RESEARCH PAPER

Biomimetic Strategies for Remineralization of Dental Hard Tissues: A Review

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ABSTRACT

Dental caries and erosive tooth wear remain among the most prevalent chronic non-communicable diseases worldwide, driving a paradigm shift from operative restoration toward regenerative strategies that recapitulate the biological processes governing tooth formation. Biomimetic remineralization is the artificial replication of the chemical principles, molecular templates, and crystallographic pathways operative during amelogenesis and dentinogenesis has emerged as a transformative, minimally invasive approach to restoring not merely the mineral content but also the hierarchical microarchitecture of damaged dental hard tissues. This narrative review synthesizes the biological basis of dental biomineralization, the major categories of biomimetic agents, their clinical applications, and the emerging frontiers that will shape the next decade of research and practice.

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Introduction

Mature enamel is acellular and entirely lacks the capacity for biological self-repair following damage, making its loss irreversible in the conventional restorative paradigm. Conventional operative dentistry though effective necessitates removal of residual tooth structure and restores neither the biological continuity nor the hierarchical microarchitecture of native enamel or dentin. The concept of biomimetic remineralization, derived from *bios* (life) and *mimesis* (imitation), addresses this fundamental limitation by deploying molecular scaffolds, mineral precursors, and physicochemical environments that mirror those present during natural tooth development.[1,2]

This approach is mechanistically distinct from traditional fluoride-based remineralization. Fluoride primarily

promotes fluorapatite deposition at the enamel surface, improving acid resistance but not recreating the prismatic rod architecture or restoring subsurface lesion depth. Biomimetic systems, by contrast, aim to guide crystal nucleation, orientation, and hierarchical organization throughout the depth of a lesion, functioning as artificial analogs of the enamel matrix proteins that orchestrate natural enamel formation.[2,3] The field therefore sits at the intersection of structural biology, nanotechnology, materials science, and clinical cariology.

Biological Foundations

Enamel Biomineralization

Enamel formation (amelogenesis) is governed by ameloblast-secreted extracellular matrix proteins — predominantly amelogenin (~90% of organic matrix), along with ameloblastin, enamelin, and amelotin. Amelogenin self-assembles into supramolecular nanospheres (~15–20 nm diameter) that serve as transient scaffolds, regulating the nucleation and parallel alignment of apatite crystallites into the hierarchical prismatic enamel structure. Central to biomimetic design is the concept of non-classical crystallization: rather than direct ion-by-ion deposition, natural enamel mineralization proceeds through fluidic amorphous calcium phosphate (ACP) nanoprecursors that are subsequently transformed into ordered crystalline apatite via a mesoscopic assembly process. This ACP-precursor pathway allows spatially controlled mineral deposition while maintaining a reservoir of reactive, transformable mineral phase which are principles that underpin the design of virtually all modern biomimetic agents.[4,5]

Dentin Mineralization and Collagen-Mineral Interactions

Dentin mineralization proceeds in intimate association with the type I collagen fibrillar scaffold. The gap and overlap zones of the collagen D-period provide nucleation sites for intrafibrillar mineral deposition, a process directed by dentin non-collagenous proteins (NCPs) — particularly dentin phosphoprotein (DPP), dentin matrix protein-1 (DMP-1), and bone sialoprotein. DPP, the most acidic protein in the body, nucleates apatite within collagen fibrils by sequestering calcium ions and directing mineral deposition along the fibril axis. In carious demineralization, both inorganic mineral and the collagen organic matrix are at risk, the latter degraded by host matrix metalloproteinases (MMPs) and cysteine cathepsins activated in the acidic carious microenvironment. Successful dentin remineralization must therefore address both mineral deposition and organic matrix preservation.[6]

Role of Saliva

Saliva maintains the physiological equilibrium between demineralization and remineralization through multiple mechanisms: bicarbonate-mediated pH buffering, calcium and phosphate supersaturation relative to enamel apatite, and a family of mineralizing and anti-nucleating proteins. Statherin, a tyrosine-rich 43-amino acid phosphoprotein, is the most potent known inhibitor of spontaneous calcium phosphate precipitation, adsorbing to enamel and maintaining supersaturation while permitting orderly crystal growth. Proline-rich proteins, histatins, and leucine-rich amelogenin peptides (LRAP) further modulate mineral homeostasis at the enamel surface. These salivary proteins have served as direct molecular inspiration for synthetic biomimetic peptide families now under clinical investigation.[7]

Biomimetic Agents for Enamel Remineralization

Self-Assembling Peptides (P11-4)

