Applications of Nanoparticles in Dentistry

Subjects: Dentistry, Oral Surgery & Medicine

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Interest in the topic of nanoparticles (NPs) and nanomaterials used in dentistry is growing in research as well as clinical settings. An increasing number of nanomaterials have been developed and tested, enabling novel solutions unavailable in dentistry before. The shape and size of these particles influences the physicochemical properties of a substance, which in turn impacts their absorption characteristics. Nanomaterials have unique structures and properties that distinguish them from other materials. In the dental field, nanoparticles have a variety of applications, such as nanocomposites, antimicrobial nanomaterials and bio-mineralization systems.

Keywords: nanoparticles ; dentistry ; nanomaterials

1. Introduction

Nanoparticles are routinely defined as ultrafine units with dimensions between about 1 and 100 nm (nm; 1 nm = 10^9 m) that show properties that are not found in bulk samples of the same material [1]. Nanoparticles exist in the natural world and are also created as a result of human activities. Because of their submicroscopic size, they have unique material characteristics, and manufactured nanoparticles may find practical applications in a variety of areas, including medicine, engineering, catalysis and environmental remediation [2]. Some research is suggesting that novel size-dependent properties alone, rather than particle size, should be the primary criterion in any definition of nanoparticles [1]. The unique properties of NPs, including their surface to volume ratio, antibacterial action, physical, mechanical, and biological characteristics and unique particle size have rendered them effective vehicles for dental applications [3]. Although inorganic nanoparticles provide the opportunity to localize bioactive agents to the target sites and protect them from degradation through acute toxicity mechanisms, the long-term toxicity of such materials can present serious health dangers [4]. This and further interest in the use of NPs calls for deeper understanding of the topic and special care in designing research involving them.

2. Antimicrobial Functions

2.1. Antibacterial and Antifungal Function

Often, to achieve antibacterial/antifungal properties, specific NPs are incorporated. Those NPs mainly present the ability to damage cellular membranes through membrane penetration and induction of cell lysis, or the ROS scavenging mechanism.

The NPs antibacterial mechanism of action is based on NPs binding to the cell and causing surface charges. This interaction with the peptidoglycan of the cell wall and subsequently with the cell membrane limits protein synthesis, and as a consequence prevents the replication of bacterial DNA. Thus, the antifungal action of NPs is mainly focused on infiltration and lysis of the cell wall.

Through redox reactions, NPs induce a high level of reactive oxygen species (ROS), creating intracellular oxidative stress conditions. If the superoxide and hydroxyl radicals (ROS) are not neutralized by antioxidants, they cause protein degradation and DNA damage and destroy the cell wall. Above all that, ROS, together with simultaneously created reactive nitrogen intermediates (RNI), connect to the lipid membrane of the cell, disturbing the trans-membrane balance and consequently contributing to cell death.

The other reaction involved in induction of cell lysis is centered on nitric oxide-releasing NPs. The reactive nitrogen oxide intermediates (RNOS), formed by interaction of NPs with the cell, enter the reaction with selected bacterial protein amino acids (such as Cys, Met, Tyr, and Phe) and selected DNA chain bases (such as C, A, and G) and lead to their damage. At the same time, RNOS promotes an increase in the concentration of ROS, which in turn increases the destruction of bacterial DNA.

Nanoparticles in the endodontics field have been used in a number of applications including antimicrobial administration, mainly aimed at improving overall oral health, particularly by eliminating biofilms [5]. Research focused on improving photobiological activity showed the superiority of the nanoemulsion of zinc phthalocyanine (ZnPc-NE) free zinc phthalocyanine (ZnPc). Besides, cytotoxicity studies showed that just nanoemulsions alone, without any additions (blank-NE), showed good antimicrobial activity against Enterococcus faecalis and Staphylococcus aureus. Thus, clove oil nanoemulsion can act as a nanocarrier to promote ZnPc photosensitizing activity against pathogenic microorganisms in resistant endodontic infections [6]. Additionally, there are studies reporting the use of samarium-cobalt targets, which work as permanent magnets for nanoparticles' synthesization through pulsed laser ablation in liquid (PLAL) that could be exploited as a novel method of synthesis for effective small-particle antimicrobials [7]. Another endodontic application of research into gutta percha–sealer–tooth interface revealed that the coating of sealers with a combination of silver NPs and chitosan NPs allows superior antibacterial activity. This is caused by induced oxidative stress and membrane damage to the bacteria; due to this, synthesized alternative filling materials can possibly provide high success rates in root canal therapies in clinical procedures [8]. The addition of NPs can improve not only the properties of materials that are intended to stay in the oral cavity, but also the therapeutic effects of medicaments or irrigants. There were novel attempts to create silver nanoparticles (AgNPs) with a graphene oxide (GO) matrix (Ag-GO) that could effectively act as an endodontic irrigation method. Studies showed that the antimicrobial efficacy of Ag-GO was comparable to that of 2% CHX and 1% NaOCl, which could simplify irrigation the sequence and suppress the risk of formation of a precipitate [9].

