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Biomimetic Dentin Remineralization Using Amino Acid-Modified Nanofibrous Scaffolds: A Review

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ABSTRACT

Dentin demineralization, a hallmark of dental caries, poses a significant challenge to the long-term preservation of tooth structure and function. Traditional remineralization approaches often fail to restore the intrafibrillar mineral architecture necessary for mechanical resilience. In recent years, biomimetic strategies have emerged as promising alternatives, leveraging analogues of non-collagenous proteins (NCPs) and functional scaffolds to replicate natural dentinogenesis. Electrospun nanofibrous scaffolds, particularly those fabricated from polycaprolactone (PCL) and reinforced with nanohydroxyapatite (nHA), have demonstrated substantial potential in mimicking the extracellular matrix and promoting hierarchical mineral deposition. Moreover, acidic amino acids such as glutamic acid and its polymeric derivatives have shown remarkable efficacy in stabilizing amorphous calcium phosphate (ACP) and facilitating its transformation into hydroxyapatite within collagen matrices. This review synthesizes current knowledge on dentin ultrastructure, demineralization mechanisms, biomineralization pathways, and the design of scaffold-based delivery systems. It highlights emerging evidence supporting the integration of glutamic acid into PCL/nHA nanofibrous scaffolds for functional dentin regeneration. While these strategies mark a significant advancement in regenerative dentistry, clinical translation requires further investigation into long-term biocompatibility, ion release dynamics, and scaffold–cell interactions. This review underscores the potential of amino acid-based scaffolds in reshaping the future of biologically guided dentin remineralization.

Keywords: *Dentin remineralization, Biomimetic scaffolds, Electrospinning, Polycaprolactone (PCL), Nanohydroxyapatite (nHA), Glutamic acid, Tissue engineering*

1. INTRODUCTION

Dentin is a mineralized connective tissue that forms the bulk of the tooth and plays a vital role in maintaining mechanical resilience and pulpal vitality. It is composed of approximately 70% hydroxyapatite, 20% organic matrix—primarily type I collagen—and 10% water by weight (Goldberg et al., 2011). Unlike enamel, dentin retains a degree of reparative potential via the activity of odontoblasts and pulp-derived stem cells. However, this regenerative capacity is significantly compromised in the presence of carious or traumatic lesions, where acidogenic bacterial metabolism initiates the dissolution of hydroxyapatite and exposes the underlying collagen network (Braga and Habelitz, 2019; Sajini, 2023).

Traditional remineralization strategies predominantly promote extrafibrillar mineral deposition, which often fails to replicate the complex hierarchical architecture of native dentin. In contrast, biomimetic remineralization techniques aim to restore both structure and function by facilitating intrafibrillar mineral deposition, thereby closely emulating natural dentinogenesis (He et al., 2019; Wen et al., 2023). These approaches are inspired by the role of non-collagenous proteins (NCPs), such as

dentin phosphoprotein (DPP) and dentin matrix protein 1 (DMP1), which guide mineral nucleation and growth within the collagen scaffold (Zhang et al., 2016; Prasad, Butler and Qin, 2010).

Electrospun nanofibrous scaffolds have gained prominence for their ability to mimic the native extracellular matrix, offering high surface area, tunable porosity, and topographical cues that facilitate cell adhesion and mineral deposition (Mondal, Griffith and Venkatraman, 2016). Polycaprolactone (PCL)-based scaffolds, particularly when reinforced with nanohydroxyapatite (nHA), provide enhanced bioactivity and mechanical strength suitable for dentin tissue engineering (Dwivedi et al., 2020). Furthermore, the incorporation of acidic amino acids such as glutamic acid has demonstrated the potential to functionally substitute matrix-bound proteins by stabilizing amorphous calcium phosphate (ACP) and directing its transformation into hydroxyapatite (Zhang et al., 2019; Gandolfi et al., 2011).

This review synthesizes current knowledge on dentin structure, demineralization, biomineralization mechanisms, and regenerative scaffold systems, with a particular emphasis on amino acid-functionalized nanofibrous scaffolds. It highlights their translational potential in biomimetic dentin regeneration and outlines future directions in scaffold design and clinical application.

2. STRUCTURAL AND PATHOLOGICAL BASIS OF DENTIN DEMINERALIZATION

2.1 Dentin Microarchitecture and Composition

Dentin exhibits a unique hierarchical structure that underpins its functional integrity. It consists of three principal zones—mantle dentin, circumpulpal dentin, and predentin—each with distinct collagen arrangements and mineral densities. Mantle dentin, situated beneath the dentinoenamel junction, contains larger collagen fibrils and lower mineral content, functioning primarily in stress absorption (Goldberg et al., 2011). Circumpulpal dentin, which forms the bulk of primary dentin, features densely packed type I collagen and tubular architecture that supports mechanical strength (Zhang et al., 2016). Predentin, the innermost layer, remains unmineralized and comprises a proteoglycan-rich collagen matrix continuously deposited by odontoblasts to maintain the mineralization front (He et al., 2019).

