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NANOTECHNOLOGY FOR PERIODONTAL DISEASE

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ABSTRACT

Periodontitis, a disease involving supportive structures of the teeth prevails in all groups, ethnicities, races and both genders. Antibacterial agents have been used effectively in the management of periodontal infection. Systemic administration of drugs leads to therapeutic concentrations at the site of infection, but for short periods of time, forcing repeated dosing for longer periods. The conventional treatment consists of tooth surface mechanical cleaning and root planning, associated or not to the systemic use of high concentrations of antibiotics, but with reduced effectiveness, and adverse effects. Periodontal disease is a localized inflammatory disorder, with tissue destruction resulting from the host response to bacterial antigens and irritants. Several other risk factors, such as smoking, hormonal changes, diabetes, drugs, disease, and genetic factors, play an important role in the progression of periodontal disease. . Both systemic (liposomes, microspheres, nanoparticles, hydrogels) and local (fibers, patches, films, gels) antibiotic/antimicrobial approaches have their important place in periodontal therapy. The medical and dental field has seen several technological revolutions that have changed clinical practice. One concept which has and holds further promise in bringing about a paradigm shift in the field of diagnostics and management is nanotechnology. Nanotechnology refers to the control and manipulation (10-9m) of matter at nanometer dimension. Although the nanoscale is small in size, its potential is vast. It has an impact on every industry counting semiconductors, manufacturing, and biotechnology. With the increasing demand for advances in diagnosis and treatment modalities, nanotechnology is being considered as a groundbreaking and viable research subject. This technology, which deals with matter in nanodimensions, has widened our views of poorly understood health issues and provided novel means of diagnosis and treatment. The overall goal of this article is to provide the clinician with information related to the pathogenesis, and current nanotechnological systems for an effective treatment of periodontal disease.

INTRODUCTION

"Periodontitis" is a common chronic disease that leads to the destruction of tooth-supporting tissues, absorption of alveolar bone, and, finally, tooth loss[1],[2]. Considerable research has focused on the etiology of human periodontal disease,[3] and it has been generally accepted that chronic periodontitis is induced by microorganisms. Periodontal pockets provide a moist, warm, nutritious, and anaerobic environment that profits microbial colonization and multiplication[4]. Previous research demonstrated that only 10 to 30 bacteria species, mainly Gram-negative anaerobic bacteria, live here,[5] but it has now been found that approximately 500 bacterial taxa sojourn here[4]. The amounts and species of the bacteria are variable in different parts of the biofilm and depend on the effectiveness of oral hygiene procedures, depth of pocket, flow of gingival crevice fluid (GCF), type of interacting microbes, and so on[6],[7]. A recent study has indicated that periodontal disease not only affects human oral health but may also induce several systemic diseases[8].

Gingivitis and periodontitis are the two major forms of inflammatory diseases affecting the periodontium. Gingivitis is inflammation of the gingiva that does not result in clinical attachment loss. Periodontitis is inflammation of the gingival and the adjacent attachment apparatus and is characterized by loss of connective tissue attachment and alveolar bone. Each of these diseases may be subclassified based upon etiology, clinical presentation, or associated complicating factors. Gingivitis is a reversible disease. Therapy is aimed primarily at reduction of etiologic factors to reduce or eliminate inflammation, thereby allowing gingival tissues to heal. Appropriate supportive periodontal maintenance that includes personal and professional care is important in preventing re-initiation of inflammation. Therapeutic approaches for periodontitis fall into two major categories: 1) anti-infective treatment, which is designed to halt the progression of periodontal attachment loss by removing etiologic factors; and 2) regenerative therapy, which includes anti-infective treatment and is intended to restore structures destroyed by disease. Essential to both treatment approaches is the inclusion of periodontal maintenance procedures. Inflammation of the periodontium may result from many causes (eg, bacteria, trauma). However, most forms of gingivitis and periodontitis result from the accumulation of tooth-adherent microorganisms. Prominent risk factors for development of chronic periodontitis include the presence of specific subgingival bacteria, tobacco use, diabetes Furthermore, there is evidence that other factors can contribute to periodontal disease pathogenesis: environmental, genetic, and systemic (eg, diabetes). Periodontitis is a chronic bacterial infection that affects the gums and bones supporting teeth, untreated gingivitis can advance to periodontitis [9]. Gingivitis is often caused by inadequate oral hygiene. Periodontal disease can affect one tooth or many teeth. It begins when the bacteria in plaque as the disease progresses, the pockets deepen and more gum tissues and bone are destroyed. Often this destructive process has very mild symptoms. Eventually teeth become loosened and may have to be removed. Periodontal pocket provides an ideal environment for the growth of anaerobic pathogenic bacteria such as actinobacillus Actinomycetemcomitans, Bacteroides gingivalis, Bacteroides melaninogenicus subspecies intermedius, Porphyromonas gingivalis and Provetellaintermedia [10].