In the case of dental prosthetics applications, metal oxides nanomaterials revealed cytotoxicity to Candida and other microbes present in oral biofilms, including the PMMA denture surface. However, they needed to be used in low concentrations in order to not impact the mechanical properties negatively [10].

Another clinical setting with a high risk of infection is dental implant surgery, after which antibiotics are commonly prescribed for prophylaxis of bacterial infections. However, bacteria's drug resistance may increase the risk of infections, leading to implant failure. Unfortunately, use of regular hydroxyapatite (HA) as scaffolds in implant dentistry has one main issue, namely the accumulation of microorganisms on HA. To overcome this, an antibacterial hydroxyapatite (HAp) scaffold was developed by immobilizing chlorhexidine (CHX)-loaded human serum albumin (HSA) nanoparticles onto implant surfaces. This intervention allowed effective antibacterial activity against *S. mutans* directly to the implant's surface [11]. The use of CuO nanoparticles or TiO_2 nanoparticles can also decrease the accumulation of microorganisms including Streptococcus mutans on HA [12]. To increase the antibacterial effect against *E. coli* and *S. aureus* even more, porous nanocrystalline hydroxyapatite was impregnated with copper, gold and silver NPs. Although enhancement of antimicrobial abilities occurred, cytotoxicity studies suggested that gold nanoparticle-impregnated HAp has the highest biocompatibility [13].

2.2. Antiviral Function

The primary goal of NPs used for their antiviral properties is to neutralize the virus before it invades the host cells. One of the first steps in viral infection is the initial encounter with host cell receptors. If stopping viral penetration can be achieved at this point through NPs, the infection can be omitted successfully. Unfortunately, this regulatory step can vary between different viruses from nonspecific to very specific pathways. Recently, new nanotechnological strategies to create an antiviral coating that inhibits viral transmission showed additional solutions. A possible mode of action was preventing viral entry into the host cell through anti-transfection action, or through making it impossible to interact with negatively charged DNA and RNA.

Interest in this field concerned carbon dots/quantum carbon dots, graphene oxide (GO) and metal NPs. Positively charged curcumin-derived cationic carbon dots resulted in aggregation of the virus, reducing viral infectivity (with inhibition efficiency over 50% at the concentration of 125 g/mL) through viral cell binding inhibition and the induction of certain changes in viral protein structure.

Negatively charged GO NPs integrated into the material, making it possible to change the polarization of the cellular membrane and deactivate the virus before its penetration. This difference in charge between GO NPs sheets and the virus causes wrapping of the sheet around the virus, and due to the roughness of its surface, simultaneous tearing of the cellular membrane or capsid protein layer. Additionally, the excellent thermal conductivity of these NPs and the high light to heat conversion potential of infrared radiation were proposed as other strategies to capture viral cells and their inactivation.

Metal NPs can interfere with viral infection through various methods:

- by reactive oxygen species (ROS) generation;

- by physical abrasion of the membrane incurred due to interaction with nanoparticles;
- by loss of membrane integrity due to nanoparticle binding; and
- by the release of metal ions from the nanoparticles.

The silver (Ag) NPs seem to be most promising because they present a multifaceted mode of action not limited to a single pathway. Generation of ROS disrupts the cell wall and plasma components, as well as inhibiting viral cell metabolism. Other metal NPs investigated in this subject are Copper (Cu), Cobalt (Co) and Zinc (Zn), but their antiviral abilities are more limited than Ag [14].