At the microscopic level, dentin is characterized by its tubular system, comprising peritubular and intertubular regions. Peritubular dentin is hypermineralized, collagen-deficient, and forms a stiff ring around the tubules, whereas intertubular dentin contains a hydrated collagen matrix embedded with hydroxyapatite and serves as the primary load-bearing phase (Tjäderhane et al., 2009). The organic matrix is primarily type I collagen (~90%), interspersed with non-collagenous proteins (NCPs) such as dentin matrix protein 1 (DMP1), dentin phosphoprotein (DPP), osteopontin, and proteoglycans—each contributing to mineral regulation and matrix stability (Linde, 1989; Zhang et al., 2016). The inorganic component, carbonated hydroxyapatite, is smaller and less crystalline than enamel, rendering dentin more susceptible to acid dissolution (Goldberg et al., 2011).

2.2 Mechanisms of Dentin Demineralization

Dentin demineralization is initiated when oral pH falls below the critical threshold (~6.5), leading to dissolution of carbonated hydroxyapatite crystals (Paschalis, Tan and Nancollas, 1996). This vulnerability is exacerbated by dentin's high porosity, carbonate substitution, and organic matrix content (Braga and Habelitz, 2019). The demineralization cascade typically begins in the peritubular dentin due to its high mineral content, before extending into the intertubular matrix, exposing collagen fibrils to degradation (Zhang et al., 2016).

Acidogenic bacteria such as *Streptococcus mutans* and *Lactobacilli* play a central role, fermenting dietary carbohydrates into organic acids—primarily lactic acid—that penetrate through dentinal tubules (Sajini, 2023). The sustained low pH disrupts the mineral–collagen interface, and further exacerbates matrix breakdown. Once exposed, the collagen scaffold is susceptible to host-derived proteolytic enzymes, particularly matrix metalloproteinases (MMPs) and cysteine cathepsins, which are activated under acidic conditions (Zhong et al., 2015). This enzymatic degradation compromises the fibrillar structure required for successful remineralization, converting the tissue into a biologically non-restorable substrate (Braga and Habelitz, 2019).

2.3 Demineralization Gradient and Regenerative Potential

Histologically, demineralized dentin presents in two zones: an outer infected layer, which is irreversibly damaged, and an inner affected layer, which retains partially demineralized collagen with intact cross-links and residual apatite (Sajini, 2023). The inner zone remains amenable to remineralization through biomimetic means, provided the scaffold and mineral precursors can adequately infiltrate and restore the collagen architecture. Microhardness profiles and imaging studies support this gradient, indicating that targeted therapies must differentiate between the regenerative potential of each zone (Lee et al., 2023).

Thermodynamic factors such as ion activity product (IAP), lattice substitutions, and surface energy influence solubility and crystal behavior within the dentin matrix (Paschalis et al., 1996). Substitutions like carbonate and magnesium destabilize the hydroxyapatite lattice, decreasing acid resistance and complicating re-precipitation under dynamic oral conditions (Braga

and Habelitz, 2019).

3. BIOMINERALIZATION MECHANISMS IN DENTIN

Biomineralization is a biologically regulated process through which minerals are deposited within organic matrices to form hard tissues such as dentin, enamel, and bone. In dentinogenesis, this process is finely orchestrated by odontoblasts, which secrete a collagen-rich matrix interspersed with non-collagenous proteins (NCPs) that regulate mineral deposition, orientation, and maturation (Prasad, Butler and Qin, 2010; Zhang et al., 2016).

3.1 Classical vs Non-Classical Biomineralization

The **classical theory** of dentin biomineralization posits that mineral formation occurs through an ion-by-ion assembly of calcium (Ca^{2+}) and phosphate (PO_4^{3-}) into hydroxyapatite (HA) crystals. These ions nucleate and grow on the surface of collagen fibrils or pre-existing seed crystals, leading to **extrafibrillar mineralization** (Goldberg et al., 2011). However, this mechanism cannot fully explain the intrafibrillar mineralization observed in native dentin, which is critical for restoring mechanical strength.

