

Review Article

Apatite-Based Biomaterials in Dentistry: Advances, Clinical Applications, and Future Perspectives

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Abstract

Apatite-based compounds, particularly hydroxyapatite (HAp) and fluorapatite, are fundamental to the composition of dental and skeletal hard tissues and have become integral to preventive, restorative, and regenerative dentistry. Their close chemical similarity to natural enamel and bone, combined with excellent biocompatibility, bioactivity, and low solubility, underpins their diverse clinical applications. Accordingly, this review synthesized current evidence on the use of stoichiometric and ion-substituted apatites, with a focus on nano-HAp (nHAp), in caries prevention, enamel remineralization, dentin hypersensitivity reduction, acid erosion protection, restorative materials, endodontic therapies, periodontal regeneration, and implant surface modification. Key findings indicated that nHAp exhibits comparable or superior remineralization potential to fluoride in early enamel lesions, effectively occludes dentinal tubules, and enhances the bioactivity of restorative cements and adhesives. In addition, it was revealed that ion substitutions (e.g., fluoride, zinc, strontium, magnesium, and silicon) improve mechanical performance, osteoconductivity, and antimicrobial properties. Despite these advantages, challenges persist in the large-scale production of high-purity nanoparticles, ensuring long-term clinical durability in the oral environment and standardizing material characterization. Although safety profiles remain favorable, further longitudinal studies are required to confirm the efficacy and biocompatibility of emerging apatite-based formulations. Future implications include the development of multifunctional, “smart” biomaterials integrating apatites with responsive ion release and targeted biofilm resistance, aimed at improving restoration longevity, implant integration, and preservation of natural dentition.

Keywords: Apatite-based compounds, Hydroxyapatite, Fluorapatite, Dentistry



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Introduction

Apatite compounds, especially hydroxyapatite (HAp) and fluorapatite (FAP), play a fundamental role in the mineral composition of the human body. The majority of the hard dental tissues (enamel and dentin) and bone are composed of HAp crystals (1, 2). Due to their high chemical stability, excellent biocompatibility, and extremely low solubility, these materials are among the most important biomaterials that are used in dentistry (3, 4). HAp is a calcium (Ca) phosphate with the general formula $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, which has a hexagonal crystal lattice. In addition, FAP is formed when fluoride ions replace hydroxyl groups in the HAp lattice (formula $\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$). This substitution increases the crystal stability while significantly decreasing its solubility in acids. In other words, FAP is more resistant to acid attack and has greater hardness than HAp while maintaining similar biocompatibility. These

properties form the foundation for the extensive use of these compounds in preventing caries and various dental treatments (5-7).

The unique features of HAp, such as bioactivity (the ability to form a chemical bond with living tissue) and osteoconductivity, have made it an ideal option for restorative applications and maxillofacial surgery. However, the low fracture toughness and inherent brittleness of pure HAp limit its use in load-bearing areas. To improve these properties, research has focused on ionic substitution within the apatite structure, introducing beneficial ions (e.g., fluoride, zinc (Zn), strontium, silicon, and the like) into the HAp crystal lattice, which can enhance both its mechanical and biological characteristics (8).

In the following sections, the various applications of apatite compounds, including pure HAp, nanocrystalline forms, and ion-substituted apatites, in different dental



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fields are discussed in detail. Each section is supported by the latest evidence and documented studies to demonstrate the role of these compounds in prevention and treatment (Figure 1).

Enamel Remineralization and Caries Prevention

Dental enamel is the hardest tissue in the body, with 96% of its weight composed of mineral content (2, 7). This mineral is mostly constituted of carbonate HAp (similar to stoichiometric HAp but containing carbonate and trace ions, such as magnesium (Mg) and sodium). The presence of fluoride ions in the oral environment can replace hydroxyl groups in the enamel's apatite lattice, forming FAp, or hydroxyfluorapatite, and thereby making enamel more resistant to acids (9, 10). Fluoride accelerates the growth of apatite crystals and reduces their solubility, thereby enhancing the process of remineralization. Therefore, fluoride-containing toothpastes have long been prescribed as the standard for preventing dental caries (11, 12) (Figure 2).

However, studies over the past two decades have shown that nHAp can act as an alternative or complement to fluoride in oral hygiene products. Due to its size and structural similarity to natural enamel crystallites, nHAp can bind to the enamel surface and penetrate into its microdefects. When incorporated into toothpaste or mouthwash formulations, these nanoparticles (NPs) can infiltrate early carious lesions and directly replace lost minerals. Moreover, laboratory and clinical studies have demonstrated that nHAp toothpastes are as effective as fluoride toothpastes in remineralizing demineralized enamel, and in some indices, they even perform better (1-3). In one study, several types of toothpaste (containing nHAp, nHAp + Zn carbonate, and amine fluoride) were compared, and it was observed that toothpastes containing nHAp (with or without Zn) produced remineralization of demineralized enamel and dentin comparable to or greater than that of amine fluoride toothpaste (13).