2.3. Multiple/Simultaneous Mechanism

An ideal antimicrobial material would combine both antiviral and antibacterial activity.

Those efforts were based on either the NPs-induced ability to link to the DNA, prevention of RNA synthesis, cell membrane damage or an enzymatic inhibition.

Metallic NPs show promising results in this area due to presentation of antibacterial actions, including the production of reactive oxygen species, cation release, biomolecule damages, ATP depletion and membrane interaction, but also due to regulation of gene and protein profiles (transcriptomic and proteomic) also affecting viruses [15].

On the other hand, non-metallic NPs are also very promising antimicrobial adjuvants. Quaternary ammonium polyethylenimine (QA-PEI) nanoparticles are non-toxic and exhibit antibacterial activity. This makes them potential biocidal additives in various dental composite materials, such as dimethacrylate-based restorative materials, dental cements, root canal pastes and orthodontic adhesives, without deteriorating the products' structures or mechanical properties [16].

Organic-derived NPs like chitosan NPs offer simultaneous antibacterial and antifungal properties, which makes them a promising addition to tissue conditioners which tackles the issue of bacteria and fungi growth on complete dentures [17].

3. Property Improvement Functions

3.1. Reinforcement Function

Due to the similar modes of action and functions of different NPs—the improvement of mechanical properties—this topic was subdivided into particular types of NPs.

The incorporation of CNs into GICs shows reinforcement through fibrillar aggregation of nanoparticles interspersed in the matrix. This results in significantly improved mechanical properties (Maxxion-31.6%; Vidrion R-49.43%; Vitro Molar-37.79%; Ketac Molar Easy Mix-48.78% and Fuji Gold Label 9-32.33%) and increased F-release of all tested GICs [18].

The addition of chitosan NPs to the GICs also results in an increase in fluoride and the induction of moisture during the maturation stage of setting through electrostatic interaction with the carboxylic acid group of the GIC liquid. This also provides supplementary mechanical properties' enhancement of GICs [19].

Nanodiamonds (ND) are an allotrope of carbon nanoparticles which exhibit superior physical, mechanical, thermal and optical characteristics on their own due to their unique spherical shape which contains a diamond-like structure at the core with a graphitic carbon outer shell. Their qualities and high biocompatibility makes them an attractive additive for the development of multifunctional polymer composites [20]. Use of a trace amount of ND (0.5%), in combination with acrylic resin or composite resin, noticeably improves flexural strength and decreases surface roughness [21].

The nHAp are structurally the closest to natural dental apatite, a main component of the tooth structure. High biocompatibility, and the ability to achieve precise and appropriate morphology, stoichiometry and purity allows seamless improvement of the mechanical and chemical properties of the materials they are incorporated into. Particular interest was established in mechanically improving already bioactive materials such as glass ionomer cements, especially in terms of shear bond strength [22].

Silicon colloidal nanoparticle clusters (SCNCs) can strengthen the structure of inorganic fillers within dental resin composites through the calcination process. Studies have shown enhancement of the flexural properties and hardness of composites. Unfortunately, their addition could decrease overall compressive strength; this is often tackled through use of building blocks made of the silica NPs, or through simultaneous use of another type of filler [23].

The lasting clinical effect of a composite restoration depends on the properties of the dental adhesive. The incorporation of Si nanoparticles (10% and 15%) into the polymeric bonding system increases its bond strength compared with the unmodified adhesive resin, and improves hybrid layer formation within the dentin. However, the addition of Si particles to the adhesive reduced its conversion rate compared with the unfilled adhesive (0% Si-control) [24].

Another solution was proposed by LalehSolhi et al. by adding a Si-containing hybrid nanoparticle of 0.5 wt.% (poly (acrylic acid)-grafted nanoclay/nanosilica, abbreviated as PAA-g–NC–Sil, for adhesive. The bonding system containing PAA-g–NC–Sil showed better dispersion stability and, consequently, the highest shear strength without reducing the degree of conversion compared with the adhesive without fillers [25]. Another application of SiO_2 nanofibers with stabilized silver nanoparticles (SiO_2/Ag) was incorporating them into a composite resin. This modification increased the hardness of the composite, which also retained its flexural strength, even after aging in water for 30 days. The most promising seems to be the addition of silanized nanofibers to the composite (SiO_2/Ag-0.5S) at a concentration of 0.5 wt.%, as such material shows greater inhibition of *S. mutans*, satisfactory parameters of roughness and flexural strength and better impact strength compared with the control [26].

