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Biomaterials in dentistry: Advances in tissue engineering for dental restoration

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***Abstract*---**Background: In regenerative medicine, advances in biomaterials have significantly impacted various medical fields, including dentistry. The use of implants, both metallic and non-metallic, has raised concerns about bacterial adhesion and biofilm formation, which can lead to complications such as peri-implantitis. Innovations in drug delivery systems and additive manufacturing technologies offer new solutions to these challenges. Methods: The review explores recent developments in biomaterials for dental restoration, focusing on drug-eluting implants, additive manufacturing, nanotechnology, and biocompatible coatings. The study evaluates the effectiveness of various drug delivery systems, including hydrogels, nanoparticles, and polymers, and discusses advancements in 3D printing and surface coatings. Results: Additive manufacturing technologies, such as 3D printing, have enabled the creation of precise models and drug delivery systems. Nanotechnology has introduced new materials with improved antimicrobial properties and targeted drug delivery capabilities. Innovations in coatings, such as hydroxyapatite (HA) and calcium phosphate, have enhanced osseointegration and reduced infection risks. Additionally, nanomaterials like gold and silver nanoparticles have shown promise in improving implant functionality and reducing bacterial colonization. Conclusion: Advances in biomaterials and manufacturing technologies have significantly improved the effectiveness and safety of dental implants. The development of localized drug delivery systems, enhanced by 3D printing and nanotechnology, offers promising solutions to common challenges such as bacterial infections and poor osseointegration. Future research should focus on optimizing these technologies and addressing remaining challenges to further enhance dental restoration outcomes.

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Keywords---Biomaterials, Dental Implants, Drug Delivery Systems, Additive Manufacturing, Nanotechnology, Hydroxyapatite, Calcium Phosphate.

Introduction

In the field of regenerative medicine, significant strides have been made in enhancing patients' quality of life and longevity. The advancement of biomedical implants has notably influenced contemporary healthcare. Implants composed of both metallic and non-metallic biomaterials, whether permanent or temporary, are prevalent in various specialties such as orthopedics, maxillofacial and cranial surgery, ophthalmology, and neurosurgery. Biomaterials, irrespective of their anatomical placement, are prone to bacterial adhesion and biofilm formation, identifying them as a category of materials susceptible to such complications [1,2,3,4].

The targeted delivery of local medications to tissues can minimize the use of systemic antimicrobials. Beyond hydrogels and nanoparticles, polymers have also been evaluated for the release of topical antibiotics [5]. It is essential that drug concentrations at the implant site remain stable and effective to prevent bacterial resistance. Given the longevity expected of dental implants, drug-release coatings must possess the capability to recharge or replace themselves as required. PDLA is a suitable drug delivery agent, although its effectiveness is temporary. For over two decades, minocycline microspheres have been utilized to manage infections around implants [6,7,8,9]. Although peri-implantitis commonly manifests as a chronic, slow-developing condition, it can emerge shortly after surgery or even years later. If left untreated, peri-implantitis may lead to significant bone loss surrounding the implant, osteomyelitis, abscesses, sinusitis, pneumonia, and pathological fractures of the jawbone [1].

Additive manufacturing (AM) technologies, such as 3D printing, offer the capability to fabricate a variety of devices with numerous potential applications. Among these, bioengineering stands out as particularly promising. 3D printing research enables the creation of models that closely mimic biological tissues such as bones, cartilage, or heart valves. AM technology allows for precise geometric design. The increasing demand for tissue engineering, antimicrobial and anti-biofouling devices, and regenerative medicine has driven researchers to explore novel manufacturing technologies to address tissue and organ shortages and the immunological challenges of implanted devices. Various fields benefit from this technology, including the creation of artificial hips, knees, heart valves, stents, and vascular grafts from polymeric materials, enhancing both quality of life and, in some cases, longevity [10,11,12,13,14]. In oral medicine, localized drug delivery systems are employed to treat oral diseases. The precision of 3D printing enables the design of unique drug delivery systems. For instance, chlorhexidine-coated mouthguards inhibit bacterial growth in the mouth. Wearable oral delivery devices, such as 3D-printed mouthguards with preloaded drugs, can provide effective, personalized dental therapeutics [15,16].

