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# MODERN APPROACHES TO ENAMEL REMINERALIZATION

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**Annotation.** This article analyzes modern approaches to enamel remineralization based on scientific literature, systematic reviews, and clinical guidelines. Dental enamel is the hardest and most highly mineralized tissue in the human body, composed of approximately 96% hydroxyapatite. However, enamel is susceptible to demineralization through acid attacks from cariogenic bacteria, leading to the formation of white spot lesions and dental caries. The principles of minimally invasive dentistry clearly dictate the need for clinically effective measures to remineralize early enamel caries lesions.Remineralization represents a paradigm shift from traditional surgical approaches to biological management of early caries. The article examines the biological basis of enamel remineralization, traditional agents (fluoride therapies, calcium-phosphate systems), emerging biomimetic strategies (self-assembling peptides, dendrimers, hydrogels, bioactive glass, nano-hydroxyapatite), and the clinical effectiveness of each approach based on randomized controlled trials, systematic reviews, and evidence-based clinical guidelines. Special attention is given to non-fluoridated agents, including casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), nano-hydroxyapatite (nHA), and biomimetic protein matrices.

**Keywords:** enamel remineralization, fluoride therapy, hydroxyapatite, CPP-ACP, biomimetic agents, non-fluoridated remineralization, early caries, white spot lesions, preventive dentistry.

Dental enamel is the hardest and most highly mineralized tissue in the human body, consisting of approximately 96% hydroxyapatite, 3% water, and 1% organic material. Its highly ordered hierarchical structure—composed of millions of

interwoven hydroxyapatite crystallites arranged in a complex prismatic architecture—provides exceptional mechanical properties and resistance to wear. Despite its remarkable hardness and mineral density, enamel is susceptible to demineralization through acid attacks from cariogenic bacteria that metabolize fermentable carbohydrates, producing organic acids that dissolve hydroxyapatite crystals. This process of demineralization, when it exceeds the natural remineralization capacity of saliva, leads to the formation of white spot lesions—the earliest visible sign of enamel demineralization—and ultimately to dental caries. Dental caries remains one of the most prevalent chronic diseases worldwide, affecting 30% to 90% of children and adults across different populations. Traditional approaches to managing early caries have focused on surgical intervention—drilling and filling cavities. However, the principles of minimally invasive dentistry clearly dictate the need for clinically effective measures to remineralize early enamel caries lesions.Remineralization represents a paradigm shift from traditional surgical approaches to biological management of early caries. Modern approaches to enamel remineralization encompass a spectrum of agents, ranging from traditional fluoride therapies to innovative biomimetic technologies that aim to restore enamel structure and function by mimicking the natural process of enamel development. This article provides a comprehensive analysis of modern approaches to enamel remineralization, examining the evidence base for each strategy and their clinical applications.

The biological basis of enamel remineralization is rooted in the dynamic equilibrium between demineralization and remineralization that constantly occurs on the tooth surface. Remineralization is the natural process by which calcium and phosphate ions are deposited back into demineralized enamel from saliva. Saliva is supersaturated with calcium and phosphate ions, providing a constant reservoir for remineralization. However, when the oral environment becomes acidic (pH below the critical value of approximately 5.5), this supersaturation is lost, and

demineralization predominates. The process of remineralization involves the precipitation of calcium and phosphate ions onto the partially dissolved hydroxyapatite crystallites, restoring mineral density and hardness. This process can be enhanced by the presence of fluoride, which accelerates the precipitation of calcium and phosphate and forms fluorapatite—a more acid-resistant mineral than hydroxyapatite. It can also be enhanced by the delivery of additional calcium and phosphate ions via remineralizing agents, by the removal of bacterial biofilm and dietary sugars, and by the stimulation of salivary flow. The success of remineralization therapy depends on several factors: the severity and depth of the lesion, the availability of calcium and phosphate ions, the presence of fluoride, the pH of the oral environment, and patient compliance. Early enamel lesions confined to the outer layers of enamel have the greatest potential for complete remineralization, whereas deeper lesions involving dentin may require more intensive intervention.