Nano-inorganic fillers SiO_2, ZrO_2, HA, and Al_2O_3 were added to the tested composites in a constant proportion (40% by weight). The results showed that dental composites reinforced with silica nanoparticles had superior properties compared with other types of prepared nanocomposites in terms of diametrical tensile and compressive strength [27]. The possibility of strengthening PMMA resin for permanent and temporary restorations with pure silica nanoparticles and triethoxy vinyl silane-modified silica nanoparticles was also investigated. The results of the study suggest that both types of nanoparticles, especially at low concentrations, can improve the durability of permanent prosthetic restorations, as they can effectively increase the fracture toughness, elastic modulus and glass transition temperature of PMMA resins [28].

PMMA (polymethyl methacrylate) acrylic resin is used to make denture bases, but its mechanical properties may be insufficient for this role. The incorporation of ZrO_2 nanoparticles into the PMMA resin significantly improved flexural strength, flexural modulus (15%, 22%, respectively), fracture toughness and surface hardness, with an optimal zirconia concentration of 3%–5% by weight. However, the distribution of ZrO_2 nanoparticles in the polymer matrix was not uniform, and there were agglomerations that reduced the impact strength [29]. The addition of untreated zirconia nanofillers to PMMA used in 2.5% concentration proved to increase flexural strength and surface hardness; therefore, they can be used for reinforcing dentures and other dental appliances conventionally created from PMMA [30]. Temporary restorations play an important role in protecting the hard and soft tissues of the oral cavity and ensuring function and aesthetics during the preparation of final restorations. Temporary restorations must have sufficient flexural strength to resist chewing deformation and sufficient surface hardness to resist abrasion. In the case of works carried out in the aesthetic zone, color stability is also of great importance. Zirconium nanoparticles have desirable properties, such as high hardness, biocompatibility and white color. For this reason, the addition of zirconia nano to acrylic resins may be a suitable method to improve temporary restorative materials [31].

Silica nanoparticles are the filler types present in almost all commercial dental materials. Particles containing silica are highly reactive to organosilanes and allow simple, effective coupling with the resin phase. However, silica nanoparticles also have some limitations, including radiolucency and poor mechanical properties. Therefore, a question was raised as to whether the use of non-silicate nanoparticles such as zirconia, as a substitution for silica, would actually result in restorative materials with improved properties. This material showed improved and more stable mechanical properties as compared with nanosilica-based references [32]. The authors of another study followed a similar direction, evaluating the effect of several types of surface treatment of nano si-zirconia fillers on the mechanical properties of the dental resin composite. This surface treatment involved conditioning the nano si-zirconia fillers with MDP phosphate ester monomer to mediate the chemical bond between the zirconia fillers and the resin matrix. The authors also evaluated the cytotoxicity of these composites to ensure the clinical safety of this modification. MDP-conditioned nano-zirconia fillers improve the mechanical properties of resin composites, and are potentially safe for clinical use as they show no significant cellular cytotoxicity [33].

ZnO NPs’ addition can also slightly improve the mechanical and handling properties of GICs, although they are mainly used for possible combination of property improvement and therapeutic functions [34].

The OMMT NPs or nanoclays are mainly used as novel nanofillers intercalated into structures of the nanocomposites. Their main function is the reinforcement and limitation of polymerization shrinkage through extensive filler distribution into the polymer matrix; however, their incorporation into composite resin increases flexural modulus and decreases flexural strength at a high filler loading [35].

To address the challenge of poor resin infiltration of dentin's conventional total etching during the bonding procedure, products incorporating superparamagnetic iron oxide nanoparticles (SPIONs) were developed. Under the guided magnetic field, SPIONs-doped adhesives increase the bond strength, which surpasses the reduction caused by hydrostatic pulpal pressure. They also improved dentin's adhesion without changing material's physicochemical properties [36].