Drug-eluting implants are designed to prevent infections associated with dental and orthopedic implants. Metallic implants are frequently coated with polymeric or ceramic layers to embed drugs, though these coatings can present complications such as detachment, chemical degradation, and corrosion. Consequently, inorganic coatings are under investigation as potential drug delivery systems. Despite limited focus on metallic drug-eluting systems, this mini-review aims to summarize recent developments in implant drug delivery systems [6,17,18]. Dental implants, sealed with healing abutments, which are permanent permucosal implants, face increased infection risks and potential failure. Reducing bacterial presence around biomaterials can promote healing. Due to the straightforward design and structure of healing abutments, they can be easily adapted into temporary local drug delivery systems. Effective infection prevention and enhancement of implant-tissue interfaces are critical to reducing bacterial infiltration during the implant healing process [1,19,20,21,22].

Nanotechnology is increasingly significant in dentistry for its potential to improve material properties at the nanoscale. Nanomaterials can be customized for interaction with biological systems and targeted delivery. In dental implants, biomaterials are vital for providing strength, biocompatibility, and integration with surrounding tissues. Nano-based drug delivery systems offer localized and sustained release of therapeutic agents, which is particularly beneficial in the oral environment. Nanoformulations allow precise control over drug release kinetics, thereby enhancing therapeutic efficacy while minimizing side effects. Nano coatings on implant surfaces can reduce microbial adhesion and infection risk and may improve osseointegration by fostering better interaction with surrounding bone tissues. Engineering biomaterials to deliver anti-inflammatory drugs can help mitigate inflammation related to implantation. Ensuring the biocompatibility and long-term safety of nano and biomaterials in the oral environment presents significant challenges, requiring navigation of regulatory and translational hurdles for practical clinical applications. Recent studies and clinical trials have explored specific nanoparticle formulations demonstrating success in dental implant drug delivery [1,2,23,24,25,26,27,28,29]. This review article discusses the current applications of nano and biomaterials in the drug delivery systems for dental implants.

Biomaterials and Dental Applications:

The potential of biocompatible materials and systems has been brought to light by dental and oral illnesses. Biomaterials can be used to replace or improve any organ, tissue, or bodily function that involves direct electrical interaction with biological tissues. Because these materials have characteristics similar to those of biological tissues, dental researchers frequently study hyaluronic acid, collagen, gelatin, and chitosan [30,31, 32]. There are several uses for calcium phosphate (CP) in dentistry and maxillofacial surgery. Microbial biofilms and external infections have caused numerous bone transplant and dental implant procedures to fail. Antibiotics and CP together can lower infection rates and enhance results. Doped carriers with appropriate mechanical and physicochemical qualities and CP are necessary for the effective delivery of antibiotics [33]. Calcium pyrophosphate, metaphosphate, and orthophosphates are produced during pyrophosphate hydrolysis under physiological circumstances. Antibiotics for

controlled release may also be included in the CP matrix, either for treatment or prevention [4,34,35]. As a result, a lot of ceramic nanoscaffolds that encapsulate drugs and facilitate drug delivery, cell proliferation, and tissue regeneration have multiple uses. When it comes to mechanical support, ceramic scaffolds are usually better than polymeric ones. Drug-release kinetics can be regulated by optimizing the surface area, grain size, and calcium-to-phosphorus ratio of calcium phosphate nanoparticles. Hollow silica nanospheres, which allow for time-delayed, multi-stage drug release and may store up to eight times more medicines than their solid counterparts, have been created using self-templating molecules under strict supervision [28, 36].

A number of growth factors, including VEGF, BMPs, PDGF, and IGFs, are essential for craniofacial development [37]. The process of skeletal development and bone production involves the activation of Smad-dependent and MAPK signaling pathways. During trauma or infection, fibroblast growth factor signaling affects bone regeneration, remodeling, and wound healing [38]. While VEGF influences the proliferation, vascularization, and ossification of the maxillary, palatine, and calvarial mesenchyme, IGFs assist the formation and maintenance of the skeleton. Patients with significant craniofacial deformities may not recover as well if there are imbalances in these growth factors [39]. Growth factors have a short circulation half-life, restricted diffusion, quick degradation, and cleavage, which means that high doses and frequent injections are necessary to induce particular biological responses [40]. In vivo, ECM molecules stabilize and safeguard growth factors. For the release of growth factors to be localized and sustained, appropriate carrier systems are required [41]. Growth factor-ensnaring materials include hydrogels, nanofibrous membranes, micro/nanoparticles, and sponges [42]. Rats with near-complete healing of size abnormalities have been found to receive simultaneous dose of BMP-2 and VEGF [43, 44]. The release of growth factors can be regulated by using different immobilization methods [45]. Preclinical and clinical trials of these delivery methods are scarce, despite a great deal of in vitro study. treatments utilizing rhBMP-2 embedded in absorbable collagen sponges for sinus lifts and alveolar ridge augmentations are among the commercially accessible rhBMP-based treatments [46, 47]. Clinical use of carrier-based grafts is permitted, such as OP-1 Putty with rhBMP-7 [48]. In addition to preserving regulated release kinetics, growth factor-containing materials offer a porous osteoconductive structure that promotes bone ingrowth. It is possible to speed up bone regeneration by combining or giving different growth factors one after the other. Different delivery vehicles have successfully encouraged bone repair and angiogenesis, despite difficulties in figuring out the best concentrations, tailoring release profiles, and managing gradients and timing [49,50,51]. For instance, during phase I/II human clinical studies, combinations of PDGF/IGF-I in methylcellulose gels have demonstrated enhanced defect filling in periodontal lesions [52,53]. In peri-implant environments, newer techniques simulate the soft tissues and bone around the implant. In order to improve osseointegration and soft tissue integration and lessen biofilm-induced peri-implant inflammation, dental implant surfaces have been modified using a variety of extracellular matrix proteins, peptides, and growth factors. Over time, osteoconductive or antibacterial molecules may be released from titanium surfaces coated with bioabsorbable polymeric coatings. Hydroxyapatite (HA) has been applied to titanium surfaces using physiologically simulated calcium and

