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Nanotechnology in Regenerative Periodontal Therapy: Current Insights and Future Directions

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Abstract

Periodontitis is a biofilm-mediated inflammatory disease characterized by progressive destruction of supporting tissues of the periodontal region, for which traditional regenerative therapies have produced repair rather than true regeneration more often. Nanotechnology thus offers a novel approach by enabling targeted and sustained delivery of antimicrobial, anti-inflammatory, and osteogenic agents; nano-engineered scaffolds mimic the extracellular matrix. Preclinical investigations have shown promise by using polymeric, metallic, ceramic, and hybrid nanoparticles to improve immunomodulation, angiogenesis, infection control, and regeneration of bone-cementum-PDL. Recent advances in nano composite membranes, smart nano carriers, and stem cell-integrated nano-scaffolds have shown superior regenerative outcomes compared to conventional approaches of guided tissue regeneration. In most cases, maximum successes of the conventional regenerative approaches have only provided tissue repair rather than regeneration of the periodontal areas affected by periodontitis, a chronic inflammatory condition mediated by biofilm. Nanotechnology plays a vital role as this novel approach facilitates the sustained delivery of anti-inflammatory, antimicrobial, and osteogenic compounds while mimicking the periodontal matrix. Nanoparticles such as polymeric, metallic, ceramic, and hybrid nanoparticles made of these materials have gained much promise of success while treating periodontitis while compared to conventional approaches such as GTR. Recent advances of nano composites, nano carriers, and stem cell-based nano scaffolds have demonstrated much regenerative capability compared to conventional approaches. This review provide insights on nanotechnology in regenerative periodontal therapy and future of the scientific applications of periodontal regeneration.

Keywords: Nanoparticles; Periodontal regeneration; Chitosan; PLGA; Nanohydroxyapatite; Regenerative dentistry.

INTRODUCTION

Periodontitis is a chronic, biofilm-driven inflammatory disease characterised by the progressive destruction of gingival connective tissue, periodontal ligament (PDL), cementum, and alveolar bone ultimately leading to tooth mobility and tooth loss if untreated. It affects nearly half of the global adult population and remains one of the primary causes of tooth loss worldwide, with significant implications for mastication, aesthetics and systemic health [1]. The disease process is initiated by pathogenic bacterial biofilms in the subgingival niche, which trigger a dysregulated host immune–inflammatory response leading to connective tissue breakdown and bone resorption through the release of cytokines, proteases and reactive oxygen species (ROS) [2].

Conventional treatment modalities, including scaling and root planing, open flap debridement, bone grafting, guided tissue regeneration (GTR) and biologically active agents such as enamel matrix derivatives, platelet concentrates and recombinant growth factors aim to eliminate infection, reduce inflammation, and facilitate healing [3]. However, these approaches often result in repair characterised by long junctional epithelium formation rather than true regeneration of the original periodontal architecture comprising bone, cementum and a functionally oriented PDL [4]. Moreover, the success of regenerative procedures is often limited by factors such as inadequate cellular recruitment, rapid degradation of signalling molecules, poor control over release kinetics and the complexity of the local microenvironment [5].

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True periodontal regeneration requires orchestrated, spatiotemporal coordination of multiple biological events, including: (a) effective infection control and biofilm eradication in the periodontal pocket (b) modulation of the inflammatory milieu to transition from a pro-inflammatory to a pro-healing environment and (c) recruitment, proliferation and differentiation of osteogenic, cementogenic and fibroblastic progenitor cells to re-establish the bone-cementum-PDL complex with proper fiber orientation [6]. Achieving this intricate interplay with conventional materials and techniques remains challenging.

Nanotechnology provides a transformative platform to overcome these limitations by enabling precise control at the molecular and cellular levels. Engineered nanoparticles (NPs), including polymeric, metallic, ceramic, and lipid-based systems, can serve as multifunctional therapeutic carriers capable of targeted, sustained delivery of antimicrobials, anti-inflammatory agents and growth factors directly to periodontal defects [7]. Furthermore, nanostructured scaffolds and nanofibrous matrices mimic the extracellular matrix (ECM) topography, enhancing cellular adhesion, migration and differentiation while providing mechanical stability and biological signalling cues essential for regeneration [8].