Dentin Hypersensitivity Reduction

Dentin hypersensitivity is often due to exposed dentinal

tubules following the loss of enamel or cementum. One of the most effective methods to reduce sensitivity is through sealing or occluding these tubules (14). Owing to its ability to provide Ca and phosphate ions, HAp can form a mineralized layer on the dentin surface, effectively sealing the tubule openings (15-16). Clinical research has shown that using toothpaste containing 2% nHAp in patients with hypersensitivity significantly reduces sensitivity in a short period, an effect attributed to the formation of a mineral layer and tubule occlusion. In one clinical trial, after a 14-day hydrogen peroxide bleaching treatment (which typically causes post-bleaching hypersensitivity), patients immediately began using nHAp toothpaste. The results indicated that the group using nHAp experienced significantly less and shorter-lasting sensitivity compared to the control group (17, 18). In another comparative study, HAp-containing toothpaste provided the most effective occlusion of dentinal tubules compared to fluoride-containing and bioglass-containing toothpastes (scanning electron microscopy images confirmed the highest level of tubule occlusion in the HAp group); however, fluoride toothpaste performed slightly better in increasing remineralization and raising environmental pH (19, 20). Overall, the obtained evidence suggests that products containing apatite (pure nHAp, bioglass, or ion-substituted, such as Zn-HAp) are among the most effective agents for reducing dentin hypersensitivity and may even serve as first-line treatments (21). For example, Zn-HAp toothpastes, in addition to occluding tubules, can promote gingival health through the antimicrobial effects of Zn (13, 22).

Protection Against Acid Erosion

The increased consumption of acidic beverages and foods (e.g., energy drinks or processed fruit juices) has led to a higher prevalence of enamel erosion, especially among children and adolescents. A novel preventive approach under investigation is the use of nHAp to reduce the destructive effects of acids on enamel. In one study, an acidic sports drink (Powerade®) was enriched with different concentrations of nHAp, and its effect on

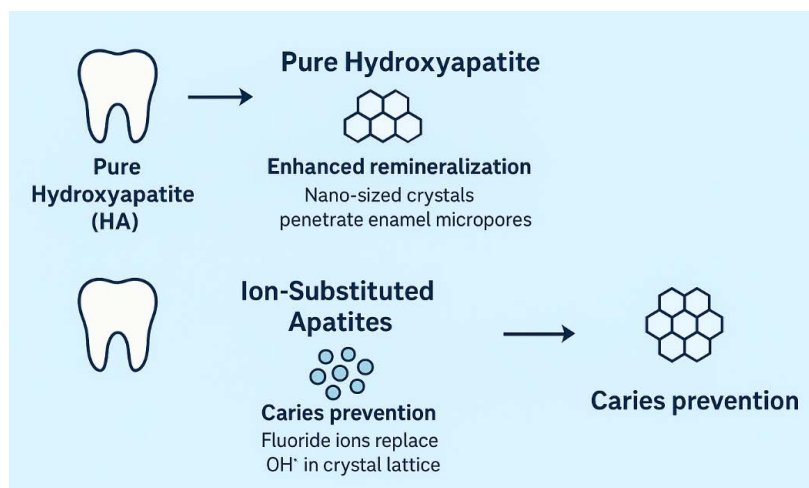


Figure 1. Apatite's Role in Dental Care

dental enamel was assessed. The results demonstrated that the surface hardness of the enamel after exposure was greater when the nHAp concentration was higher, thereby reducing softening and erosion (17). In another study, after immersing teeth in beer (to simulate acidic erosion conditions), they were placed in an nHAp solution. Microhardness measurements indicated that the hardness of nHAp-treated enamel returned almost to its original level, whereas the control group (acid without HAp treatment) showed a sharp and lasting decrease in hardness. These findings confirm that the presence of apatite can neutralize the harmful effects of acidic environments and protect enamel against erosion (19). Additionally, preventive use of apatite-containing oral hygiene products (HAp-enriched mouth rinses, gels, and the like) can act as a shield against erosion. For example, mouth rinses containing nHAp and Zn ions not only provide the benefits of HAp toothpastes but also inhibit bacterial growth without causing tooth staining like chlorhexidine. Interestingly, a comparative study reported that Zn-HAp toothpaste provided better enamel protection against acidic beverages than fluoride toothpaste, reducing enamel demineralization to a greater extent. Therefore, incorporating apatites into preventive regimens, from toothpaste to mouth rinses and topical treatments, can significantly reduce caries, hypersensitivity, and erosion (23).