The **non-classical pathway**, in contrast, involves the formation and stabilization of amorphous calcium phosphate (ACP) nanoclusters or nanoparticles. These particles are small enough to infiltrate the 40 nm-wide gap zones within the collagen fibrils. Once inside, they undergo a transformation into crystalline hydroxyapatite, resulting in **intrafibrillar mineralization** (He et al., 2019; Wen et al., 2023). This mechanism is mediated by acidic matrix proteins or their analogues that function as **templating agents**, preventing premature crystallization and directing mineral formation inside the collagen matrix.

3.2 Role of Collagen and Non-Collagenous Proteins

Type I collagen provides the structural template for dentin mineralization. Its periodic D-banding pattern forms discrete gap zones that facilitate intrafibrillar mineral infiltration (Tjäderhane et al., 2009). However, mineralization is not solely a passive infiltration process; it requires precise regulation by non-collagenous proteins (NCPs). These include:

- **Dentin Matrix Protein 1 (DMP1)**: Facilitates nucleation and promotes organized crystal formation within collagen fibrils (Linde, 1989).
- **Dentin Phosphoprotein (DPP)**: A highly acidic, phosphate-rich molecule that binds Ca^{2+} ions and controls the transformation of ACP into hydroxyapatite (Prasad et al., 2010).
- **Osteopontin and Bone Sialoprotein**: Modulate mineral maturation and crystal alignment.

Synthetic analogues such as polyacrylic acid (PAA), polyaspartic acid (pAsp), and glutamic acid-based peptides have been investigated to mimic NCP function, enhancing intrafibrillar mineralization in demineralized dentin matrices (Zhang et al., 2019).

3.3 Biomimetic Approaches Using Scaffolds and Hydrogels

Recent strategies aim to replicate the biomineralization environment using scaffolds or hydrogel delivery systems loaded with mineral precursors and analogues of NCPs. These biomimetic delivery platforms can localize ACP precursors at the lesion site, infiltrate exposed collagen fibrils and Promote organized remineralization from the inside out (He et al., 2019)

Scaffold-guided remineralization not only restores the mineral content but also reestablishes mechanical properties when intrafibrillar mineralization is achieved. Electrospun nanofibers of PCL, modified with nHA and acidic amino acids like glutamic acid, serve as a promising delivery vehicle by providing both structural support and functional bioactivity(Dwivedi et al., 2020).

4. BIOMIMETIC REMINERALIZATION STRATEGIES

Contemporary remineralization approaches in dentistry are evolving from simple ion-based therapies to biomimetic systems that replicate natural mineralization processes. The ultimate goal is not only to restore mineral content but also to rebuild the hierarchical structure of dentin through intrafibrillar mineralization, thereby reinstating both function and mechanical strength.

4.1 Conventional Remineralization Agents: Benefits and Limitations

Fluoride

Fluoride remains the cornerstone of preventive remineralization. It reduces enamel solubility by forming fluorapatite and enhances remineralization by attracting calcium and phosphate ions (Featherstone, 2008). However, in dentin, its effect is limited to extrafibrillar deposition, and it does not adequately restore collagen architecture (Tjäderhane et al., 2009).

Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP)

CPP-ACP complexes stabilize calcium and phosphate ions and maintain a state of supersaturation, aiding in the re-deposition

of minerals (Reynolds, 2008). Although effective in enamel, the macromolecular size of casein peptides restricts penetration into collagen fibrils, thus limiting true biomimetic regeneration in dentin.

4.2 Non-Collagenous Protein Analogues and Self-Assembling Peptides

To overcome the limitations of conventional agents, synthetic analogues of non-collagenous proteins (NCPs) have been developed to mimic the role of natural mineralization regulators.

- **Polyaspartic acid (pAsp)** and **polyacrylic acid (PAA)** can stabilize amorphous calcium phosphate (ACP) nanoparticles, facilitating their infiltration into collagen fibrils and subsequent transformation into hydroxyapatite (Zhang et al., 2019).
- **Self-assembling peptides (e.g., P11-4)** form β-sheet structures that nucleate hydroxyapatite and can infiltrate into demineralized dentin, promoting intrafibrillar remineralization (Kind et al., 2017).
- **Aspartate–serine–serine (DSS) repeats**, derived from NCPs like DPP, are gaining attention for their role in targeted mineralization along collagen matrices (Wen et al., 2023).

4.3 Scaffold-Based Delivery Systems for Biomimetic Remineralization

Electrospun Nanofibrous Scaffolds

Electrospun nanofibers mimic the **architecture of the extracellular matrix** and offer a platform for sustained and localized delivery of mineralizing agents. Polycaprolactone (PCL)-based scaffolds can be incorporated with Nanohydroxyapatite (nHA) which provides a bioactive mineral source, Glutamic acid or DSS peptides stabilize ACP and promote collagen binding. These scaffolds not only support mineral deposition but also influence cell behavior, facilitating dentin regeneration in both in vitro and in vivo models (Dwivedi et al., 2020).