Fluoride therapy remains the cornerstone of modern enamel remineralization and caries prevention. Fluoride exerts its cariostatic effect through multiple mechanisms. It inhibits demineralization by adsorbing to the surface of hydroxyapatite crystals and making them less soluble. It enhances remineralization by accelerating the precipitation of calcium and phosphate ions onto the partially dissolved crystal surfaces. It also inhibits bacterial metabolism by interfering with enolase and ATPase activity in cariogenic bacteria. Professional topical fluoride applications in the form of fluoride varnishes (5% NaF) and gels are recommended for individuals at moderate to high caries risk. Fluoride varnishes have demonstrated the highest effect in enamel remineralization among various delivery methods.Regular application of fluoride varnish has been shown to arrest and remineralize early enamel lesions. Fluoride toothpastes containing 1000-1500 ppm fluoride are the most widely used and cost-effective method of fluoride delivery for daily home use. High-concentration fluoride toothpastes (5000 ppm) are available by prescription for

individuals at high caries risk. However, concerns about fluoride toxicity, particularly in children, have driven interest in non-fluoridated remineralizing agents.

Calcium phosphate-based systems represent a significant advancement in non-fluoridated remineralization. Among these, casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) has been extensively studied and clinically applied. CPP-ACP, derived from milk casein, stabilizes calcium and phosphate ions in an amorphous state, delivering them to the tooth surface where they are released to promote remineralization. CPP-ACP gels have demonstrated effectiveness in remineralizing early enamel lesions.Available in various forms—including toothpastes, chewing gums, mouthwashes, and professional topical agents (e.g., GC Tooth Mousse)—CPP-ACP is particularly useful for patients with moderate to high caries risk, xerostomia, or orthodontic patients with white spot lesions. The evidence suggests that CPP-ACP plays a promising role in promoting enamel remineralization and reducing demineralization without the concerns associated with fluoride toxicity.Recent clinical trials have evaluated the remineralizing potential of biomimetic scaffolds, including Pchi-ACP, on enamel white spot lesions over a 12-month period. Pchi-ACP demonstrated superior clinical effectiveness in remineralizing early enamel lesions compared to SAP-P11–4 and CPP-ACP, supporting its potential as a promising preventive and regenerative treatment option.

Nano-hydroxyapatite (nHA) has emerged as one of the most promising biomimetic agents for enamel remineralization. Nano-hydroxyapatite is a synthetic form of hydroxyapatite with particle sizes in the nanometer range, offering structural and chemical similarity to natural enamel hydroxyapatite. It has shown potential as a remineralizing agent.Nanohydroxyapatite has been extensively studied in both in vitro and clinical settings. A systematic review evaluated the remineralization potential of casein phosphopeptide–amorphous calcium phosphate,

nanohydroxyapatite crystals, and bioactive glass on initial enamel lesions.1Clinical trials have demonstrated that zinc-hydroxyapatite-based toothpaste is more effective than magnesium strontium carbonate hydroxyapatite toothpaste in enhancing enamel remineralization in the short-term period.2Another randomized clinical trial aims to evaluate the efficacy of two commercially available toothpastes containing hydroxyapatite in the remineralization of early enamel lesions, helping to determine whether biomimetic hydroxyapatite offers superior benefits in maintaining enamel health compared to conventional formulations.Ongoing clinical trials are evaluating nano-hydroxyapatite toothpaste in children with Molar-Incisor Hypomineralization (MIH) to assess its effectiveness and safety.Nano-hydroxyapatite offers several advantages: it is non-toxic, biocompatible, and does not carry the risks associated with fluoride toxicity; it provides a direct source of calcium and phosphate ions for remineralization; and it can be incorporated into toothpastes, mouthwashes, and professional products.

Bioactive glass represents another important class of remineralizing agents. Bioactive glass particles release calcium, phosphate, and silicate ions when exposed to saliva, promoting the formation of a hydroxycarbonate apatite layer on the tooth surface. Bioactive glass has been shown to remineralize enamel, dentin, and cementum.It has been investigated for the treatment of enamel demineralization, dentin hypersensitivity, and the enhancement of bond durability.The mechanism of action involves the rapid release of ions and the formation of a crystalline apatite layer that physically occludes dentinal tubules and promotes remineralization of

1 Remineralization potential of casein phosphopeptide–amorphous calcium phosphate, nanohydroxyapatite crystals, and bioactive glass on initial enamel lesions: a systematic review and meta-analysis // Int J Clin Pediatr Dent. – 2025.