Applications in Restorative Materials

Resin Composites and Silanes

Today, extensive efforts are being made to improve the properties of commonly used restorative materials, such as resin composites and dental cements. One innovative approach is the incorporation of nHAp fillers into these materials to render them both bioactive and mechanically stronger (2). As a filler, nHAp not only enhances the mechanical strength of the restorative material but also, due to the release of mineral ions, can protect the environment around the restoration from demineralization and even promote remineralization at the restoration–tooth interface. For example, adding varying percentages of nHAp to a resin composite was evaluated in a laboratory study, and the results revealed improvements in thermal stability and mechanical properties, with the best outcomes



Figure 2. Preventive Applications

obtained when nHAp was combined with a certain amount of other NPs (e.g., Al_2O_3). Such nano-hybrid composites can be utilized for cavity restorations with high strength and lower risk of secondary caries (8). Additionally, coating the surface of impression materials with nHAp particles has been explored in research phases, with the potential to improve detail reproduction and compatibility with oral tissues. Although this application is still in the laboratory stage, the introduction of the “nano-impression materials” concept illustrates the broad potential applications of nHAp in all dental specialties (13) (Figure 3).

Glass Ionomer Cements and Calcium-Based Dental Materials

GICs are widely used restorative and luting materials that are valued for their fluoride release and chemical bonding to tooth structure. However, their relatively low mechanical strength has always been a challenge. Studies have shown that adding apatite particles (HAp and even FAp) to GICs can improve their mechanical properties. Overall, it has been reported that adding about 5% nHAp can increase the compressive strength of GIC from ~160 MPa to ~177–179 MPa, with similar improvements in tensile and flexural strength (1). The improvement is likely due to filling matrix voids and the participation of apatite in the bonding network. Moreover, the presence of apatite leads to the gradual release of Ca and phosphate, which can enhance the antimicrobial and anti-caries properties of the surface of the restoration. Thus, producing apatite-containing GICs (either commercially or as chairside additives) can result in restorations with greater durability and dual restorative-preventive properties (8).

Fissure Sealants and Pit-and-Fissure Materials

Fissure sealants used to prevent caries in posterior tooth pits and fissures have also been modified with apatite. In one investigation, adding nHAp to a fissure sealant improved its characteristics; nHAp-containing sealant filled pits and fissures more uniformly and exhibited fewer voids or gaps (2). Additionally, fluoride release was greater

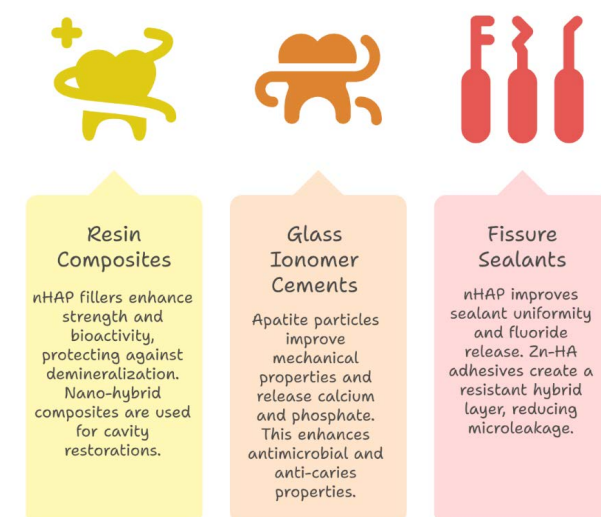


Figure 3. Applications in Restorative Materials

in the nHAp group compared to the conventional sealants. Similarly, dental adhesive systems have been explored with added nHAp or Zn-HAp, showing the potential to create a more resistant hybrid layer and reduce microleakage (3). For example, a Zn-HAp adhesive effectively covered the etched dentin surface and filled tubules in scanning electron microscopy imaging, whereas adhesives with traditional agents (e.g., potassium oxalate) did not achieve this coverage (8). Although in some fluid permeability tests, other formulations performed better, the results indicated the high potential of apatite in improving dental bonding materials. These advancements suggest that in the future, it is probable to observe more bioactive restorative materials where apatite compounds are integrated into formulations, granting restorations self-remineralizing or anti-caries capabilities (22).