Often, to achieve advancement in mechanical properties, different NPs are used; various forms of them are also used. This practice, used in the production of adhesives, is mainly based on the superiority of nanofillers over microfillers in terms of improving the strength of the adhesive layer and the influence of the viscosity, without adversely affecting the material's polymerization reaction [37]. The use of a combination of high concentrations of nano-ZrO_2, low % nano-SiO_2 and 1 and 1.5 wt.% nano-Al_2O_3 enhanced mechanical properties, improved repair strength and increased the flexural strength of repaired denture bases [38].

3.2. Wear Protection Function

The subject of property improvement through nanoparticle integration would not be complete without mentioning diamond NPs' ability to smoothen the material surface. The use of those NPs give a unique opportunity to achieve increased wear protection properties. Through a variety of friction and wear tests, nanodiamonds proved to decrease surface roughness. This subject is especially important in dentistry due to everyday use of toothbrushes. Mechanical cleaning of the tooth surface by toothbrush bristles can potentially increase the roughness of the tooth's surface over time. This phenomenon can lead to increased tissue wear and redeposition of the bacteria. Studies have shown that correct use of a soft-tufted toothbrush in combination with a nanodiamond suspension for oral hygiene applications can provide a protective effect on the enamel and the dentine surfaces, making them smoother, so it is harder for bacteria to adhere [39].

This ability of nanodiamonds was also used to enhance resistance to friction and wear of poly(methylmethacrylate)-based intraoral appliances (such as splints, dental and maxillofacial prosthesis) so they can better withstand the mechanical and microbial impact existent in the harsh environment of the oral cavity. The use of nanodiamonds as fillers not only significantly improved mechanical properties by strengthening the material (11.88%–17.60%); by making its surface smoother, it elevated resistance to the biofilm formation of Streptococcus mutans without any notable impact possibly associated with the functionalization of the nanodiamond particles [40].

4. Therapeutic Functions

4.1. Anti-Caries Function

The literature highlights the number of NPs presenting different modes of action yet achieving the same outcome: a decrease in oral caries. The NPs tackling this problem focus on diminishing Streptococcus mutans populations or inducing teeth remineralization processes [41]. The chitosan- and nanodiamond-modified glass ionomers proved noticeable *S. mutans* reduction, and as a consequence, the best disruption of its biofilm formation compared with the same GICs without the modification [42][43]. Adversely, silver nanoparticles added to GICs (NanoAg-GIC) presented increased compressive strength of the material and inhibition of *E. coli* and *S. mutans* population growth [44]. Furthermore, there were developed materials targeting directly bacterial pathogens. Catalytic nanoparticles (CAT-NP) containing biocompatible Fe_3O_4 and exhibiting peroxidase-like activity trigger extracellular matrix degradation and cause bacterial death within biofilm. They additionally reduce apatite demineralization in acidic conditions [45]. Additionally, the use of glucose-oxidase nanohybrids, which catalyze glucose present in biofilms to increase intrinsic H_2O_2, directly targets Streptococcus mutans (pathogen) without affecting Streptococcus oralis (commensal). Their mode of action was based on iron oxide nanoparticles also with peroxidase-like activity [46].

Moreover, some materials are aimed to induce remineralization processes. Cements containing amorphous calcium-phosphate nanoparticles showed good bond strength to enamel and continuous calcium and phosphate ion recharge/re-release capability, which induced remineralization reactions. It also increased the local pH, preventing additional harm from cariogenic bacteria [47]. Furthermore, adhesive resins with zinc nanoparticles (ZnNPs) exhibit antimicrobial capacities against aerobic bacteria and proved to be bactericidal against anaerobic bacterial strains (Streptococcus mutans, Streptococcus mitis, and Lactobacillus spp.) through creation of oxidative stress, thus improving material infiltration and enabling remineralization properties [48]. Likewise, Ca-NPs and Zn-NPs used in treated dentin exhibited sealing properties within dentinal tubules, thus decreasing microleakage and strengthening the root dentin by inducing the remineralization process after endodontic treatment [49].