phosphorus-containing bodily fluids [54,55,56]. Osteoconductive coatings, such as HA, are by nature calcium-phosphorus. The materials' biodegradation properties are affected by various factors, including coating thickness, crystallinity, and calcium/phosphorus ratios. The standard atmospheric plasma-spraying technique, plasma spraying, is frequently used to apply HA to titanium implant surfaces. Factors like the composition of the flame and the velocity of spraying have an impact on the chemical and physical properties of the spray [23, 29]. After five years, clinical success rates for HA-coated implants were over 95%; however, after ten years, these rates fell to less than 80%, possibly as a result of problems with the HA coating layer. To further assess calcium-phosphorus coatings, clinical investigations are required [13,29,57]. By replacing lost teeth with implants, which frequently use materials like titanium and its alloys, oral function and aesthetics are restored. Tooth replacement has been revolutionized by dental implants, which are renowned for their high success rates. Osseointegration is the process by which an implant's mechanical characteristics cause it to fuse with the surrounding bone. Through novel implant designs, surface alterations, and implant-abutment linkages, ongoing research seeks to improve long-term efficacy and cosmetic results [24,58,59,60]. Porous HA can be produced by hydrothermally converting calcium-based coral or bone, sacrificial porogen destruction, repeated reticulated foam scaffolds, or ceramic slip foaming. Drug delivery methods can be constructed using spherically porous HA granules. The structure of these granules can be changed by varying the amounts of sodium chloride and water. This can be investigated for the release of antibacterial or anti-inflammatory drugs at the sites of implantation. For regulated drug release, HA granules with intricate microchannel architectures are being studied [28,58,61,62].

The biocompatibility of HA coating surfaces with hard tissue is demonstrated by the direct attachment of osteoblasts to them. It has been observed that HA-coated metal implants improve bone apposition and inhibit the release of metal ions into the bone. On the other hand, problems with the HA coating layer, including worn or delaminated particles, might promote inflammation and hinder bone healing. In load-bearing regions, thick coating layers may also raise the chance of implant breakage. The long-term clinical benefits of plasma-sprayed HA have not consistently been achieved by other calcium-phosphorus coatings, despite their exploration [29,63,64, 65]. Since HA resembles natural bone mineral, it is a perfect material for implants and bone grafts because it encourages bone cell adhesion and osteointegration. In tissue engineering, HA is employed as a scaffold material to promote tissue growth, nutrition delivery, and cell infiltration. Because HA scaffolds' porous shape resembles the extracellular matrix found in nature, it encourages tissue growth and offers mechanical support. These implants have the ability to create new tissues, regenerate bone, and repair cartilage. A new age of customized implants has been brought about by the integration of HA with additive manufacturing and 3D printing [24,63,66,67].

Higher bone tissue integration has been observed using TiO2 nanotubes containing HA. Heat-sensitive biomolecules and polymeric materials can be deposited on TiO2 nanotubes through modifications with carbon nanotubes, polymers, and proteins, as well as matrix-assisted pulsed laser evaporation (MAPLE) processes. Osteogenic cell stimulation can be achieved by coating

titanium or HA with bioabsorbable compounds. Peptides and peptidomimetics have been used as titanium surface additions in recent times. Through covalent binding, trapping, and adsorption, biomolecules' diverse range of chemical and functional properties promote bone repair. The extracellular matrix of titanium dental implants contains collagen, which promotes soft tissue growth and osseointegration, strengthening the bond between the implant and the gum. Cell adhesion to the extracellular matrix is facilitated by coating titanium with osteopontin and bone sialoprotein. Large extracellular matrix proteins can nevertheless be helpful even if they have a limited chemical stability and are quickly reabsorbed in bodily fluids [54,68]. The potential of HA carriers in drug delivery systems, which provide targeted and regulated release for a range of biological applications, has drawn attention [24].

