioxidant | osteogenesis; redox buffering | | |

**4. Essential trace metals: zinc, copper, manganese, and iron**

Zinc is the most abundant trace element in bone and the most mechanistically versatile. Structurally, it is indispensable to the large family of zinc-finger transcription factors, several of which cooperate with RUNX2 to drive osteogenic gene expression, and it is a catalytic cofactor for alkaline phosphatase and for the matrix metalloproteinases that remodel the provisional matrix. Functionally, zinc stimulates osteoblast proliferation, differentiation, and type I collagen synthesis while simultaneously suppressing osteoclastogenesis, an effect mediated in part through dampened RANKL-driven NFATc1 signalling, so that its net action favours formation over resorption during callus maturation [22]. Because zinc cannot be stored and is tightly handled by ZIP and ZnT transporters, local availability at the fracture site depends directly on dietary intake and systemic status [8,23].

Copper's signature role in healing is enzymatic: it is the obligate cofactor of lysyl oxidase, which catalyses the covalent cross-linking of collagen and elastin fibrils that confers tensile strength on the maturing callus. A poorly cross-linked matrix, as seen in copper deficiency, yields mechanically incompetent bone regardless of adequate collagen quantity [24,25]. Copper is also strongly pro-angiogenic, it stabilises HIF-1α and promotes VEGF-driven endothelial migration, thereby coupling vascular ingrowth to osteogenesis, and copper-releasing scaffolds have been shown to accelerate bone-defect healing while creating an antioxidant, antibacterial peri-implant microenvironment [24,26]. Copper thus operates across two of the three axes simultaneously: matrix maturation and, via HIF/VEGF, signalling.

Manganese contributes principally to the earliest, cartilaginous phase of repair. It is a cofactor for the glycosyltransferases that assemble the proteoglycans and glycosaminoglycans of the soft-callus template, and $Mn^{2+}$ enhances integrin–ligand affinity, supporting osteoprogenitor adhesion and migration [27]. In parallel, manganese is the catalytic metal of mitochondrial superoxide dismutase (Mn-SOD/SOD2), a frontline antioxidant that protects differentiating osteoblasts from oxidative damage, placing manganese on the redox axis as well [7]. Its influence on osteoblast proliferation and differentiation is concentration-dependent, with supraphysiological levels becoming cytotoxic.

Iron exemplifies the double-edged nature of redox-active metals. As a cofactor, ferrous iron is required by prolyl and lysyl hydroxylases for the post-translational hydroxylation that stabilises the collagen triple helix, and by the HIF prolyl hydroxylases that set HIF-1α stability – so iron availability tunes both matrix maturation and the hypoxia-driven angiogenic response. Iron-regulatory proteins additionally intersect the BMP signalling pathway that governs both systemic iron handling and osteoblast function, linking iron and bone homeostasis at the molecular level [28]. Yet iron is a potent generator of reactive oxygen species through Fenton chemistry; iron overload promotes lipid peroxidation and ferroptotic death of osteoblasts, impairing bone formation and tilting the balance toward resorption, which is why both iron deficiency and iron excess are associated with reduced bone mineral density and fragility [29,30]. Iron therefore embodies the central tension of this review – the same chemistry that enables catalysis, in excess, becomes destructive.

Collectively, the essential trace metals act at defined nodes of the healing network rather than as generic supplements: zinc and manganese on osteoblast commitment, copper and iron on collagen cross-linking and hydroxylation, copper and iron on angiogenic signalling, and manganese, copper, and iron on redox balance. Figure 2 maps these entry points onto the core signalling architecture.