P11-4 (Curodont™ Repair, credentis AG) is an 11-amino acid designer peptide that self-assembles into a three-dimensional beta-sheet fibrillar scaffold at physiologic pH within early enamel caries lesions, mimicking the enamel organic matrix and providing nucleation sites for hydroxyapatite deposition throughout the lesion body. This subsurface remineralization distinguishes P11-4 from surface-acting fluoride varnishes. Clinical and in-vivo studies have confirmed its safety and efficacy in children with early pit-and-fissure caries and in post-orthodontic white spot lesions (WSLs), where it produced clinically significant reductions in lesion fluorescence at 3 and 6 months. A 2025 comparative study in orthodontic WSLs found that nano-HA groups produced the most intense remineralization by SEM analysis, while P11-4 demonstrated meaningful mineral recovery superior to non-treated controls. A fluoride-containing variant (P11-4F) combined with CPP-ACFP demonstrated positive remineralization at days 7 and 30.[8,9]

Amelogenin-Derived Peptides

The leucine-rich amelogenin peptide (LRAP), an alternatively spliced amelogenin product retaining only the N- and C-terminal domains, regulates hydroxyapatite

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crystal length and organization in a phosphorylation-dependent manner, making it a targeted molecular tool for biomimetic mineralization. A 2025 scoping review confirmed that LRAP significantly contributes to enamel formation and HAP crystal organization in demineralized lesions. Synthetic analogs such as QP5 combined with fluoride synergistically enhance remineralization of artificial enamel caries in vitro, while the peptides P26 and P32 incorporated into chitosan hydrogel form characteristic amelogenin-like nanospheres and demonstrate effective remineralization potential for incipient decay. Recombinant amelogenin TRAP peptide demonstrated significantly improved calcium binding and remineralization outcomes by micro-CT and polarized light microscopy compared with remineralizing medium alone.[10]

Statherin-Derived Peptides

Inspired by statherin's capacity to regulate calcium phosphate precipitation, DE-11 is a biomimetic peptide incorporating the N-terminal six-residue statherin sequence extended by an acidic mineralization tail, demonstrated strong hydroxyapatite adsorption, directed HAP crystallization, and promoted in situ remineralization of initial enamel caries lesions with higher surface microhardness recovery, lower mineral loss, and reduced lesion depth compared with negative controls.[3,11]

Casein Phosphopeptide–Amorphous Calcium Phosphate (CPP-ACP)

CPP-ACP (MI Paste, GC Corporation) is the most extensively studied and clinically deployed biomimetic remineralization system. The casein phosphopeptide stabilizes ACP clusters through its –Ser(P)-Ser(P)-Ser(P)-Glu-Glu– sequence, creating a reservoir of bioavailable calcium and phosphate ions at the tooth–biofilm interface.[12] Unlike surface fluoride, CPP-ACP promotes deeper penetration of mineral ions into the lesion body, making it particularly effective for the optical management of subsurface WSLs. A PROSPERO-registered systematic review (2025) confirmed clinical evidence for WSL remineralization with CPP-ACP, and a meta-analysis reported that CPP-ACP/CPP-ACPF had a more promising remineralizing impact than fluoride alone. Systematic review evidence also supports CPP-ACP added to foodstuffs (chewing gum, candy, milk) for remineralization activity with ancillary antibacterial effects on dental biofilm.[12,13,14]

Nano-Hydroxyapatite (n-HAP)

Nano-sized hydroxyapatite particles (10–100 nm) chemically and crystallographically mimic biological enamel apatite and integrate into demineralized surfaces through epitaxial adsorption, filling surface microcracks and subsurface porosities. A pH-cycling study found comparable hardness recovery between n-HAP toothpaste, tricalcium phosphate toothpaste, and fluoride toothpaste, with polarized light microscopy revealing a greater decrease in carious lesion depth with n-HAP. Multi-substituted HAP formulations incorporating magnesium, zinc, strontium, and silicon which mimic the naturally substituted apatite of enamel showed superior remineralizing efficacy compared with pure HAP. The favorable safety profile of n-HAP makes it suitable for pediatric populations and patients with milk protein allergies contraindicated for CPP-ACP.[15]

Biomimetic Remineralization of Dentin

Polymer-Guided and PAMAM Dendrimer Systems

The foundational work of Tay and Pashley demonstrated that resin-dentin hybrid layers could be remineralized by supplementing a Portland cement/simulated body fluid system with polyacrylic acid (PAA) and polyvinylphosphonic acid (PVPA) as biomimetic analogs of DPP and DMP-1, respectively, producing both intrafibrillar and interfibrillar apatite within demineralized collagen fibrils after 2–4 months. Poly(amidoamine) (PAMAM) dendrimers extend this approach by serving as hyperbranched, structurally defined NCP analogs. Phosphorylated PAMAM dendrimers direct intrafibrillar mineralization of demineralized dentin confirmed by ATR-FTIR, XRD, and EDS, while carboxyl-terminated PAMAM (PAMAM-COOH) combines biomimetic remineralization with MMP inhibitory activity, outperforming chlorhexidine at matched concentrations. Combined PAMAM with Biodentine produced the most pronounced root dentin remineralization in cyclic acid/saliva in vitro models.[5,16]