The biocompatibility and osseointegration of metallic implants are typically improved by HA coatings, which lowers the chance of implant failure and gradually increases stability. HA and other bioactive coatings promote bone growth and healing around implants by imitating natural bone materials. Bioactive coatings greatly enhance dental implants, particularly in difficult clinical situations. Researchers are concentrating on creating multipurpose coatings, refining coating methods, and investigating novel materials. The composition and adherence of HA coatings are improved by employing methods including electrochemical deposition, plasma spraying, and biomimetic mineralization. In the domains of orthopedics, dentistry, and other biomedical sciences, improvements in coating techniques are enhancing the longevity and functionality of implants. Because of its low cytotoxicity, little inflammatory response, biocompatibility, and suitability for regenerative medicine applications, HA is one of the most beneficial drug carriers [24,69,70]. Coatings have significantly improved the mechanical and biological characteristics of implants in implant dentistry. By improving zirconia's biocompatibility, antimicrobial qualities, and bioactivity, bioactive coatings can encourage the production of hydroxyapatite and the creation of new bone [71].

The host's immunological response to the implanted material has a major impact on the successful integration of biomaterials into host tissue and the ensuing clinical results. Regenerative results can be enhanced by comprehending these complex interactions between the immune system and biomaterial [72]. Inflammatory responses are initiated upon implantation to safeguard neighboring tissues, and host plasma proteins bind to the biomaterial surface to form a first layer of proteins [73]. Fibrinogen is essential for drawing in inflammatory cells, promoting platelet adhesion, and creating clots that sustain the development of cells [74, 75]. Biocompatible biomaterials work better when there is a modulated immune response. Immune cells including lymphocytes, mast cells, and macrophages affect the type of immune response. Mast cells can impede tissue regeneration and promote fibrosis rather than healing by releasing pro-fibrogenic cytokines and chemicals that induce fibrosis [76]. While M2 macrophages aid in wound healing, M1 macrophages are involved in classical activation [77,78]. The shift from proinflammatory M1 macrophages to antiinflammatory M2 macrophages is necessary for bone repair [79, 80]. By getting beyond the restrictions of natural bone grafts, bone replacement biomaterials—including CP biomaterials like DCP bioceramics—offer orthopedic and dental patients

substantial benefits [81]. In order to optimize these biomaterials for regeneration results akin to those of genuine bone grafts, the immune response must be modulated as opposed to suppressed. In order to promote desired immune responses and enable tissue/material integration and remodeling, smart biomaterials have been designed [82]. ECM proteins have the ability to affect cytokine release and immune cell adherence, and signaling molecules can activate immunological responses by triggering TLRs on resident immune cells [83].

The studies on zirconia and hydroxyapatite (HA) coatings highlights several key findings:

1. **Cho et al. (2015)** demonstrated that HA-coated zirconia improved surface wettability and osteogenic potential, although cell proliferation was lower on HA-coated zirconia compared to uncoated zirconia. The study suggests that HA coatings promote osteogenesis and enhance surface modification [84].
2. **Kim et al. (2011)** found that combining HA with 4-Hexylresorcinol (4-HR) enhanced adhesion efficiency compared to HA alone. The HA+4-HR coating showed significantly higher osteocalcin expression, increased bone formation, and improved bone-to-implant contact values. This combination also resulted in more durable implants [85].
3. **Lee et al. (2014)** reported that collagen and HA coatings (CH) on implants improved bone formation around the implant and bone-in-crack compared to uncoated and HA-only surfaces. CH coatings were more effective than BMP-2 coatings in stimulating new bone formation and increasing bone-to-implant contact (BIC) [86].
4. **Laranjeira et al. (2014)** investigated silica-coated zirconia surfaces and found that microstructured bioactive coatings reduced bacterial adhesion and improved soft tissue adhesion. Silica coatings were effective in decreasing biofilm formation and enhancing protein adsorption [87].
5. **Pardun et al. (2015)** explored various ratios of Y-TZP and HA coatings and observed that HA dissolution stimulated osteoblast adhesion and proliferation. However, while the bioactivity of calcium phosphate increased in simulated body fluid, its mechanical and chemical stability decreased. Coatings with higher tetragonal zirconia content showed better interfacial bonding and mechanical strength [26].
6. These findings underscore the potential of different coating strategies to enhance the biocompatibility, durability, and functionality of dental and orthopedic implants. The choice of coating materials and techniques can significantly impact the effectiveness of implants in promoting bone integration and reducing complications.