Nanotechnology and dental drug delivery devices:

The term nanotechnology was first introduced by Richard Feynman in 1959 to the scientific approach of creating functional materials, devices and systems through control of atoms on a nanometer scale and exploitation of novel phenomena and properties at that length scale [11,12]. This was practically made possible by Eric Drexler in the mid-1980s when he emphasized the potential of molecular nanotechnology [13,14]. The term "Nano" is derived from the Greek word "dwarf ". More simply speaking, one nanometer is one-billionth or 10-9 of a meter [12,15-18]. What makes the concept of nanotechnology exciting is that their size is smaller than the critical lengths defining many physical events. With the application of nanotechnology in the medical field, it would be possible to customize the diagnostics and treatment plans based on the genetics of each patient [19,20]. Nanotechnology is very diverse, ranging from extensions of conventional device physics to completely new approaches based upon molecular self-assembly dealing with development of new materials to investigating whether we can directly control matter on atomic scale [21]. The technology can be comfortably applied to the fields of medicine and dentistry to yield the terms nanomedicine and nanodentistry respectively. The objective of this short review is to discuss what nanotechnology holds for dental practice in future.

Approaches in Nanotechnology

Three approaches have been followed in production of nanoparticles, namely Bottom up approach, Top down approach and functional approach [22]. The functional approach disregards the method of production of a nanoparticle, and the objective is to produce a nanoparticle with a specific functionality. The fields of science and technology have witnessed the fabrication of several nanoparticles that we come across and use in our day to day lives, many a times not realizing it is part of the future revolution. The various nanoparticles are nano pores, nanotubes, quantum dots, nanoshells, dendrimers, liposomes, nanorods, fullerenes, nanospheres, nanowires, nanobelts, nanorings, nanocapsules [23]. This list of nanoparticles is by no means exhaustive.

Properties of Nanomaterials

Nanomaterials are those materials with components less than 100 nm in at least one dimension, including clusters of atoms, grains less than 100 nm in size, fibers that are less than 100 nm diameter, films less than 100 nm in thickness, nanoholes, and composites that are a combination of these [25]. They exhibit much better performance properties than traditional materials which include enhanced toughness, stiffness, improved transparency, increased scratch, abrasion, solvent and heat resistance, and decreased gas permeability [24]. Nanoparticles have a greater surface area per unit mass than compared with larger particles [26]. Self-assembly is an important feature of nanostructured materials. Here, an autonomous organization of components into patterns or structures without human intervention occurs [27]. Two main approaches are used in nanotechnology. In the 'bottom up' approach materials and components are built from molecular components which assemble themselves chemically by principles of molecular recognition. In the 'top down' approach, nano objects are constructed from larger entities without atomic level control [28].

Role of nanomaterials in biofilm treatment and prevention

Nanotechnology is a multidisciplinary scientific field focused on materials whose physical and chemical properties can be controlled at the nanoscale range (1–100 nm) by incorporating chemistry, engineering, and manufacturing principles [29]. The convergence of nanotechnology and medicine, termed "nanomedicine", can potentially advance the fight against a range of diseases. [30]. In particular, the application of nanomedicine for biofilm therapy can sustain drug release over time, increase solubility and bioavailability, decrease aggregation, and improve efficacy[31-33]. Various nanoparticle drug delivery carriers such as lipid-, polymer-, and nanometal-based carrier systems, have been developed to prevent bacterial colonization and biofilm formation as described below.

Liposomal delivery to biofilms

Among several promising nanoparticle drug-delivery systems, liposomes represent an advanced technology to deliver active molecules to the site of action; several formulations are already in clinical use. Liposomes can carry both hydrophobic and hydrophilic drugs, have slow clearance rates,34-35 and may deliver agents at increased concentrations, both in biofilm interfaces 36,37 or phagocytosed by cells harboring intracellular pathogens[38–

42]. These specific liposomal characteristics are especially advantageous for antibiotic treatment to counter biofilm formation on medical devices and interfaces.

Liposome encapsulation in medical devices

Liposomes encapsulating ciprofloxacin have been sequestered in polyethylene glycol (PEG) with rhGH (PEG-GH) and coated onto the surface of catheters; such coatings can completely inhibit bacterial adhesion for 1 week[43]. Similarly, liposomal ciprofloxacin hydrogel-coated silicone coupons prevented bacterial colonization during ***P. aeruginosa*** induced peritonitis in male Sprague-Dawley rats[44]. The ciprofloxacin-loaded liposomal hydrogels have also been incorporated in silicone Foley catheters to evaluate catheter-associated nosocomial urinary tract infections [45]. Insertion of these catheter (size 10 F) into New Zealand white rabbits and subsequent challenge with 5×10^6 virulent *E. coli* at the urethral meatus twice daily for 3 days resulted in a significant delay in average time to positive urine culture (from 3.5 to 5.3 days) and a 30% decrease in the rate of bacteriuria. Thus, this technology can potentially improve patient well-being and reduce health care costs [46].