Chitosan-Based and Peptide Nanoparticle Delivery

Carboxymethyl chitosan (CMC)/ACP nanocomplexes achieved intrafibrillar and interfibrillar mineralization in a deep caries tooth model, with CMC serving dual roles as ACP stabilizer and collagen-targeting moiety.[17] Trimethyl chitosan (TMC) nanoparticles loaded with the amelogenin-derived peptide QP5 simultaneously promoted dentin remineralization and inhibited endogenous MMP activity, addressing the two principal mechanisms of resin-dentin bond degradation in a single

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formulation. Amino acid-modified electrospun nanofibrous PCL/nHAP scaffolds further recapitulate the NCP-guided biomineralization process: glutamic acid residues mimic the acidic domains of NCPs, sequestering calcium ions and facilitating their organized deposition within collagen fibrils.[2,17]

MMP Inhibition and Matrix Preservation

The integration of MMP inhibition into biomimetic remineralization systems addresses the mechanism of collagen matrix degradation that undermines both natural remineralization and adhesive restoration longevity. MMP-2, -3, -8, -9, and -20 present in dentin and saliva degrade the collagen-rich hybrid layer, resulting in nanoleakage and bond degradation in aged restorations. Biomimetic peptide-based MMP inhibitors incorporated into chitosan nanoparticle delivery systems combine physical mineral deposition with biochemical matrix protection, representing an elegant multifunctional approach to extending the longevity of adhesive restorations.[18]

Bioactive Glasses and Calcium Silicate Materials

NovaMin (calcium sodium phosphosilicate) releases calcium, sodium, phosphate, and silica ions that react with saliva to deposit a hydroxyapatite-like layer on enamel and within dentinal tubules, confirmed by SEM and EDS analysis. BioMin F, a second-generation fluoride-containing bioactive glass, drives fluorapatite formation — a more acid-resistant phase than hydroxyapatite. Strontium-doped bioactive glass demonstrated superior mineral regain compared with BioMin and NovaMin in WSL remineralization studies, suggesting that ionic substitution enhances bioactive glass performance.[19] Calcium silicate-based materials (CSMs) such as MTA, Biodentine, and TheraCal LC promote biomineralization at the material-dentin interface through calcium, silicon, and hydroxyl ion release, with Biodentine additionally stimulating odontoblastic differentiation and reparative dentin formation via TGF-β1 upregulation. These materials find primary application in vital pulp therapy and perforation repair, where their bioactivity contributes to functional dentin-pulp complex restoration.[19,20]

Clinical Applications

White Spot Lesions

WSLs are the earliest visible manifestation of enamel caries and a common sequela of fixed orthodontic therapy, with incidence rates reported up to 50–97% in some populations represent the primary clinical arena for biomimetic remineralization. The intact superficial enamel of early WSLs permits diffusion of biomimetic agents into the lesion body, a prerequisite for non-invasive management. CPP-ACP's capacity for deeper mineral delivery, P11-4's beta-sheet scaffolding mechanism, and n-HAP's epitaxial mineral deposition have all demonstrated efficacy in clinical and in-vivo studies. A 2025 systematic review and meta-analysis of remineralizing agents for WSLs synthesized comparative evidence across fluoride and non-fluoride biomimetic systems, reinforcing clinical decision-making.[21,22]

Dentin Hypersensitivity

Biomimetic tubule occlusion addresses the structural pathology of dentin hypersensitivity by depositing mineral within patent dentinal tubules rather than providing temporary neural desensitization. Polyaspartic acid–calcium and magnesium (PAsp-Ca&Mg) complex treatment achieved in-depth tubule occlusion to approximately 100 μm in vitro and in rabbit incisors in vivo, significantly reducing dentin permeability even after acid and abrasive challenge. Biomimetic Janus particles (JPs) induced complete tubule occlusion with resistance to one hour of ultrasonication and 1000 rounds of thermal cycling, representing a robust advance over mineral plugs vulnerable to mechanical removal.[20,23]

Cutting-Edge Advances

Elastin-Like Recombinamers (ELRs) and Supramolecular Enamel Regeneration

The most significant recent breakthrough was reported in *Nature Communications* (November 2025) by researchers at the University of Nottingham. Tunable elastin-like recombinamer (ELR) matrices, recombinant protein polymers combining elastin-like sequences with bioactive mineralization domains were engineered to mimic the ameloblast-elaborated enamel matrix. Applied topically to teeth with varying erosion severity, the ELR matrix triggered epitaxial apatite crystal growth that recreated the hierarchical architecture of both aprismatic and prismatic enamel, as well as exposed dentin, restoring mechanical and microtribological properties equivalent to or exceeding those of native enamel.[12,18] Transmission electron microscopy confirmed crystallographic integration between newly deposited mineral and dentin collagen fibrils, with collagen fibrils re-aligning parallel to the mineralizing nanocrystals. The system's capacity to regenerate enamel independently of erosion depth extending to fully exposed dentin had not previously been demonstrated by any available technology.[24]