In addition, inorganic nanomaterials such as nano-hydroxyapatite, bioactive glass, titanium dioxide, and zinc oxide nanoparticles exhibit inherent antimicrobial and osteoinductive properties, thereby reducing bacterial load while promoting mineralisation and tissue regeneration through ion release and modulation of osteogenic gene expression [9]. Recent advances in nanocomposite biomaterials, nanofiber membranes, and stimuli-responsive nanocarriers have shown promising preclinical outcomes in promoting new bone and cementum formation, enhancing angiogenesis, and achieving superior attachment gains compared to conventional GTR membranes [9].

The purpose of this review is therefore to synthesise the current evidence on the application of nanotechnology in regenerative periodontal therapy. It aims to discuss fundamental principles, classes of nanoparticles, their biological mechanisms, and recent advancements in regenerative applications. Furthermore, it highlights key preclinical and early clinical findings, translational challenges, and future directions that may facilitate the successful clinical integration of nanotechnology-enabled strategies for true periodontal regeneration [10].

PRINCIPLES OF NANOTECHNOLOGY IN PERIODONTAL THERAPY

Definition and unique physicochemical properties

Nanoparticles are materials with primary dimensions in the nanometre range (commonly 1-100 nm) whose physicochemical properties differ from bulk analogues, high surface-to-volume ratio, tunable surface chemistry, and size-dependent cellular interactions. These features enable high loading of therapeutic cargo (small molecules, proteins, nucleic acids), controlled release kinetics via degradation or diffusion, and surface functionalization for cell-targeting [11].

Interaction with biological tissues

At the nanoscale, topography and surface chemistry influence protein adsorption (protein corona formation), integrin engagement, focal adhesion dynamics and downstream signalling cascades (e.g., RUNX2, Wnt/β-catenin, MAPK) that drive osteogenesis and angiogenesis. Nanofibrous scaffolds and nHA-decorated surfaces mimic the native ECM architecture and enhance stem cell adhesion and lineage specification [12].

Therapeutic advantages for periodontal regeneration

Key regenerative advantages of nanomaterials include: (1) localized, sustained delivery of antimicrobials and biologics, reducing systemic exposure and dose (2) intrinsic or functionalized antibacterial properties (metal or polymeric NPs) that help control reinfection at the surgical site (3) osteoconductive and osteoinductive cues from bioactive ceramics and ion-releasing glasses and (4) scaffold mechanics and porosity tunable at nanoscale for optimal cell infiltration and vascular ingrowth [13,14]. These properties are strategically valuable because periodontal defects present a contaminated, mechanically loaded and microbiologically complex microenvironment [15].

TYPES OF NANOPARTICLES USED

Polymeric nanoparticles

Biodegradable polymers such as chitosan, poly(lactic-co-glycolic acid) (PLGA), and alginate are among the most extensively explored nanocarrier systems in periodontal applications owing to their excellent biocompatibility, biodegradability, and tunable degradation kinetics [16,17]. These polymers are capable of encapsulating diverse therapeutic agents, including antimicrobials, anti-inflammatory drugs, growth factors, and signalling peptides, and releasing them in a controlled and sustained manner, thereby maintaining effective local concentrations while minimising systemic exposure [18].

Chitosan

Chitosan-based nanoparticles have gained remarkable attention because of their cationic nature, mucoadhesive properties, and intrinsic antimicrobial activity. Derived from chitin through alkaline N-deacetylation, chitosan’s positively charged amino groups enable electrostatic interactions with the negatively charged bacterial cell walls, leading to increased membrane permeability and bacterial lysis [19]. This mechanism underlies its broad-spectrum antibacterial efficacy against major periodontal pathogens such as *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, and *Fusobacterium nucleatum* [20].

Beyond inherent antimicrobial activity, chitosan serves as an excellent carrier for local drug delivery. Chitosan nanoparticles can encapsulate antibiotics (e.g., minocycline, metronidazole), antiseptics (e.g., chlorhexidine), or antimicrobial peptides to enhance their stability and prolong retention in periodontal pockets. Their mucoadhesive nature ensures prolonged residence time at the diseased site, reducing the need for repeated administration. Additionally, chitosan can be engineered into injectable hydrogels, nanofibers, or membrane-surface nano reservoirs, supporting both antimicrobial and regenerative functions [21,22].