Applications in Endodontics and Pulp-Dentin Regeneration

Direct Pulp Capping and Dentin Repair

The mineralization-inducing ability of HAp has attracted attention in endodontics. Many Ca-based materials used in vital pulp therapy (e.g., mineral trioxide aggregate [MTA] and Ca hydroxide) aim to create a hard dentin bridge over the exposed pulp. Research has shown that Ca-silicate materials, such as MTA, release Ca-hydroxide in the presence of body fluids, leading to HAp precipitation on their surfaces (1). This apatite layer plays a key role in sealing the pulp chamber and stimulating pulp cells to form reparative dentin. Indeed, apatite formation is one of the reasons for MTA's success in inducing dentin bridges. Following these findings, researchers have directly tested nHAp as a pulp-capping material. Preliminary results revealed that nHAp paste or suspension applied to exposed pulp can stimulate localized mineralization without causing severe inflammation. Although MTA and traditional materials remain the gold standard, future formulations of pure or ion-substituted apatites (e.g., nanocrystalline hydroxyfluorapatite) could emerge as safe and effective pulp therapy agents (3, 22).

Several in vivo and comparative studies have further highlighted the biological potential of nHAp for vital pulp therapy. For example, an in vivo rat model using nHAp/polyamide-66 as a direct pulp-capping agent demonstrated significant odontoblastic differentiation and microvascular regeneration around the exposure site (23). Similarly, a study using hybrid nHAp scaffolds confirmed their biocompatibility and reparative dentin induction in pulpitis models (24). Nevertheless, systematic reviews comparing

MTA and Biodentine indicate that while both materials display comparable dentin bridge thickness and clinical success rates, nHAp formulations still require optimization and long-term clinical validation before achieving equivalent reliability in human applications (25) (Table 1).

Pulp Tissue Engineering and Root Regeneration

In modern regenerative endodontics, the goal is to create an environment where stem cells can differentiate within the root canal and form new vital tissue (e.g., dentin/pulp). In this context, bioactive scaffolds are essential (2). Due to its similarity to the mineral phase of teeth, HAp is an excellent scaffold for guiding odontoblast differentiation (26, 27). One study showed that a gelatin/nHAp scaffold promoted odontoblastic differentiation of dental pulp stem cells and enhanced dentin matrix formation. In another experiment, polycaprolactone nanofibers impregnated with nHAp provided a suitable surface for human pulp cell adhesion and proliferation, with mineralized matrix deposition observed after 3 weeks in culture (28). Moreover, combining nHAp with biopolymers, such as silica-enriched chitosan, led to the development of bilayer membranes that have been successfully used in guided tissue regeneration (particularly for periodontal defects). These silica-HAp nanocomposite membranes exhibited bioactivity and osteoconductivity suitable for reconstructing oral bone tissue (29, 30) (Figure 4).

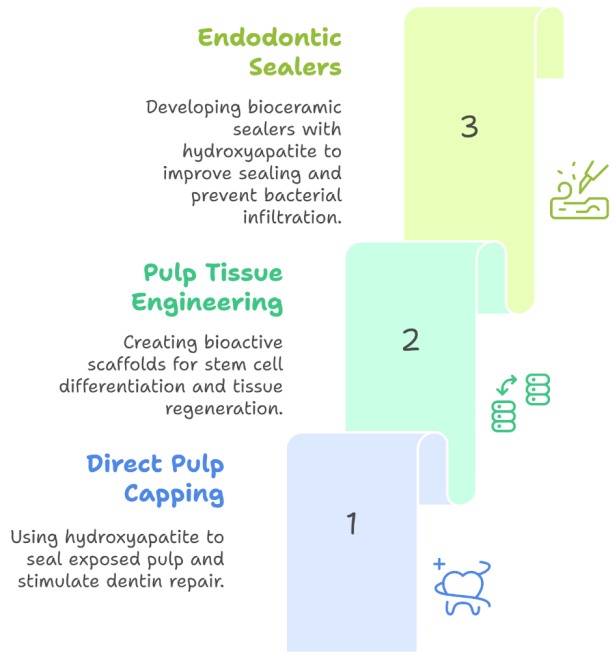


Figure 4. Applications in Endodontics

Table 1. Comparison of nHAp and MTA in Direct Pulp Capping Treatment

Property	Nano-Hydroxyapatite	Mineral Trioxide Aggregate
Time for action	Faster (quick activation on the dentin surface)	Moderate (requires time to form a dentin bridge)
Dentin bridge formation	Excellent (forms a mineral layer)	Excellent (forms a dentin bridge)
Antibacterial effect	Limited (less effective against bacteria)	Very good (effective antibacterial action)
Clinical stability	Requires longer-term studies	Very good (reliable in long-term treatments)

Note. nHAp: Nano-hydroxyapatite; MTA: Mineral trioxide aggregate.