5. TISSUE ENGINEERING STRATEGIES IN DENTIN REGENERATION

Tissue engineering in dentistry is a multidisciplinary domain that seeks to restore lost dental structures by combining principles of cell biology, biomaterials, and biomechanics. Unlike conventional restorative methods that merely fill defects, tissue engineering aims to regenerate dentin-pulp complexes through biologically active scaffolds, cells, and signaling molecules (Bansal et al., 2021).

5.1 Key Components of Dentin Tissue Engineering

The successful regeneration of dentin relies on three interdependent components:

1. Scaffold

An ideal scaffold provides structural support, mimics the extracellular matrix (ECM), and serves as a delivery vehicle for cells and bioactive molecules. Electrospun nanofibers, hydrogels, and 3D-printed constructs are commonly employed in dental applications (Dwivedi et al., 2020).

2. Cells

The primary cellular candidates are:

- Human dental pulp stem cells (hDPSCs)
- Stem cells from exfoliated deciduous teeth (SHED)
- Mesenchymal stem cells (MSCs)

These cells are capable of odontogenic and osteogenic differentiation, responding to local microenvironmental cues and contributing to reparative dentin formation (Huang et al., 2009).

3. Signaling Molecules

Growth factors such as bone morphogenetic proteins (BMPs), transforming growth factor-beta (TGF-β), fibroblast growth factors (FGFs), and vascular endothelial growth factor (VEGF) orchestrate cellular proliferation, migration, and differentiation (Bansal et al., 2021). Their controlled delivery from scaffolds enhances regenerative outcomes.

5.2 Strategies for Functional Scaffold Design

Electrospun Nanofibers

Electrospinning enables the fabrication of ECM-like architectures with tunable fiber diameter, alignment, and porosity. Polymers such as polycaprolactone (PCL), often blended with nanohydroxyapatite (nHA) or bioactive peptides, have been employed to promote mineralization and cellular integration (Mondal et al., 2016). Their high surface-area-to-volume ratio enhances protein adsorption and ion exchange.

Hydrogel-Based Systems

Hydrogels offer a hydrated 3D network that supports cell encapsulation, proliferation, and migration. Natural polymers like alginate, collagen, and gelatin, or synthetic ones like PEG and PGA, are used. These systems may be injectable and are increasingly studied as carriers for controlled release of ions and growth factors.

5.3 Functionalization with Bioactive Molecules

Recent studies have focused on functionalizing scaffolds with bioactive ligands to enhance regenerative signaling. For example Glutamic acid which mimics acidic residues of NCPs and binds calcium ions, facilitating intrafibrillar mineralization (Zhang et al., 2019). DSS peptides promote specific adhesion and hydroxyapatite nucleation along collagen fibrils (Wen et al., 2023). Surface modification techniques (e.g., plasma treatment, peptide grafting) are employed to enhance scaffold bioactivity and host integration.

6. POLYCAPROLACTONE (PCL) AND NANOHYDROXYAPATITE (NHA) IN SCAFFOLD DESIGN

The selection of scaffold material is a pivotal factor in regenerative dentistry, as it directly influences mechanical strength, biodegradation rate, bioactivity, and cellular interactions. Among the various polymers and composites used, polycaprolactone (PCL) and nanohydroxyapatite (nHA) have garnered substantial attention due to their biocompatibility, functional synergy, and relevance to hard tissue engineering (Dwivedi et al., 2020; Mondal et al., 2016).

6.1 Polycaprolactone (PCL): A Synthetic ECM Mimic

PCL is a biodegradable polyester approved by the FDA for biomedical applications. Its advantages are biocompatibility (Woodruff and Hutmacher, 2010), mechanical Stability, high tensile strength and durability, and slow degradation rate.

6.2 Nanohydroxyapatite (nHA): Bioactive Reinforcement

nHA is the nano-scale form of hydroxyapatite, which constitutes the primary inorganic component of dentin and bone. Its role in composite scaffolds includes chemical similarity to bone mineral, osteoconductivity, bioactivity, supports nucleation of mineral phases, aiding remineralization and cellular differentiation (Zhang et al., 2019).

6.3 PCL/nHA Composite Scaffolds

The combination of PCL and nHA results in a scaffold that balances mechanical strength with bioactivity. Advantages include enhanced mineral deposition, improved cell attachment, tunable degradation and porosity.