Recent studies have explored statin-loaded chitosan nanoparticles as promising immunomodulatory and osteogenic systems. Statins, known for their pleiotropic effects, promote osteoblastic differentiation and inhibit osteoclastic resorption. The local delivery of simvastatin or rosuvastatin via chitosan carriers demonstrated enhanced alveolar bone regeneration in experimental periodontitis and critical-sized bone defect models in dogs and mice. Moreover, chitosan-based nano reservoirs have been incorporated into barrier membranes to facilitate sustained release of growth factors such as BMP-2, resulting in improved biocalcification and osseointegration in maxillary bone regeneration contexts [23].

PLGA

PLGA, poly (lactic-co-glycolic acid) nanoparticles represent one of the most versatile and FDA-approved drug delivery systems. As a copolymer of lactic and glycolic acids, PLGA undergoes hydrolytic degradation into biocompatible byproducts, which are naturally metabolised through the Krebs cycle, thus ensuring minimal cytotoxicity [24]. PLGA-based nanoparticles and scaffolds, including barrier membranes, sponges, and gels, are widely used in periodontal applications to deliver antibiotics, anti-inflammatory agents, and regenerative molecules [25].

Despite its advantages, PLGA may exhibit an initial burst release due to rapid surface desorption of drugs, potentially leading to cytotoxic peaks or suboptimal therapeutic windows. To overcome this, core-shell PLGA-chitosan nanoparticles have been developed, wherein the chitosan shell modulates drug release kinetics and enhance mucoadhesion. The shell thickness can be tuned to achieve sequential or sustained drug delivery [26]. For example, Lee *et al*. demonstrated that PLGA-chitosan nanoparticles delivering tetracycline (for infection control) and lovastatin (for bone regeneration) sequentially enhanced alveolar bone and PDL regeneration in a canine model [27].

Furthermore, PLGA nanoparticles have been employed as carriers for curcumin, silver ions, and immunomodulatory drugs, leading to reduced inflammatory cytokine secretion and bacterial growth in *in vitro* and *in vivo* studies [28].

Notably, PLGA nanocarriers loaded with methylene blue have been integrated into photodynamic therapy (PDT) for periodontal pocket treatment, allowing localised delivery of photosensitizers that minimise bacterial resistance and enhance therapeutic efficacy [29].

Alginate

Alginate, another naturally derived anionic polysaccharide, has also been utilised to formulate nanoparticles or hybrid gels with calcium crosslinking. Its high biocompatibility and mild gelation properties make it a useful matrix for encapsulating growth factors and living cells, promoting angiogenesis and tissue integration when combined with chitosan or PLGA systems [30,31].

Bioactive and ceramic nanoparticles — nano-hydroxyapatite, calcium phosphate, silica, bioactive glass

Bioactive and ceramic nanoparticles play a critical role in reconstructing mineralised tissue due to their compositional similarity to bone and cementum. Nano-hydroxyapatite (nHA) and calcium phosphate nanoparticles mimic the inorganic mineral phase of bone, providing osteoconductive and osteoinductive cues that enhance mineral nucleation and integration with host tissues [32,33]. Their nanoscale surface roughness and high surface-to-volume ratio promote protein adsorption and osteoblast attachment, facilitating bone matrix formation.

Mesoporous silica nanoparticles (MSNs) offer tunable pore sizes and high surface area, enabling simultaneous encapsulation of small drugs and large biomolecules such as growth factors or peptides. Their surfaces can be doped with therapeutic ions such as copper (Cu^{2+}) or strontium (Sr^{2+}), imparting antimicrobial and osteogenic properties via modulation of cellular signalling pathways and suppression of inflammatory mediators [34].

Bioactive glass nanoparticles are another promising class of inorganic nanomaterials that release silicon (Si), calcium (Ca), and phosphorus (P) ions during dissolution, which stimulate osteogenic gene expression and angiogenesis through activation of the β-catenin and BMP pathways.These nanoparticles can also be incorporated into polymeric scaffolds to enhance mechanical properties and cellular interactions, forming bioactive composite membranes with improved regenerative potential [35].