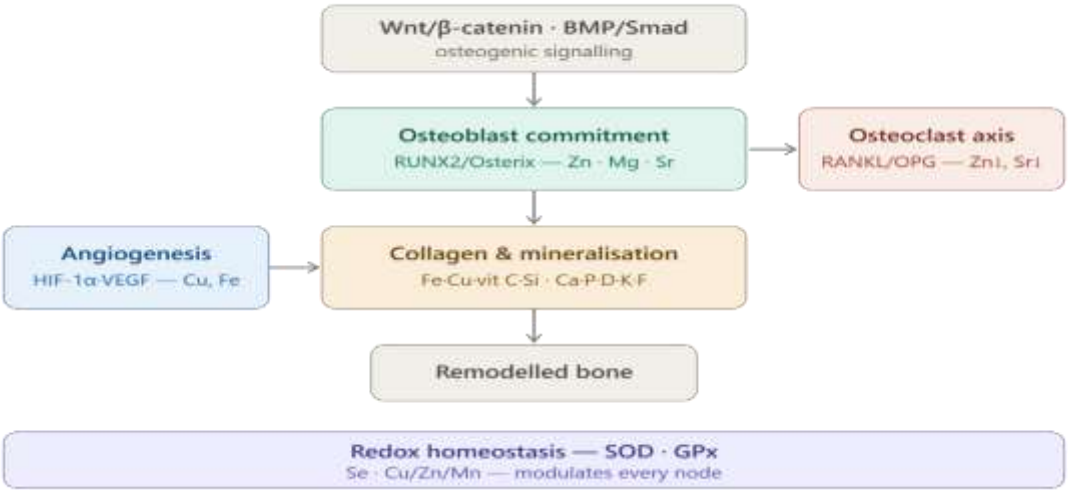


**Figure 2. Central healing signaling network with marked micronutrient entry points (according to functional modules)**

**5. Redox-active and structural trace elements: selenium, strontium, boron, silicon, and fluoride**

Selenium acts almost entirely on the redox axis. Incorporated as selenocysteine into the selenoproteins, principally the glutathione peroxidases and thioredoxin reductases, it forms the enzymatic backbone of cellular antioxidant defence, detoxifying the peroxides generated in the inflammatory and mineralising phases of repair [7,31]. By limiting oxidative damage to differentiating osteoblasts and by restraining redox-sensitive, RANKL-driven osteoclastogenesis, selenium favours net bone formation. Consistent with this mechanism, meta-analysis shows that higher dietary and serum selenium are positively associated with bone mineral density and with a lower risk of osteoporosis and hip fracture [32].

Strontium is a chemical congener of calcium and the only osteotropic element with a clinically exploited dual action: it simultaneously stimulates osteoblast replication and differentiation, partly through the calcium-sensing receptor and Wnt signaling, and suppresses osteoclast differentiation and activity by raising the OPG-to-RANKL ratio, uncoupling formation from resorption in favour of the former. It also substitutes for calcium in the apatite lattice, and strontium-functionalised scaffolds and cements are being developed to enhance defect healing on this basis [22].

Boron influences bone indirectly, chiefly by modulating the metabolism of the steroid hormones and vitamin D that themselves regulate skeletal turnover; it prolongs the biological activity of 25-hydroxyvitamin D and affects calcium and magnesium handling. Controlled supplementation on the order of a few milligrams per day is associated with improved bone mineral density, while its proposed roles in membrane integrity and cell signalling remain incompletely defined and its therapeutic window bounded by toxicity at higher intakes [33].

Silicon is concentrated at active calcification fronts in immature bone and supports the matrix axis: it promotes type I collagen synthesis and cross-linking and enhances osteoblast differentiation, so that silicon-substituted calcium phosphates and bioactive glasses accelerate mineralisation and are widely used in bone-graft substitutes [25, 34].

Fluoride is the clearest illustration of dose-dependence. By substituting for hydroxyl ions in hydroxyapatite it forms fluorapatite, larger, more acid-resistant crystals, and at low concentrations it can stimulate osteoblast proliferation. In excess, however, fluoride produces skeletal fluorosis: hypermineralised yet brittle, poorly remodelled bone of inferior mechanical quality, reinforcing that the benefit of every osteotropic element is confined to a physiological window [18].

Taken together, this group extends the two organising themes of the review beyond the classical trace metals: selenium anchors the redox axis alongside the Cu/Zn/Mn superoxide dismutases, silicon reinforces the matrix axis, strontium acts bidirectionally on the signalling axis, and boron and fluoride underscore that homeostatic dosing, not maximal supply, governs the outcome (Table 2).