The incorporation of nanomaterials into dental implants offers promising advancements in drug delivery and antimicrobial properties. Here's a summary of the key points related to different nanomaterials used in dental implants:

1. Nanomaterials in Drug Delivery and Implant Coatings:

- **Metallic Nanoparticles:** Various metallic nanoparticles, such as gold, silver, and zinc oxide, have been used to enhance dental implant functionality. They can offer antibacterial properties, improve osseointegration, and facilitate targeted drug delivery.

2. Gold Nanoparticles (AuNPs):

- **Properties and Applications:** Gold nanoparticles are used for drug delivery, imaging, and diagnostics. They are effective in delivering drugs, proteins, peptides, and genes. Gold nanoparticles are also used in dental implants for their antimicrobial properties and to improve the detection of periodontal disease.
- **Size and Toxicity:** Nanoparticles between 20 and 50 nm are highly effective, but those towards the higher end of this range may exhibit toxicity. Gold nanoparticles are synthesized in various shapes for different applications [89, 94].

3. Nano-silver (nAg):

- **Antibacterial Properties:** Silver nanoparticles are renowned for their antibacterial effects and are utilized in dental implants, periodontology, and bone regeneration. They prevent bacterial contamination and maintain biocompatibility.
- **Applications and Effectiveness:** Coatings with silver nanoparticles can significantly reduce bacterial colonization. Various studies have demonstrated their efficacy in preventing infection and improving bone formation [96, 97, 99, 100, 101, 102].

4. Titanium (Ti) Implants:

- **Historical Use and Improvements:** Titanium implants have been widely used due to their low failure rates. Recent advancements include surface modifications and the incorporation of nanomaterials to improve osseointegration and reduce biofilm formation.
- **Nanomaterial Coatings:** Ti implants coated with nanoparticles such as silver, zinc oxide, or other materials enhance antimicrobial properties and improve bone integration. Nanocomposite coatings and controlled drug release systems are also being developed to improve implant performance [105, 106, 107, 108].

5. Zinc Oxide (ZnO):

- **Properties and Benefits:** ZnO nanoparticles offer antimicrobial properties and promote osteoblast proliferation, which can enhance bone growth and reduce infection risk. They are used in combination with other materials to improve implant surfaces [110, 111, 112].

6. Ceramic Nanoparticles:

- **Applications in Drug Delivery:** Ceramic nanoparticles like titanium, silica, and alumina are explored as drug carriers. Nano-hydroxyapatite (nHA) is particularly notable for its biocompatibility and ability to deliver drugs to bone tissue. nHA-based drug delivery systems are being developed for treating bone diseases and infections [90, 25, 113].

These advancements underscore the potential of nanomaterials to significantly enhance the performance and safety of dental implants. By leveraging their unique properties, researchers aim to improve implant durability, reduce infection rates, and facilitate better integration with bone and soft tissues.

Conclusion

The integration of advanced biomaterials and innovative manufacturing techniques has substantially transformed the field of dental restoration. The development of drug-eluting implants, bolstered by additive manufacturing

technologies like 3D printing, has provided new avenues for improving implant design and functionality. These technologies enable the precise fabrication of implants and delivery systems, tailored to the unique needs of individual patients. Nanotechnology has played a crucial role in enhancing the performance of dental implants. Nanomaterials, including gold, silver, and zinc oxide nanoparticles, have been incorporated into implant coatings and drug delivery systems to offer antimicrobial properties and targeted therapeutic effects. These advancements help address the common issue of bacterial infection and biofilm formation, which can compromise implant success and longevity. The use of hydroxyapatite (HA) and calcium phosphate coatings has shown promise in improving the biocompatibility and osseointegration of dental implants. These materials mimic natural bone and promote better integration with surrounding tissues. However, challenges remain in ensuring the durability and stability of these coatings over the long term. Additionally, the incorporation of growth factors and the development of smart biomaterials that modulate the immune response offer new strategies for enhancing tissue regeneration and implant success. Research into these areas continues to evolve, aiming to overcome current limitations and improve clinical outcomes. Overall, the advancements in biomaterials and manufacturing technologies offer significant improvements in dental restoration. Continued research and innovation are essential to further refine these technologies, optimize their performance, and address the remaining challenges in implant dentistry. The future of dental implants will likely see continued progress in material science and personalized treatment approaches, enhancing both the effectiveness and patient experience in dental restoration.

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