2 Hydroxyapatite toothpastes and enamel remineralization: a randomized controlled clinical trial. – 2025.

early enamel lesions. Bioactive glass products are available in toothpaste formulations (e.g., NovaMin, Biomin) and as professional treatment agents.3

Biomimetic strategies represent the cutting edge of enamel remineralization research. These approaches aim to mimic the natural process of enamel development (amelogenesis) to achieve in-situ enamel remineralization with structural and mechanical properties comparable to natural enamel.Various strategies have been explored, including self-assembling peptides, dendrimers, hydrogels, electrospun mats, and protein- and peptide-guided mineralization systems.One of the most active areas of research involves protein- and peptide-guided mineralization systems that are engineered to mimic the role of enamel matrix proteins during tooth development, guiding calcium and phosphate ions into organized hydroxyapatite crystal structures.Self-assembling peptides have been designed to mimic the function of amelogenin—the key protein involved in enamel formation. These peptides self-assemble into nanofiber networks that template the growth of oriented hydroxyapatite crystals, replicating the hierarchical structure of natural enamel. Recent advances include the development of a supramolecular protein matrix using disordered elastin-like recombinamer molecules to emulate key structural and functional features of the β-rich fibrillar amelogenin matrix driving epitaxial and hierarchical mineralization in dental enamel.Researchers have also developed novel biomimetic systems incorporating pectin/ACP complexes to mimic amelogenesis, providing a biocompatible approach to enamel remineralization that mimics natural amelogenesis.4Another promising approach involves combining an amyloid-like protein coating with a carboxymethyl chitosan/amorphous calcium phosphate

3 Research progress of bioactive glass in the remineralization of dental hard tissue. – 2025.

4 Utilizing pectin/ACP complexes to mimic amelogenesis for biomimetic enamel regeneration // ScienceDirect. – 2026.

nanocomposite for biomimetic dental enamel remineralization, which not only enhances enamel remineralization but also prevents bacterial adhesion.The synergistic promotion of biomimetic enamel remineralization using amelogenin, amelotin, and ameloblastin C-terminal peptides has been investigated in vitro.Chondroitin sulfate has been used to develop a biomimetic mineralization strategy to reconstruct the intricate hierarchical structure of enamel and restore its mechanical properties.However, many of these biomimetic strategies remain at the laboratory or preclinical stage, and translation to clinical practice faces significant challenges, including demonstrating efficacy in vivo, ensuring safety and biocompatibility, and developing cost-effective delivery systems.

Non-invasive management of early carious lesions is emphasized in modern dentistry, shifting from invasive restorative techniques to preventive, minimally invasive strategies focusing on early detection and intervention.Evidence-based clinical guidelines, such as those developed using the GRADE methodology, have provided recommendations for optimized strategies for non-invasive treatment of incipient enamel caries.These guidelines emphasize remineralization, as well as protecting and sealing lesions that have not produced cavities or have limited shallow defects.The selection of remineralizing agents should be guided by the patient's caries risk assessment—individuals at high risk may benefit from prescription-strength fluoride toothpaste, professional fluoride varnish applications, and adjunctive use of CPP-ACP or nano-hydroxyapatite products. Patient compliance and education are critical for successful remineralization therapy. Patients should be educated on proper oral hygiene techniques, dietary modification (particularly reducing the frequency of sugar consumption), and the importance of regular dental visits.

In conclusion, modern approaches to enamel remineralization have evolved significantly, offering a spectrum of strategies ranging from traditional fluoride therapies to innovative biomimetic technologies. Fluoride remains the cornerstone

of remineralization therapy, with fluoride varnishes demonstrating the highest clinical effect.Non-fluoridated agents, including CPP-ACP and nano-hydroxyapatite, provide effective alternatives for patients with concerns about fluoride exposure or in populations with adequate fluoride exposure, playing a promising role in promoting enamel remineralization without the concerns associated with fluoride toxicity.Emerging biomimetic strategies—self-assembling peptides, protein matrices, and peptide-guided mineralization systems—represent the frontier of enamel repair research, aiming to replicate the natural process of enamel formation and achieve structural regeneration rather than simply mineral deposition.The shift from invasive restorative approaches to preventive, non-invasive management of early caries aligns with the principles of minimally invasive dentistry.Evidence-based clinical guidelines and systematic reviews emphasize the importance of early detection, personalized risk assessment, and appropriate selection of remineralizing agents.As research continues to advance, the future of enamel remineralization promises more effective, safe, and accessible options for maintaining dental health and preventing caries progression. The integration of biomimetic technologies with clinical practice, combined with ongoing patient education and preventive care, will be essential for reducing the global burden of dental caries and preserving natural tooth structure.

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