Liposomes as drug delivery carriers to biofilm interfaces

A wide range of liposomes can also directly affect bacterial interactions during biofilm formation without the need for a device [47-53]. For example, pegylated cationic liposomes can inhibit adsorption of bacteria to biofilms, as the polyethylene glycol mole percent of component lipid is increased from 0% to 9% [51]. It is interesting to note that these interactions are generally an interplay of biofilm, liposomal, and surface type. For example, *Streptococcus sanguis* and *S. salivarius* biofilms respond differently to liposomes loaded with triclosan, with superior effects against *S. sanguis* [52]. Similar to biofilm type, the interaction of surface component and liposomes can cause contrasting outcomes. For example, solid supported vesicles enable adsorption of liposomes on the surface of metal nanoparticles (eg, zinc citrate particles), but result in antagonistic action particularly against *Streptococcus oralis* biofilms [49]. Despite this, due to targeted delivery, a variety of liposomes are effective in inhibiting bacterial biofilm growth at lower drug concentrations, compared to equivalent concentrations of free drug in inhibiting cell growth.

Role of nanotechnology in dental biofilm

Silver nanotechnology chemistry has proven to be effective against biofilms. Silver disrupts critical functions in a microorganism. It has high affinity towards negatively charged side groups on biological molecules such as sulfdryl, carboxyl, and phosphate groups distributed throughout microbial cells. Silver attacks multiple sites within the cell to inactivate critical physiological functions such as cell wall synthesis, membrane transport, nucleic acid synthesis (DNA and RNA) and translation, protein folding and function and electron transport.

Nanotechnology -Role in periodontics

Periodontal drug delivery

Recently, Pinon-Segundo et al [54] produced and characterized triclosan-loaded nanoparticles by the emulsification–diffusion process, in an attempt to obtain a novel delivery system adequate for the treatment of periodontal disease. The nanoparticles were prepared using poly (D, L-lactide-coglycolide), poly (D,L-lactide) and cellulose acetate phthalate. poly (vinyl alcohol) was used as stabilizer. These triclosannanoparticles behave as a homogeneous polymer matrix-type delivery system, with the drug (triclosan) molecularly dispersed. A preliminary in vivo study using these nanoparticles has been performed in dogs with only the gingival index (GI) and bleeding on probing (bleeding on probing) being determined [54]. With respect to the gingival index (GI), at days 1 and 8, it was found that a severe inflammation was detected in control and experimental sites (GI ¼ 3). It was concluded that triclosan nanoparticles were able to effect a reduction of the inflammation of the experimental sites. Timed release of drugs may occur from biodegradable nanospheres. A good example is Arestin in which tetracycline is incorporated into microspheres for drug delivery by local means to a periodontal pocket [55].

Oral prophylaxis

Nanorobots incorporated in mouthwash could identify and destroy pathogenic bacteria leaving behind harmless oral flora to flourish in the oral ecosystem. It would also identify food particles, tar tar, plaque lift them from the teeth to be rinsed away. Being suspended in liquid and able to swim about, they reach surfaces beyond bristles of tooth brush or the fibres of floss. Continuous debridement of supra and sub gingival calculus would be done by nanorobots incorporated in dentifrices. They provide a continuous barrier to halitosis [59].

Periodontal tissue engineering

Nanotechnology has got the potential to produce nonbiologic self-assembling systems for tissue engineering purposes [56]. Self-assembling systems are those which automatically undergo prespecified assemblies much in line with known biologic systems associated with cells and tissues. It is possible to create polymer scaffolds in the future for cell seeding, growth factor delivery and tissue engineering via nanodevices implanted to sites of tissue damage.

Dentinal hypersensitivity

Natural hypersensitive teeth have eight times higher surface density of dentinal tubules and diameter with twice as large as nonsensitive teeth. Reconstructive dental nanorobots, using native biological materials, could selectively and precisely occlude specific tubules within minutes, offering patients a quick and permanent cure [57].

Tooth repair

Chen et al [58] made use of nanotechnology to simulate the natural biomineralisation process to create the hardest tissue in the body, the enamel by using highly organized microarchitectural units of nano-rod like calcium hydroxapatite crystals arranged parallel to each other.

CONCLUSION

Nanotechnology is a relatively novel field, which involves manipulation of matter at the molecular level, including individual molecules and the interactions among them. It focuses on achieving positional control with a high degree of specificity, thereby achieving the desired physical and chemical properties. Nanotechnology will revolutionize health care, especially dentistry, more profoundly than many other developments of the past. It has the potential to bring out significant benefits, such as improved health. However, as with any other technology, it also carries a potential for misuse and abuse. The evolution of nanotechnology will help dentists with more precision made materials, drugs and equipments by which both the safety and patient compliance are enhanced.

From the recent advances in periodontal drug delivery systems it can be said that the antibiotic-free, nanoparticles technology has an immense opportunity for the designing of a novel, low-dose and effective treatment method, easy-to-use and more effective than the regular drugs and medicines which act systemically.

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