**6. Osteotropic vitamins: D, K, and C**

Vitamin D is the principal endocrine regulator of the mineral substrate for healing. Its active metabolite, 1α,25-dihydroxyvitamin $D_3$, binds the nuclear vitamin D receptor (VDR) to promote intestinal calcium and phosphate absorption, securing the ionic supply on which hard-callus mineralisation depends. Crucially, its action is not purely endocrine: osteoblasts express both the activating enzyme 1α-hydroxylase (CYP27B1) and the VDR, allowing locally generated 1,25-D to act in an autocrine and paracrine manner that directs osteoblast proliferation, differentiation, and matrix mineralisation in a strictly stage-dependent fashion, with distinct gene sets regulated before versus during mineralisation [35]. Common VDR polymorphisms modulate bone mineral density and fracture risk, and deficiency produces the defective mineralisation of rickets and osteomalacia, with correspondingly impaired callus formation.

Vitamin K operates through a single, decisive biochemical step. As the cofactor for γ-glutamyl carboxylase, it enables the post-translational γ-carboxylation of the Gla proteins osteocalcin and matrix Gla protein (MGP). Carboxylated osteocalcin acquires the capacity to chelate calcium and couple mineral deposition to matrix quality and mechanical strength, while carboxylated MGP restrains inappropriate and vascular calcification; menaquinone-4 additionally acts as a ligand for the nuclear steroid and xenobiotic receptor. Through these routes vitamin K increases osteoblastogenesis and decreases osteoclast formation and activity, so that inadequate vitamin K leaves osteocalcin and MGP undercarboxylated and mineral coupling impaired [10].

Vitamin C is the most axis-spanning of the vitamins. Its classical and obligatory role is as cofactor for the prolyl and lysyl hydroxylases that hydroxylate collagen, stabilising the triple helix and enabling cross-link formation; loss of this function in scurvy collapses the integrity of bone and connective tissue. Beyond matrix chemistry, vitamin C epigenetically licenses osteoblastogenesis: as a cofactor for TET DNA dioxygenases and Jumonji-domain histone demethylases it shapes 5-hydroxymethylcytosine and histone-methylation marks at pro-osteogenic loci, and osteogenic differentiation is continuously and specifically dependent on ascorbate availability [36]. As a direct free-radical scavenger it also contributes to redox homeostasis. Vitamin C therefore acts simultaneously on all three organising axes – matrix maturation, osteogenic signalling, and redox balance.

Together, the osteotropic vitamins complete the mechanistic framework: vitamin D governs mineral-substrate supply and stage-dependent osteoblast programming, vitamin K controls Gla-protein-mediated coupling of mineral to matrix, and vitamin C bridges collagen chemistry, epigenetic priming, and antioxidant defence. With

these entries, every micronutrient class considered in this review can be located on the shared molecular map of the healing cascade (Table 2).

**7. Cross-talk, synergy, and deficiency signatures**

The preceding sections treated each micronutrient in isolation, but their actions converge on a small number of shared molecular hubs, and it is at these hubs that synergy and antagonism emerge. Three convergences are pivotal. First, antioxidant defence is inherently multi-elemental: copper and zinc constitute cytosolic superoxide dismutase, manganese constitutes its mitochondrial isoform, and selenium powers the glutathione peroxidases, so the integrity of the entire redox axis depends on the simultaneous adequacy of all four elements, and a single deficiency weakens the whole [7]. Second, collagen maturation is a relay: iron and vitamin C together drive the prolyl and lysyl hydroxylases that stabilise the triple helix, after which copper-dependent lysyl oxidase forms the covalent cross-links – a sequential dependency in which any missing cofactor leaves the matrix mechanically incompetent [37]. Third, mineral targeting is cooperative: vitamin D mobilises calcium and phosphate, and vitamin K then carboxylates osteocalcin and matrix Gla protein so that the mobilised calcium is directed into the bone matrix rather than the vasculature, making the vitamin D–vitamin K–calcium triad genuinely synergistic [9, 38].

Antagonisms are equally consequential and are usually competitive. Excess zinc induces intestinal metallothionein and thereby suppresses copper and iron uptake, so aggressive zinc supplementation can precipitate a functional copper deficiency and, with it, defective lysyl oxidase cross-linking [8]. High calcium loads competitively inhibit non-heme iron and zinc absorption, and strontium competes with calcium both at the calcium-sensing receptor and within the apatite lattice, distorting mineral quality when supplied in excess. Iron overload, by generating reactive oxygen species, directly opposes the antioxidant capacity provided by selenium and manganese [39]. The recurring lesson is that outcomes are governed by element ratios and a homeostatic window, not by maximal supply of any one nutrient (Table 3).