Endodontic Sealers and Root Filling Materials

In root canal treatment, one of the main goals is to completely fill the canal system and prevent bacterial infiltration. New bioceramic sealers containing Ca phosphates and silicates react with moisture inside the canal to form HAp. For example, MTA-based or Ca-silicate-based sealers reinforced with HAp create an apatite layer after setting, which improves adhesion to canal dentin and enhances sealing. These sealers, in addition to physical sealing, have antimicrobial properties due to Ca^{2+} and OH^- release. It has been reported that adding nHAp to some sealers (or coating gutta-percha cones with nHAp) can reduce microleakage while improving the biocompatibility of endodontic materials (1, 8).

Applications in Periodontology and Jawbone Regeneration

Bone Grafting and Defect Filling

HAp was first used for repairing bone defects about a century ago, and since the 1970s, Ca phosphates have been seriously considered as bone graft materials in oral surgery. This popularity stems from the high similarity of HAp to the mineral phase of bone and teeth, which facilitates its acceptance by the body (3, 8). In dentistry, HAp granules and blocks are widely utilized for reconstructing bone defects. For instance, HAp granules have been used to treat deep periodontal pockets (vertical bone defects) to regenerate resorbed bone, implying successful defect filling. In addition, HAp powder is applied after cyst removal or apicoectomy to accelerate bone healing. In severe alveolar ridge resorption, porous HAp blocks are grafted to increase ridge width and height. One of the most widely used graft products worldwide is deproteinized bovine bone mineral (e.g., Bio-Oss®), in which organic components are removed, and the remaining structure consists of natural apatite crystals (31, 32). These materials provide an excellent scaffold for new bone growth and are slowly resorbed over several years. Pure HAp can chemically bond with bone while not inducing adverse inflammatory or toxic reactions. However, it is considered relatively non-resorbable in the body; unlike β -TCP, which is replaced by bone within months to a year, HAp can remain for years. Some studies confirm the lack of significant resorption, while others report gradual degradation. To address this issue, biphasic Ca phosphate products combining HAp with TCP have been developed to provide both scaffold stability and resorbability (33). Additionally, substituting certain ions into HAp can increase its dissolution rate and improve its replacement by bone. For example, carbonate HAp (CO_3Ap) resembles natural bone composition and resorbs faster than pure HA, aiding quicker bone regeneration. Research has also shown that combining carbonate ions with silver in HAp can create a material that prevents implant-related infections (peri-implantitis) while maintaining antimicrobial properties. Incorporating silver or Zn ions into HAp, either as coatings or graft particles, can help reduce infection risk at graft sites or around implants

while still providing the mineral scaffold for bone growth (34, 35) (Figure 5).

Guided Bone Regeneration and Ion-Substituted Hydroxyapatite

Adding beneficial ions to HAp has yielded notable results in bone repair:

- **Strontium-Substituted Hydroxyapatite:** It increases osteoblast activity and remineralization capacity; this toothpaste has been studied for root caries management, increasing dentin Ca/P ratios beyond those achieved by casein phosphopeptide-amorphous Ca phosphate (36).
- **Magnesium-Substituted Hydroxyapatite:** It is naturally present in bone and promotes bone formation. In addition, Mg-HAp granules used in alveolar ridge preservation could increase the expression of bone metabolism genes and accelerate bone regeneration. In animal studies, Mg-HAp completely regenerated bone in extraction sockets within 12 months without inflammation (37).
- **Silicon-Substituted Hydroxyapatite:** It demonstrates higher bioactivity and is applied in membranes and scaffolds for bone regeneration.
- **Cerium-Substituted Hydroxyapatite:** At low concentrations, it stimulates cell differentiation and bone formation.

These developments aim to create bone substitutes that actively support regeneration and defend against pathogens, rather than serving only as passive fillers. Ion-substituted apatites demonstrate high biocompatibility, enhanced mineralization induction, and even antibacterial properties, making them promising for periodontal

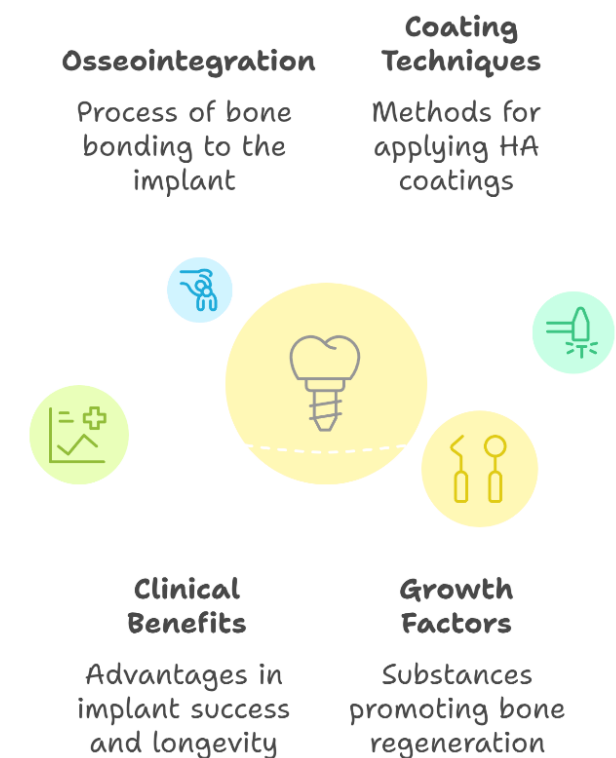


Figure 5. Enhancing Dental Implants With Hydroxyapatite Coatings

surgery and implantology (38, 39).