Hybrid and composite nanoparticles

Hybrid nanoparticle systems integrate the strengths of multiple material classes, such as polymeric flexibility, ceramic bioactivity, and metallic antimicrobial effects, to create multifunctional regenerative platforms. Examples include polymer-coated metallic cores (e.g., chitosan-coated silver or zinc oxide nanoparticles) that provide sustained antimicrobial action while minimising cytotoxicity and nanofiber scaffolds embedded with nHA or MSNs, which enhance mechanical stability and osseointegration [36]

Another innovative approach involves MSNs or PLGA nanoparticles loaded with bioactive ions and growth factors, forming dual- or multi-drug delivery systems capable of addressing infection control, inflammation resolution, and regeneration simultaneously. These composite nanoparticles act as “smart biomaterials”, releasing therapeutic agents in response to environmental stimuli such as pH, enzymes, or redox gradients found in inflamed periodontal pockets [37].

Such multifunctional hybrids hold immense promise for next-generation regenerative therapies, where antimicrobial, anti-inflammatory, and osteogenic functions can be spatially and temporally coordinated to achieve true periodontal regeneration [37].

APPLICATIONS IN REGENERATIVE PERIODONTAL THERAPY

Guided Tissue and Bone Regeneration (GTR/GBR)

Nano-reinforced membranes (electrospun nanofibers doped with nHA, bioactive glass or antibacterial NPs) improve mechanical strength, cell adhesion, and osteoconductivity over conventional membranes. Incorporating antimicrobial NPs (Ag, ZnO, Cu) into barrier membranes reduce early contamination and has improved bone fill in preclinical models, while bioactive filler particles (nHA, bioactive glass) accelerate early mineral deposition [38,39].

Drug and Growth Factor Delivery

Nanocarriers permit sustained local release of antibiotics (minocycline, tetracycline), anti-inflammatory agents (curcumin), statins (lovastatin), and growth factors (BMPs, PDGF, FGF), thereby matching therapeutic timing to the healing window (early infection control followed by prolonged osteoinduction). MSNs and PLGA/chitosan systems have been used to co-deliver antimicrobials and osteogenic drugs with improved pocket residence and anabolic outcomes [40].

Stem Cell and Scaffold Integration

Nanostructured scaffolds with aligned nanofibers and nano-bioactive fillers increase PDLSC/DPSC adhesion, proliferation and osteogenic/cementogenic differentiation via integrin-mediated signalling. Combining stem cells (autologous PDLSCs/DPSCs or MSCs) with nanoengineered scaffolds or delivering MSC-derived extracellular vesicles from NP reservoirs enhances vascularisation and bone-PDL interface formation in animal studies [41].

Smart and 3D-Printed Nanomaterials

Stimuli-responsive NPs (pH-sensitive, enzyme-sensitive) release payloads selectively in inflamed microenvironments, reducing off-target exposure; photothermal cores (Au, CuS) enable on-demand antibacterial treatment followed by regenerative stimulus [42]. Smart nano-bioinks combining nHA, bioactive glass, collagen and biodegradable polymers are being developed for 3D printing of defect-matched scaffolds that control local porosity, stiffness and bioactive factor gradients [43].

PRECLINICAL AND CLINICAL EVIDENCE

In vitro studies

In vitro data show that: polymeric NPs enhance antimicrobial delivery and reduce bacterial viability in biofilms; nHA and bioactive glass stimulate osteogenic markers (ALP, RUNX2, osteocalcin) in PDLSCs/DPSCs; and AuNPs and other nanomaterials can modulate macrophage polarisation toward pro-regenerative phenotypes [44].

Animal (preclinical) models

Systematic reviews and multiple animal studies report that NP-based gels, injectable scaffolds and NP-loaded membranes reduce alveolar bone loss and inflammatory cytokines and increase bone fill and attachment gain compared with controls. Specifically, PLGA-chitosan nanoparticles loaded with tetracycline and lovastatin enhanced bone regeneration in beagle dog defects, and the CuS-MSN-SCS nanoclusters improved bone fill and neovascularisation in rat periodontitis models [45].