These relationships also explain why deficiencies produce characteristic molecular lesions rather than generic weakness (Table 4): copper deficiency yields poorly cross-linked matrix, vitamin C deficiency unhydroxylated collagen (scurvy), vitamin D deficiency hypomineralised osteoid (osteomalacia), selenium deficiency oxidative osteoblast damage, and zinc deficiency impaired RUNX2-dependent differentiation [7,15]. In elderly and multimorbid patients, precisely those at highest risk of non-union, several subclinical deficiencies frequently coexist, and their molecular defects compound, degrading healing far more than any single shortfall would predict. This integrated, ratio-sensitive picture provides the rationale for the delivery strategies considered next.

**Table 3. Principal synergies and antagonisms among osteotropic micronutrients**

| Interaction | Elements | Molecular basis | Net effect | Refs |
|---|---|---|---|---|
| Redox defence | Cu + Zn + Mn + Se | Cu/Zn-SOD, Mn-SOD, Se-GPx act in concert | Synergistic ROS clearance | [7] |
| Collagen maturation | Fe + vitamin C + Cu | Fe/C hydroxylases → Cu-lysyl oxidase cross-linking | Synergistic (sequential) | [26,21] |
| Mineral targeting | Vitamin D + Vitamin K + Ca | D mobilises Ca/Pi; K carboxylates OCN/MGP to fix Ca in bone | Synergistic | [27,9] |
| Zn–Cu/Fe uptake | Zn vs Cu, Fe | Zn-induced metallothionein ↓ Cu/Fe absorption | Antagonistic | [8] |
| Ca–Fe/Zn uptake | Ca vs Fe, Zn | Competition for divalent-cation absorption | Antagonistic | [7] |
| Sr–Ca | Sr vs Ca | Competition at CaSR and in apatite | Antagonistic in excess | [18] |

**Table 4. Deficiency signatures on bone healing**

| Element | Molecular defect | Healing phenotype | Refs |
|---|---|---|---|
| Ca / vitamin D | Hypomineralised osteoid | Osteomalacia/rickets; weak callus | [25,15] |
| Phosphate | Insufficient apatite substrate | Defective mineralisation | [16] |
| Magnesium | Altered crystal; impaired PTH action | Brittle mineral | [15] |
| Zinc | ↓ RUNX2/ALP activity | Impaired osteoblast differentiation | [18,8] |
| Copper | ↓ lysyl oxidase cross-linking | Mechanically weak matrix | [20] |
| Iron | ↓ collagen hydroxylation (deficiency); ferroptosis (overload) | Poor matrix; ↓ osteogenesis | [21,22] |
| Selenium | ↑ oxidative osteoblast damage | Osteoblast dysfunction; ↑ resorption | [7,23] |
| Vitamin C | Unhydroxylated collagen | Scurvy; failed matrix assembly | [26] |

| | | | |
|---|---|---|---|
| Vitamin K | Undercarboxylated osteocalcin/MGP | Impaired mineral coupling; ectopic calcification | [9] |

**8. Translational perspective: bioavailability and delivery systems**

The mechanistic picture developed above has a direct practical corollary: supplying an osteotropic micronutrient is not the same as delivering it to the right place, at the right concentration, at the right phase. Orally administered micronutrients face the absorptive competition described in Section 7, variable gastrointestinal uptake, and systemic dilution, so conventional supplementation rarely achieves the targeted, phase-matched concentrations that the healing cascade requires. Chemical speciation is the first lever: amino-acid chelates such as ferrous bisglycinate are absorbed more efficiently and provoke fewer gastrointestinal adverse effects than inorganic salts, improving the fraction of an administered dose that reaches the circulation [40].

Local delivery circumvents these systemic limitations. Bone tissue engineering increasingly incorporates therapeutic ions directly into scaffolds, cements, and implants that release copper, magnesium, strontium, or zinc at the defect itself [22]. Bioactive glasses are the leading platform: silicate and borate compositions can be doped with modifying ions to tune osteogenesis and angiogenesis simultaneously, copper addition, for example, markedly enhances vascularization, and a substantial number of bioactive-glass devices have already achieved regulatory approval and clinical use, making this one of the few translationally mature routes for micronutrient-based bone therapy [41,42].