Dental Implants and Prosthodontics

Apatite-Coated Dental Implants

One of the significant advancements in the field of dental implantology has been the application of HAp coatings on metallic implant surfaces, typically titanium. Considering that commercially pure titanium is bioinert and establishes no direct chemical bond with bone, achieving complete osseointegration often requires a prolonged healing period (40, 41). Coating the implant surface with a layer of HAp allows the body to immediately interact with a surface that mimics its own hard tissue, thereby eliciting a favorable biological response. Some studies have shown that titanium implants coated with HAp exhibit substantially greater bone-to-implant contact compared to uncoated implants, with one study reporting approximately a 70% increase in the contact area. This enhanced surface interaction improves osteoblast adhesion (42, 43). More importantly, HAp possesses osteoconductive and bioactive properties, meaning that it can induce osteoblast growth and differentiation on the implant surface, forming a mineral bridge between bone and implant. As a result, the rate of osseointegration is accelerated, and the implant achieves stability in a shorter time frame. Another key advantage is the reduced risk of infection and implant failure, as HAp coatings facilitate rapid filling of the gap between the implant and surrounding bone, thereby minimizing bacterial infiltration and unwanted fibrous tissue formation (44, 45). Clinical evaluations have indicated that HAp-coated implants demonstrate higher long-term success rates and greater longevity compared to their uncoated counterparts. For example, a systematic review revealed a significantly higher 10-year survival rate for HAp-coated implants (46-48).

Various techniques have been developed to deposit apatite coatings on implants, ranging from physical methods, such as plasma spraying and physical vapor deposition, to chemical approaches, including electrochemical deposition, sol-gel processing, and biomimetic precipitation (40). Each method has its own merits and limitations. For instance, plasma spraying can produce a strong bond between the coating and the metal substrate but may compromise coating uniformity on complex geometries; conversely, chemical methods enable uniform coating on intricate surfaces and allow the incorporation of bioactive agents into the coating matrix (42-44). The ultimate goal of these techniques is to produce a porous HAp layer that immediately adsorbs proteins and osteogenic cells upon implantation, functioning as a mineral scaffold. Such implants typically achieve reliable stability within the first few weeks post-surgery. Additionally, HAp can serve as a carrier for growth factors; during the coating process, osteoinductive agents (e.g., bone morphogenetic proteins) can be incorporated into the HAp layer for gradual release, further enhancing bone regeneration. This strategy has shown promising outcomes in certain preclinical trials, with notable

increases in peri-implant bone volume (46, 47).

Other Prosthodontic and Orthodontic Applications

Direct use of HAp is relatively limited in the field of dental prosthetics, including dentures, maxillofacial prostheses, and related devices. However, ongoing research aims to enhance the biocompatibility of prosthetic surfaces in contact with oral mucosa by applying apatite-based coatings, which may also inhibit fungal and bacterial colonization (49, 50). For example, coating denture acrylic with an nHAp/silver composite has been proposed to improve tissue adhesion while providing antimicrobial properties. Furthermore, traces of HAp applications can be found in orthodontics. One area of investigation involves coating enamel surfaces with HAp-containing solutions after the removal of orthodontic brackets as a potential method for repairing white spot lesions and promoting enamel remineralization (51, 52). Additionally, the incorporation of HAp into alloys used for orthodontic mini-screws has been explored. A particularly interesting study investigated the fabrication of mini-screws from polyetheretherketone reinforced with nHAp. Molecular modeling results indicated that the addition of HAp to polyetheretherketone enhanced the affinity of these small implants for bone-related markers, such as alkaline phosphatase and insulin-like growth factor 1, potentially improving the osseointegration of mini-screws while reducing the likelihood of loosening. These findings open new perspectives for the application of apatite-based materials, even in smaller and temporary dental devices (53-55).