Clinical evidence and translational status

Clinical translation remains limited to small pilot studies and case series; early human data suggest that nanoparticle-enhanced grafts and local NP carriers are safe and may improve probing depth reduction and radiographic bone fill in the short term, but high-quality randomised control trials with histologic endpoints and long-term follow-up are lacking. Regulatory approval will require standardised characterisation, GLP/GMP manufacturing, and rigorous toxicology and biodistribution data [46].

LIMITATIONS AND SAFETY

Cytotoxicity and host response

Metal ion release (Ag^+, Cu^{2+}) and reactive oxygen species (ROS) generation are effective antibacterial mechanisms but may injure host tissues at high doses; particle size, coating, surface charge, and release kinetics strongly influence cytotoxicity. Surface functionalization (polymer shells, PEGylation, biomolecule grafting) and optimised dosing can mitigate toxicity; nevertheless, long-term local and systemic safety studies are essential [47].

Aggregation and stability in oral fluids

Nanoparticles can aggregate or be opsonised by salivary proteins, altering release profiles, biological identity and stability testing in simulated saliva and gingival crevicular fluid is necessary to predict *in vivo* behaviour [47].

Standardisation, manufacturing and regulatory management

Heterogeneity in synthesis (chemical vs. green), particle polydispersity, and inconsistent physicochemical reporting impede reproducibility and regulatory review. Standardised protocols for particle characterisation (size, zeta potential, endotoxin, batch release), sterilisation, and environmental safety are needed [48].

Ethical and environmental considerations

Large-scale manufacturing and disposal of metallic NPs raise environmental and occupational concerns; additionally, indiscriminate antimicrobial use risks selecting resistant strains. Responsible design must balance efficacy with ecological safety [48].

FUTURE PERSPECTIVES

Smart nanocarriers and gene-activated scaffolds

Gene-activated scaffolds that locally deliver plasmid DNA, mRNA or siRNA to upregulate osteoinductive factors (or silence inhibitors) can program host cells for sustained regenerative signals with lower exogenous protein doses. Nanocarriers capable of safe nucleic acid delivery to PDL progenitors are an active area of research [49].

Integration with stem-cell therapy and extracellular vesicles

Combining nano-engineered scaffolds with PDLSCs/DPSCs (or their extracellular vesicles) can harness both structural cues and paracrine signals for guided cementogenesis and oriented PDL formation; controlled release of chemotactic factors may recruit endogenous progenitors to the defect [49].

3D bioprinting and personalised constructs

Patient-specific, 3D-printed nano-bioinks (nHA/bioactive glass + polymer blends) permit fabrication of scaffolds tailored to defect geometry, mechanical demands and spatial growth factor distribution, moving toward precision, defect-specific regeneration [50].

Toward “Precision Nanoperiodontics”

Integrating point-of-care nanosensors (for biomarkers/pathogens), imaging-guided placement, and customizable NP release kinetics will enable individualised therapy: targeted antimicrobial dosing, scaffold composition matched to defect biology, and real-time monitoring of healing [50].

Conclusion

Nanotechnology provides a versatile and powerful set of tools to address the biological challenges of periodontal regeneration. Polymeric carriers (chitosan, PLGA), bioactive ceramics (nHA, bioactive glass, MSNs), metallic NPs (Au, Ag, ZnO, Cu) and hybrid composites have demonstrated preclinical regenerative effects by combining antimicrobial control, immunomodulation and osteoinduction. Early translational examples (e.g., PLGA-chitosan lovastatin/tetracycline NPs, CuS-MSN-SCS nanoclusters) illustrate the potential of multifunctional nano-platforms. However, robust clinical evidence is limited and safe clinical application requires standardised material characterisation, thorough toxicology and high-quality randomised trials with histologic endpoints. With careful design and regulation, integrating nanomaterials with stem-cell approaches and digital manufacturing can realize precision nanoperiodontics offering true, predictable regeneration of the bone-cementum-PDL complex.

Conflicts of Interest

The author reports no conflicts of interest.

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