4.2. Antibiofilm Function

4.2.1. Blocking Bacterial Sugar Consumption and Bacteriostatic Function

It was shown that use of hexagonal boron nitride NP (hBN) used in minimum inhibitory concentration exhibits bacterial and fungal sugar-consumption blockage of Streptococcus mutans, Staphylococcus pasteuri and Candida species. Establishing high bacteriostatic abilities favors its use as a potential safe oral care product [50].

Furthermore, it is worth mentioning zein-coated magnesium oxide (zMgO) nanoparticles' capability to create bacterial inhibition zones when used as dental cement. Their antimicrobial properties against C. albicans and S. aureus, thanks to their high crystalline nature and uniform distribution, show promising results for prosthetic application [51].

4.2.2. Decreasing Expression of FTF and GFT Genes in *S. mutans*

Adversely, the combination of zinc oxide nanoparticles (ZnO NPs) with hydroxyapatite nanoparticles (HAP NPs) to create Zn-substituted hydroxyapatite nanoparticles (Ca19Zn2(PO4)14 NPs) focuses on targeting bacteria through depressing the FTF (8.15 times) and GFT (8.42 times) genes' expression. Results show significant impact on *S. mutans* growth and biofilm formation as well as bacterial adherence, which makes them applicable as dental coatings [52].

4.2.3. Damaging Bacterial DNA and Growth Inhibition of Mature Biofilm

Hafnium oxide nanoparticles (Hf PS NPs) in therapeutic polymeric silane are one of the examples of NPs that are more versatile due to their dual mode of action. Hf PS NPs can penetrate into *S. mutans*, thus improving caries detection; however, at the same time, they present superior antibacterial properties through damaging bacterial DNA and as a consequence inhibiting the growth of Streptococcus mutans' mature biofilm without the need for any additional drugs [53].

4.3. Anti-Inflammatory Function

The use of particular NPs instead of conventional anti-inflammatory medication can be very beneficial to patients, simply due to more efficient action and diminished side effects. Consequently, this leads to improvement of the healing processes of damaged tissues by targeting and internalizing proinflammatory cells, releasing ions or by eliminating reactive oxygen species (ROS). Folate-functionalized bioactive glass nanoparticle BGN(F) presents those properties, and thanks to that can substantially down-regulate proinflammatory molecules, including TNF-α, IL-6, iNOS and COX-2, at both gene and protein levels; additionally, it suppresses inflammatory events, such as p38 MAPK, ERK (1/2), SAPK/JANK, IκBα, and NF-κBand, above which it can switch the macrophage polarization from M1 to M2. These profound anti-inflammatory actions consequently accelerate tissue healing [54]. Secondly, coating photosensitizer chlorin e6 onto nanoceria within nanocomposite material allowed the elimination of ROS, achieving simultaneous sterilization and inflammation elimination via a dual directional regulation effect and also the modulation of macrophage polarization from M1 to M2. Utilization of these in periodontal antibacterial photodynamic therapy could overcome the local side effects of standard treatment [55]. Other studies also suggested that incorporation of bioactive chitosan-based nanoparticles (CSnp) in antibiofilm medication upregulated proteins exhibiting antioxidant and immunoregulatory properties. This has proved to have potential beneficiary immunomodulatory effects (reduced pro-inflammatory IL-1β and nitric oxide, enhanced anti-inflammatory IL-10 and TGF-β1) on chronically inflamed periapical tissues, and regulate healing process in the treatment of apical periodontitis [56].

4.4. Whitening Properties

The main nanoparticles exhibiting whitening properties can be divided into three groups: carbide peroxide NPs, nano-hydroxyapatite and nano-encapsulated sodium metabisulfite.

Development of carbamide peroxide polymeric nanoparticles improves the stability and efficacy of most common home dental whitening agents without causing damage to the dental pulp [57]. Nano-hydroxyapatite, apart from its remineralization properties, when added even to mouth rinses over prolonged periods of time presents whitening properties higher than commercial mouth rinses [58]. To accommodate for long application time and post-whitening hypersensitivity, nano-encapsulated sodium metabisulfites were designed. Thanks to liposomal enclosures forming a layer surrounding the enamel surface, they present safer and faster alternatives to current oxidative treatments that provide satisfactory whitening action [59].