Industrial and Material Challenges

HAp and FAp have excellent biocompatibility, but their production and material properties pose several challenges. Synthesizing nHAp with consistent quality is difficult, and common methods often yield impurities and inconsistent particle sizes or morphologies. Precise control of NP size, distribution, and crystallinity is challenging, and NPs tend to agglomerate without careful stabilization (56, 57). Many fabrication processes require extreme conditions (high pH, temperature, and long reaction times) and expensive, complex procedures. As a result, only a few synthesis methods are both economically viable and capable of producing high-purity apatite NPs at scale. Other material-related limitations of HAp are its intrinsic brittleness and poor mechanical strength, especially in bulk form (58, 59). Pure HAp ceramics are not well-suited to bear heavy loads, which limits their use as standalone structural materials. In bone grafting, for example, the low resorbability of HAp can leave a residual brittle scaffold; conversely, more resorbable Ca phosphates, such as β -TCP, can lack long-term stability. These inherent trade-offs necessitate composite approaches (e.g., HA/ β -TCP biphasic ceramics) to balance scaffold persistence with resorption (60, 61) (Figure 6).

Clinical Limitations

In clinical applications, apatite-based treatments face

practical limitations in durability and efficacy over time. For instance, nHAp toothpastes and pastes can help remineralize enamel and reduce hypersensitivity by depositing a mineral layer, but the longevity of these results remains a concern. The protective HAp layer formed on enamel may be gradually worn or dissolved by saliva and dietary acids, implying that repeated application is required to maintain benefits. In addition, salivary proteins and the oral pellicle can modulate HAp's effectiveness; in vitro dentin studies have shown that the presence of saliva can alter the occlusion of tubules or mineral deposition compared to dry conditions (60). Thus, translating in vitro apatite benefits to the in vivo oral environment (with saliva, plaque, and oral flora) remains a challenge. Another limitation is that apatite additives alone may not handle complex treatment scenarios. In deep or large lesions and pulp exposures, simply applying HAp or FAp may be insufficient; these cases often rely on bulk materials (resins, glass-ionomers, or bioactive cements) to provide structure and seal. For example, while nHAp has been explored as a direct pulp-capping agent, its handling and mechanical integrity are not as robust as a setting Ca-silicate cement (62). In practice, apatite compounds frequently must be combined with carriers or binders (e.g., adhesives, composites, or cements) to be clinically usable in restorations or regenerations. This adds complexity and can attenuate the pure biological activity of the apatite. Furthermore, the incorporation of HAp into dental composites or adhesives can occasionally compromise the material's mechanical properties if the filler loading or dispersion is not optimal. Accordingly, achieving a balance between bioactivity and the functional requirements of a dental material is an ongoing practical challenge (63) (Table 2).

Research and Evidence Challenges

Despite the promise of HAp and FAp, there are gaps in the research evidence, especially regarding long-

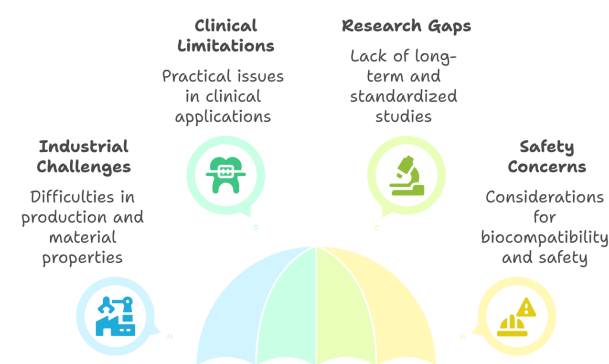


Figure 6. Challenges in Apatite Material Applications

term outcomes. Many studies demonstrating enamel remineralization or dentin repair with nHAp are short-term in vitro or in situ experiments (2). Long-term clinical trials are relatively scarce, so the longevity of apatite-induced remineralization or hypersensitivity relief remains inconclusive in some cases. For example, initial trials indicate that HAp-containing toothpastes can reduce caries and hypersensitivity, but well-designed studies over several years are needed to confirm that these benefits persist and translate into significantly lower decay rates compared to conventional fluorides (5). Another research challenge is the lack of standardization in synthesis and analysis methods. Different studies use HAp/FAp particles of varying sizes (nano vs. micro), different crystal stoichiometries or doping, and varying delivery methods, making direct comparisons difficult. Variations in particle characteristics can lead to inconsistent biological results (64). For instance, an nHAp prepared by one method might be more soluble or more highly substituted (non-stoichiometric) than another, affecting its behavior in vivo. Similarly, outcome measures differ; one study may assess surface hardness gain in enamel, while another measures lesion depth or Ca uptake, leading researchers to occasionally draw differing conclusions about "efficacy". The result is a heterogeneous body of literature. Systematic reviews frequently note that although the evidence is **encouraging**, further long-term and standardized studies are necessary to confirm the broader applicability of HAp-based interventions. Likewise, researchers are still optimizing apatite formulations (e.g., carbonate-HAp vs. FAp vs. nHAp) and delivery systems to maximize clinical effectiveness, indicating the field is very much in development (65, 66).