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Exosome-Based and Cell-Free Strategies

Dental stem cell-derived exosomes (DSC-Exos) have emerged as nanoscale cell-free biomimetic vectors mediating angiogenesis, odontoblastic differentiation, and immune regulation within the dentin-pulp complex. A PROSPERO-registered systematic review (2026) reported promising preclinical outcomes for DSC-Exos in pulp-dentin regeneration, with a 24-month clinical pilot confirming restored pulp sensitivity without safety concerns. Exosome-loaded hydroxyapatite/gelatin biomimetic scaffolds combine structural templating for tissue ingrowth with sustained exosomal cargo delivery, representing a functionally biomimetic, cell-free approach to pulp-dentin complex regeneration.[25]

Future Directions

Three-Dimensional Bioprinting

Three-dimensional bioprinting enables spatially controlled deposition of biomimetic scaffolds, cells, and signaling molecules to reconstitute dental tissue architecture. Scaffolds with gradient mineral content and organized collagen orientation mimicking the enamel-dentin-pulp transition are now achievable with modern bioprinting resolution. While whole-tooth bioprinting remains distant, scaffold-guided pulp-dentin complex regeneration following vital pulp therapy is a near-term translational target. Critical challenges include bioink printability, vascularization of larger constructs, and achieving cell-scale resolution needed for functional tubule recreation.[26,27]

Artificial Intelligence Integration

AI-powered deep learning algorithms applied to intraoral photographs, bitewing radiographs, and optical coherence tomography images can now detect early carious lesions at the ICDAS 1–2 level with accuracy approaching experienced clinicians. Machine learning models combining clinical and sociodemographic variables achieve high predictive accuracy for caries risk stratification, allowing clinicians to identify patients most likely to benefit from intensive biomimetic protocols before cavitation occurs. AI-driven quantitative monitoring of lesion remineralization progress through serial quantitative light-induced fluorescence (QLF) measurements and radiographic mineral density assessment offers the prospect of truly personalized, evidence-guided biomimetic caries management.[28]

Challenges and Limitations

The most critical limitation of the biomimetic remineralization literature is its overwhelming preponderance of in vitro evidence. A comprehensive scoping review identified 82 eligible studies, of which 73 (89%) were in vitro, only 6 were in situ, and a mere 2 were randomized clinical trials. In vitro conditions such as static ionic environments, absence of salivary protein competition, controlled pH cycling inadequately replicate the complexity of the oral cavity, which subjects materials to cyclic acid challenges, salivary dilution, biofilm competition, and mechanical loading. The field urgently requires well-designed, adequately powered, long-term randomized controlled trials with clinically meaningful endpoints beyond surface microhardness scores.

Restoration of the full hierarchical microarchitecture of enamel, its prismatic rod organization, crystallographic registry, and mechanical anisotropy has been achieved by very few systems. Most ACP-based, CPP-ACP, and n-HAP systems deposit mineral in a relatively disordered fashion, and truly hierarchical regeneration remains a challenge. Regulatory pathways for novel biomimetic agents, particularly protein-derived and peptide-based systems, impose additional barriers relating to immunogenicity assessment, batch consistency, and long-term biocompatibility evaluation. Outcome measure heterogeneity across the literature encompassing Vickers/Knoop microhardness, transverse microradiography, QLF, SEM, micro-CT, and nanoindentation further limits the synthesis of comparative evidence and the conduct of meta-analyses.

CONCLUSION

Biomimetic remineralization has evolved from a laboratory concept rooted in non-classical crystallization theory into a clinically emerging and scientifically advancing field. Systems ranging from the well-established CPP-ACP and nano-hydroxyapatite to the cutting-edge ELR supramolecular matrices and DSC-exosome platforms collectively span a continuum from near-term clinical deployment to early-stage translational research. The convergence of precision AI-guided diagnostics with multifunctional biomimetic therapeutics agents simultaneously capable of molecular scaffolding, ion delivery, MMP inhibition, and stimuli-responsive release represents the most promising direction for transforming biomimetic remineralization into a universally accessible, evidence-based cornerstone of preventive oral health care. Realizing this potential requires a concerted and sustained shift of research energy

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toward well-designed clinical trials, standardized outcome metrics, and regulatory frameworks capable of evaluating these novel biological agents at the standard demanded by patients and the profession.

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