Electrospinning of PCL/nHA blends enables the fabrication of nanofibers with diameter ranges comparable to natural collagen fibrils, promoting cellular attachment and mimicking the native ECM environment (Mondal et al., 2016).

7. ROLE OF GLUTAMIC ACID IN BIOMIMETIC MINERALIZATION

Amino acids are increasingly being explored in biomaterials research for their ability to mimic non-collagenous proteins (NCPs) involved in natural biomineralization. Among them, glutamic acid (Glu) is particularly promising due to its acidic side chain, which exhibits strong affinity for calcium ions and resembles the calcium-binding domains of dentin phosphoproteins like DPP and DMP1 (Zhang et al., 2019; Gandolfi et al., 2011).

Glutamic acid possesses two carboxylic acid groups that ionize under physiological pH, allowing the molecule to bind divalent calcium ions (Ca^{2+}), stabilize amorphous calcium phosphate (ACP), template the nucleation and transformation of hydroxyapatite (HA) within collagen fibrils. This dual functionality ion coordination and collagen interaction makes glutamic acid an ideal analogue of acidic NCPs for intrafibrillar mineralization. Glutamic acid has been successfully incorporated into electrospun PCL/nHA scaffolds, where it enhances bioactivity, supports biomineralization, and modulates scaffold degradation. These scaffolds have demonstrated improved surface wettability, protein adsorption, and mineral nucleation, making them superior to unmodified PCL or even PCL/nHA alone.

8. FUTURE PERSPECTIVES AND RESEARCH GAPS

Despite significant advances in biomimetic strategies for dentin remineralization, the clinical translation of amino acid-functionalized scaffolds and mineralizing systems remains in its infancy. Future efforts must focus on addressing the key biological, material, and translational challenges that currently limit widespread clinical adoption.

8.1 Optimization of Scaffold Design Parameters

While electrospun PCL/nHA scaffolds have shown promising results in vitro, standardization of fiber diameter, porosity, and degradation kinetics is essential to tailor them for clinical use. These parameters influence ion diffusion, cell infiltration, and remineralization depth. Further integration of smart polymers and responsive systems could allow dynamic control over ion release, pH buffering, or protein delivery in response to the lesion environment.

8.2 Mechanistic Understanding of Peptide and Amino Acid Function

Although glutamic acid and DSS-containing peptides have been experimentally validated as NCP analogues, the precise molecular interactions with collagen and mineral precursors remain incompletely understood. Research should aim to elucidate binding sites and orientation on collagen fibrils, characterize thermodynamic and kinetic factors governing ACP stabilization, and use molecular dynamics simulations to refine scaffold design. This will enable the rational development of more potent analogues with enhanced biomineralization capacity.

8.3 Cell–Scaffold Interactions and Immunomodulation

Most current studies focus on scaffold-induced mineralization, but little is known about stem cells interacting with modified scaffold surfaces, role of immune cells (macrophages, dendritic cells) in modulating regeneration, and inflammatory responses to long-term scaffold degradation. A deeper understanding of the host–biomaterial interface is crucial for designing next generation scaffolds that are both bioactive and immunotolerant.

8.4 Translation to In Vivo and Clinical Models

Current data from in vitro mineralization assays and rodent subcutaneous models provide limited insight into scaffold performance in complex oral environments. Future directions should include orthotopic models in larger animals Load-bearing simulations mimicking masticatory forces, evaluation of adhesive interface stability with restorative materials. In addition, regulatory frameworks for peptide-modified biomaterials must be streamlined to facilitate clinical translation.

9. CONCLUSION

The field of dentin remineralization is undergoing a paradigm shift, moving from surface-level ion delivery to biomimetic strategies that replicate the complexity of natural dentinogenesis. Central to this evolution are functional scaffolds particularly electrospun PCL/nHA composites that can deliver minerals and biomolecules in a controlled, site-specific manner. Among the most promising biomimetic additives are acidic amino acids like glutamic acid, which emulate the calcium-binding functionality of non-collagenous proteins and facilitate intrafibrillar mineralization.

The integration of glutamic acid into PCL/nHA scaffolds represents a powerful approach to re-establish the mechanical and biological integrity of demineralized dentin. In vitro and in vivo findings affirm their potential to guide structured mineral deposition, modulate cell behavior, and serve as platforms for regenerative therapies. However, challenges remain including the optimization of scaffold architecture, mechanistic elucidation of peptide–collagen interactions, and validation in clinically relevant models.

Continued interdisciplinary collaboration between materials scientists, biologists, and clinicians will be essential to translate these innovations into clinically deployable systems. With appropriate refinement and regulatory support, amino acid-functionalized scaffolds could redefine the future of minimally invasive, biologically guided dentin regeneration.

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