4.5. Regeneration Function

4.5.1. Bone Remodeling Function

NPs can play a special role in tissue regeneration processes due to their unique abilities. Organic-related/-based NPs are the main interest in the field of tissue regeneration scaffolds.

The carbon-derivative NPs often considered are carbon nanotubes (CNTs), carbon nanofibers (CNFs) and nanodiamonds (ND). Carbon nanomaterials such as CNTs and CNFs are inherently bioinert, having no osteoinductivity. Effective improvement of their biological properties occurs through the incorporation of CNTs/CNFs into known bioactive compounds such as calcium phosphate (CaP) and bioactive glass (BG). This enables control of cell growth and differentiation. Studies also show that these combinations are more effective than CNFs alone in terms of biocompatibility, tunable degradation ability and controllable osteocompatibility, which makes them more suitable for scaffolds used for bone tissue engineering [60]. In turn, the bioactive glass nanoparticles (BGNPs) are well established in research and have multiple clinical applications in periodontal and bone regeneration due to the mechanism of particle size-regulated bioactivity [61].

ND particles allow the improvement of the osteogenicity of osteoblast-like cells when incorporated into scaffolds. Cytotoxic and inflammatory reactions occurred at higher concentrations of NDs; therefore, to ensure safety, researchers are establishing minimum inhibitory concentration [62]. Often, integration of particular NPs with hormones can present additional regeneration properties that can help in postsurgical treatment or prevention of relapse. Injectable estrogen (17β-estradiol (E2))–nanodiamond hydrogel enabled the improvement of bone-building properties and the healing of palatal expansion in patients with cleft lip and/or palate reconstruction [63].

The possibilities of conjugating different NPs do not end there. Nowadays, multiple synthetic and natural structures can be combined to perform at a superior level.

Effective incorporation of carbonated hydroxyapatite (CHAp) into the nanofibrous structure of poly(vinyl alcohol) and chitosan as poly(vinyl alcohol)/chitosan/carbonated hydroxyapatite (PVA/CS/CHAp) proved to increase the modulus of the scaffold. At the same time, increase in CHAp concentrations directly influenced other scaffold properties, decreasing elongation at break and increasing the swelling capacity of scaffold and protein adsorption onto the scaffold which could increase the cell viability of the scaffold. This means that PVA/CS/CHAp has the potential to serve as an alternative scaffold material for superior bone tissue engineering [64]. In the topic of bone remodeling, it is very important to understand and influence the osteoblastic and osteoclastic cell activity, which, in the case of osteoporosis or osteoporotic bone defects, are crucial. Synthesis of Sr-nanocement showed promising results in osteoclastic inhibition, increased bone volume and density, enhanced production of osteopromotive proteins and more populated osteoblasts, and showed reduced signs of osteoclastic bone resorption, proving its profound bone-regenerative potential [65].

4.5.2. Bone Remodeling and Angiogenic Functions

It is vital to address angiogenic properties, especially when the treatment goal is focused on not only osteointegration, but also on restoration of angiogenesis processes within tissues.

This was tackled in one of the attempts to combine the osteoblastic function achieved by external static magnetic field (SMF) and bone formatting magnetic nanocomposite scaffolds created from polycaprolactone/magnetic NPs. The solution remarkably enhanced the new bone formation, which suggested conjugation as a possible regenerative bone-engineering application [66]. Another proposition was the creation of uniquely structured nanohybrids composed of a bioactive inorganic nanoparticle core (hydroxyapatite, bioactive glass, or mesoporous silica) encapsulated in a chitosan shell (Chit@IOC). Use of those components allowed the synthesis of nano units highly resilient to cyclic load and also the stimulation of the anti-inflammatory, pro-angiogenic and osteogenic events of relevant cells for those processes. These features make the aforementioned nanohybrids promising 3D tissue-regenerative platforms [67].

Finally, injectable nanomaterials for bone repair and regeneration, such as calcium phosphate cement (CPC) enriched by mesoporous bioactive glass nanoparticles (BGn), also show promising results. Creation of Si-Ca-(P)-based amorphous nano-islands-networking BGn increased surface area nine times compared with conventional CPC, and induced production of apatite nanocrystallites, absorbing proteins and releasing Si and Ca ions. These effects majorly stimulated the viability, osteogenesis and angiogenesis of studied cells, resulting in bone matrix formation [68].