Because micronutrient effects are concentration- and stage-dependent, magnesium, for instance, aids early vascularised regeneration but can impede biomineral deposition if supplied continuously into the maturation phase, simple burst release is suboptimal. Controlled and hierarchical multi-ion release systems built from polymer composites and hydrogels are therefore designed to match ion availability to the healing phase [43,44]. The most flexible expression of this principle is the stimuli-responsive, biopolymer-stabilised nanocarrier: metal-oxide nanoparticles embedded in polysaccharide matrices permit on-demand, spatially localised ion release while their redox-active surfaces simultaneously scavenge reactive oxygen species, addressing the matrix and redox axes in a single construct [24].

The emerging frontier, consistent with the three-axis framework of this review, is phase-matched, multi-element delivery, supplying signalling cofactors during osteoblast commitment, matrix cofactors during callus formation, and redox protection throughout, rather than uniform systemic dosing (Table 5).

**Table 5. Chemical forms, bioavailability, and delivery platforms for osteotropic micronutrients**

| Form / platform | Example elements | Key feature | Refs |
|---|---|---|---|
| Inorganic salts | Ca, Fe, Zn | Low/variable bioavailability; GI side-effects | [28] |
| Amino-acid chelates | Fe (bisglycinate), Zn | ↑ absorption; ↓ GI adverse events | [28] |
| Bioactive glasses (silicate/borate) | Si, Ca, Cu, Sr, B, Mg | Tunable ion release; regulatory-approved products | [29,30] |
| Polymer / hydrogel composites | Mg, Cu, Zn | Controlled, staged/hierarchical release | [31,19] |
| Biopolymer-stabilised nanocarriers | ZnO, $MnO_2$, $Fe_3O_4$ | On-demand localised release; ROS scavenging | [19] |

**9. Knowledge gaps and future directions**

Despite a coherent molecular rationale, the translational evidence base remains immature. The great majority of mechanistic data derive from cell and animal models, whereas human trials of micronutrients in fracture healing are few, small, and methodologically heterogeneous, leaving causality and effect size uncertain [11,45]. Four gaps are especially consequential. First, dose–response relationships and therapeutic windows are poorly quantified; several elements, iron, fluoride, manganese, and boron among them, display U-shaped curves in which both deficiency and excess impair repair, so calibrated targets, not maximal intake, must guide practice [7]. Second, the interactions and ratios emphasised in Section 7 are rarely tested in combination, yet real diets and supplements deliver these nutrients simultaneously; factorial and multi-element trial designs are needed [46]. Third, the phase-specific requirements summarised in Figure 1 are largely inferred and await validation with phase-resolved biomarkers of matrix synthesis, mineralisation, and redox status measured at the healing site [47]. Fourth, response is modified by baseline micronutrient status and by the comorbidities, ageing, diabetes, chronic kidney disease, that define the highest-risk non-union populations, arguing for stratified, personalised approaches rather than uniform supplementation [48]. Finally, the phase-matched, multi-element delivery systems outlined in Section 8 must progress from proof-of-concept to controlled clinical evaluation, with explicit attention to the long-term safety of nanocarriers [31,24]. Addressing these gaps will require standardised outcome measures and mechanism-anchored study designs.

## 10. CONCLUSION

Osteotropic micronutrients are not passive building blocks but active molecular regulators positioned along the bone-healing cascade. Interpreted through the three-axis framework advanced here, regulation of osteogenic and osteoclastic signalling, enzymatic support of collagen matrix synthesis and cross-linking, and preservation of redox homeostasis, the macrominerals, essential trace metals, redox-active and structural trace elements, and osteotropic vitamins resolve into a small set of recurring mechanisms acting at defined nodes and phases of repair. Two principles emerge with particular clarity. First, the influence of every element is dose-dependent, ratio-sensitive, and phase-specific: benefit occupies a homeostatic window bounded on one side by deficiency and on the other by toxicity, and the elements act in concert rather than in isolation. Second, this mechanistic understanding has a translational destination – phase-matched, multi-element, locally delivered systems, including biopolymer-stabilised nanocarriers, that supply the right cofactor to the right axis at the right time. Realising this potential will depend on rigorous, mechanism-guided human studies. By reframing familiar nutrients as integrated molecular modulators of repair, this review aims to provide the conceptual scaffold on which such studies, and the next generation of nutrition-based adjuncts to fracture management, can be built.

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