Biocompatibility and Safety Considerations

Ca phosphate materials, such as HAp and FAp, are generally regarded as safe and biocompatible given their chemical similarity to natural tooth and bone mineral. In fact, both enamel and bone are predominantly composed of a carbonated apatite similar to HAp. According to studies, apatite compounds are non-toxic and well-tolerated in oral and bony environments over the short term. They are bioinert in the sense of not eliciting strong immune responses, and osteoblasts and odontoblasts readily accept apatite surfaces (26, 27). However, when used in novel forms (especially NPs), there are still open questions about long-term safety and metabolic fate. NPs can have unique behaviors; for example, in vitro studies suggested that nHAp can penetrate oral mucosal tissues or be taken up by cells, which raises the concern of potential

Table 2. Comparison of Hydroxyapatite With Other Biomaterials (Fluoride, Bioglass, and Others)

Property	Hydroxyapatite	BioGlass	Fluoride
Bioactivity	Yes (it forms a chemical bond with living tissue)	Yes (it forms a bond with bone and tooth)	Yes (it enhances enamel hardness)
Acid resistance	Moderate (effective in acidic environments)	High (resistant to acid erosion)	Excellent (resistant to decay)
Resorption in the body	Low (very slow resorption)	High (faster resorption)	Very low (stable over time)
Dentin hypersensitivity	Yes (it occludes tubules)	Yes (protection against caries)	Yes (effective in reducing sensitivity)

Table 3. Comparison of Nano-Hydroxyapatite and Fluoride in Caries Prevention

Property	Nano-Hydroxyapatite	Fluoride
Remineralization capacity	High (forms mineral layer)	Moderate (enhances crystal growth)
Dentin tubule occlusion	Excellent (binds to enamel surface)	Moderate (limited efficacy)
Long-term stability	Moderate (requires frequent reapplication)	High (good long-term stability)
Antibacterial effect	Limited (less effective against bacteria)	Moderate (antibacterial effect)

systemic exposure. Some studies reported that nHAp particles might translocate through the oral epithelium into systemic circulation in extremely small amounts, and in high concentrations, these particles can have cytotoxic effects on cells. While the oral mucosa turnover is rapid (limiting prolonged NP absorption), the possibility of chronic low-level exposure over years of daily toothpaste use, for instance, warrants further study (65). Accordingly, researchers emphasize the need for long-term studies to ensure that continuous use of nHAp in products is free of any systemic or cumulative adverse effects. Another safety aspect is the fluoride content when using FAp or fluoride-doped HAp. FAp can release fluoride ions, which at appropriate levels are beneficial (supporting remineralization and even displaying antibacterial, osteogenic effects). However, excessive fluoride release could theoretically contribute to fluorosis or local toxicity; thus, FAp-based materials must be formulated to release fluoride in safe, controlled amounts. No serious adverse effects have so far been reported from HAp or FAp dental applications in clinical use, and both are considered bioactive but benign. Nevertheless, regulatory and toxicology assessments continue to monitor particle size distribution (to avoid inhalation risks in powders), purity (to avoid trace contaminants), and degradation products of these apatite materials over long durations. In summary, the biocompatibility profile of apatites is favorable, but diligent long-term evaluation is essential to fully assure safety, especially as their usage in NP form and in novel delivery systems grows (67, 68) (Table 3).

Conclusion and Outlook

Apatite-based compounds, especially HAp and FAp, have proven indispensable in preventive, restorative, and regenerative dentistry due to their chemical affinity with dental and bone mineral, excellent biocompatibility, and osteoconductivity. Advances in nanotechnology and ionic substitution have expanded their functional scope, improving mechanical strength, antibacterial activity, and remineralization capacity.

Despite these advances, challenges remain. Industrial-scale synthesis of high-purity, uniformly dispersed NPs is costly and technically demanding, while the durability of apatite-derived mineral layers in the complex oral environment requires further validation. Long-term safety data, particularly for nanoparticulate forms, are still limited, indicating the need for standardized protocols and extended clinical trials.

The future of apatite research lies in multifunctional, “smart” formulations, integrating with other bioactive

agents to deliver responsive ion release, enhanced biofilm resistance, and targeted tissue regeneration. With continued interdisciplinary collaboration and rigorous clinical evaluation, apatite compounds are poised to further improve restoration longevity, implant integration, and preservation of natural dentition.

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Competing Interests

Not applicable.

Ethical Approval

This study was approved by Research Ethics Committees of Hamadan University of Medical Sciences (Ethical code:IR.UMSHA.REC.1405.185).

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