4.5.3. Bone Remodeling and Remineralization Functions

Further research into bone remodeling led to attempts to combine these properties with the remineralization processes. These ideas led to the development of different forms of hydroxyapatite. Hydroxyapatite-based biomaterials face a set of issues, from problematic preparation to poor mechanical properties or particle size, and morphology issues in drug delivery and brittleness for bone transplantation [69].

Synthetic whitlockite (WH: Ca18Mg2(HPO4)2(PO4)12) nanoparticles allowed the transformation of the early stages of bone regeneration using a continuous supply of PO_4^{3-} and Mg^{2+} under physiological conditions. As a result, mechanically enhanced hydroxyapatite (HAP)-neo served as ‘living bone mineral’ to induce self-healing [70].

Nano-hydroxyapatite (nHAP) in the form of gelatin cryogel was also developed to work as a scaffold for bone regeneration in the treatment of craniofacial deformities, due to its biocompatibility, slow reabsorption and necessary mechanical properties. On the one hand, it has a structure like a sponge, and on the other, its plasticity allows the reconstruction of the three-dimensional bones of the facial skeleton. At the same time, as a scaffold, it can provide support for mesenchymal stem cells and enhance the bone regeneration process [71].

4.5.4. Multifunctional Regeneration in Tissue Engineering

In addition to the extremely dynamic development of calcium silicate (CS)-based materials, the challenges posed to tissue engineering by the development of biological substitutes that restore, maintain or improve damaged tissues and organ functionality remain valid.

Regeneration of tooth tissues is hampered by the complexity of their structures, but the progress in nanotechnology enabling a biomimetic approach to the problem gives hope of overcoming these difficulties [72].

Dental implants as a therapeutic option in the rehabilitation of the oral cavity of patients are becoming more and more common. The long-term success of this therapy largely depends on their surface properties and osseointegration. However, the problem of insufficient integration and peri-implantitis still remains, and the modification of implant surfaces and various types of biomaterial coatings are a tool with which it is possible to solve it. The task of the implant coating material is to accelerate the healing process by improving osseointegration and having an antibacterial effect. Therefore, nanotechnological coating materials and implant surface modification techniques to improve biocompatibility and bio-functionality, as well as decrease the risk of retrograde peri-implantitis, are an extremely important and promising topic [73][74].

Regeneration of hard tissues infected with bacteria as a result of peri-implantitis is a major challenge, even with high doses of antibiotics or surgical intervention.

In order to promote the multidirectional action necessary in such a situation, i.e., antibacterial, pro-angiogenic and osteopromoting actions, a nanoglass paste made of silicate glass particles (containing Ca, Cu) hardening in contact with an aqueous medium was tested. The ions released in this process (of silicates, calcium and copper) in therapeutically appropriate doses and in a balanced manner (for days or weeks) allowed for the reduction of the inflammatory reaction around the implants and an antibacterial effect against *E. coli* and *S. aureus.* The nanoglass paste had osteopromoting and angiogenic effects on endothelial cells in vitro, and on blood vessel formation in vivo.

Based on the above studies, this can be considered a promising form of inorganic biomaterials for the regenerative therapy of hard tissues infected with bacteria [75]. It can be particularly important in the process of osteogenesis in the therapy of craniofacial deformities, which is complex and can be divided into early and late phases, each of which are characterized by a different specificity and dynamics of repair processes.

The study proposed the use of mesoporous bioglass nanoparticles (MBGN) together with methacrylate gelatin (GelMA) if a form of a hydrogel membrane embedded with recombinant human bone morphogenetic protein-2 (rhBMP-2). Early release of rhBMP-2 allowed osteogenic differentiation of the cells. In turn, inorganic ions not only facilitated cell adhesion in the early stage, but also facilitated osteogenic differentiation in the late phase. This GelMA/MBGNs-rhBMP-2 hydrogel showed a promising strategy for the controlled and safer application of bioactive agents such as rhBMP-2 in an artificial periosteum to accelerate the repair of a critical size defect in rat skull bone [76].

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