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RESEARCH ARTICLE

"NANOPERIODONTICS": A NEW ERA IN THE MANAGEMENT OF PERIODONTAL DISEASE

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Abstract

Nanotechnology is science, engineering and technology conducted at the nanoscale that deals with the development and application of nanoparticles or nanomaterials. This field is considered as the greatest of all inventions humans have ever made till date. The associated research and applications are diverse, ranging from extensions of conventional technology to new approaches based upon the property of molecular self-assembly. Nanotechnology has been greatly advanced in the past few decades and the role of nanotechnology in field of dentistry and particularly in periodontology has evolved greatly. The use of various nanoparticles and materials has brought a new insight into the prevention, diagnosis and management of periodontal disease. In the near future invention of dental nanorobots will help in precise diagnosis and may lead us to new treatment opportunities. This review focuses on the updated applications of nanotechnology in the field of Periodontics.

Introduction:-

Periodontics is a branch of dentistry that deals with millimetre space. As the old generation say, big surprises come from small packages. Thus comes the invention of nanotechnology. Nanotechnology is a science that deals with nanoscale of materials, which is about 1-100 nm.[1]Nanoscale is defined as 1/100th of controlled and manipulated size and shape of produced devices and systems at nanometer scale.[2] This technology helps in the manufacture of biomaterials, electronic and biomedical instruments.[3]

Periodontitis is a chronic multifactorial inflammatory disease associated with the accumulation of dental plaque and characterized by progressive destruction of the teeth supporting apparatus, including the periodontal ligament and alveolar bone.[4] Periodontitis management is important for improving the quality of life of an individual. Nanotechnology provides different types of innovative and new materials that can be used in the treatment of periodontitis. In Periodontics, applications of nanotechnology are seen in periodontal regeneration, controlled drug delivery and overall oral health maintenance.

History and Background

The revolutionary concept of nanotechnology was proposed by James Clerk Maxwell in the year 1867.[1] The term Nanotechnology was coined by Prof. Kerie E Dexler.In the early 20th century Richard Zsigmondy brought the concept of nanomaterials.[5] The term Nanodentistry was coined by R A Frietas in 2000.[6] Nano dentistry involves Nanorobotics, Nanodiagnostics and Nanomaterials.

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Nanotechnology in Periodontics

Nanoparticles

Nanoparticles are available as zero dimensional, one dimensional, two dimensional and three dimensional types. Properties of nanoparticles include greater mechanical properties such as increased rigidity, firmness, better transparency, increased resistance to abrasion, heat and scratch proof, and decreased permeability of gas. They also have greater surface area and self assembly property. Nanoparticles include nanopores, nanorods, nanotubes, quantum dots, nanocaps, nanoshells, liposomes, nanobelts and nanorings.[1]

There are different approaches for manufacturing nanoparticles which include[7]
1)Bottom up approach
2)Speculative approach
3)Biomimetic approach
4)Top down approach
5)Functional approach

Of these the most conventional approach is topdown approach.

Nanoparticles for periodontal applications

1) Magnetic nanoparticles

The most commonly used drug carriers in biomedical studies among the many types of nanostructures are core-shell magnetic iron oxide nanoparticles. Chlorhexidine (CHX) a second-generation bis- biguanide antiseptic, acts on the inner cytoplasmic membrane.[8] Application of chlorhexidine is limited due to inactivation in body fluid and cytotoxicity towards native cells.[9] The use of magnetic nano particles (MNPs) could overcome these limitations of CHX. Tokajuc et al. (2017), synthesized nanosystems composed of amino silane coated magnetic nanoparticles functionalized with chlorhexidine.[9] In the presence of human saliva, MNPs with CHX displayed significantly greater bactericidal and fungicidal activity against biofilm forming microorganisms than free CHX.[9] CHX attached to MNPs has an increased ability to restrict the growth of mixed-species biofilms compared to free CHX. The induction of oxidative stress and oxidation of fungal structures may be a part of the mechanism responsible for pathogen killing. Numerous drugs like tetracycline, doxycycline, metronidazole, silver, and Harunganamadagascariensis leaf extracts can also be used as nanoparticle drug delivery systems in management of periodontal diseases.[10]

2) Zinc Oxide (ZnO) nanoparticles

It may be difficult preventing bacterial adhesion altogether in the complex oral environment. Zinc oxide (ZnO) nanoparticle-coated surfaces have anti-adhesion properties.[7] These surfaces reduce viable bacteria like S. aureus and Streptococci without cytotoxic effect on osteoblasts and human mesenchymal cells.[11] These coatings on implants could provide osteoconductive and antimicrobial functionalities to prevent failure.[7]

3) Silver nanoparticles (AgNPs)

The use of AgNPs for surface modification has emerged as a new approach. These coatings can induce death of bacteria either through cell membrane nanoparticle interactions or through secondary effects induced by long-term release of AgNPs or Ag+ ions, by the production of reactive oxygen species, by alteration of the membrane integrity, and by protein-site-specific interactions that could prevent DNA replication. These particles exhibit both high anti-adhesion and antibacterial actions against Streptococcus mutans.[12,13]

Oral Prophylaxis

Nanotechnology can be used in oral prophylaxis by incorporation of nanorobots in mouthwashes and dentifrices. Nanorobotic dentifrice (Dentifrobots) can be delivered by mouth wash or tooth paste to protect supragingival and subgingival surfaces at least once a day. Nano encapsulation is the newest approach used in delivery systems to reach the target area. The pathogenic bacteria residing in dental plaque and elsewhere could be identified and destroyed with properly designed dentifrobots. The size of dentifrobots are 1-10 microns, crawling with a speed of 1-10 meters /second.[14] Dentifrice robots would also provide a continuous barrier to halitosis, since bacterial putrefaction is the central metabolic process involved in oral malodour.[14]

Nano toothpaste contents include nanoxyd, calcium peroxide, enzymes (papain, bromelain), fluoride combination, Co-enzyme Q10, and Vitamin E. They ensure uninterrupted debridement of supra and subgingival calculus.[15] Nano-chlorhexidine is a pure non salt form of chlorhexidine prepared by mixing with mesoporous silica nanoparticles. Seneviratne et al. (2014) assessed the antibacterial properties of nano-chlorhexidine on biofilm planktonic oral pathogenic bacteria and the results showed a reduced bacterial load.

Hypersensitivity management
8-30 % of adults are affected by dentin hypersensitivity.[7] Dentifrices contain potassium nitrite, stannous fluoride, sodium monoflurophosphate and strontium chloride. Nanohydroxyapatite containing toothpastes have been found to be effective in reducing dentine hypersensitivity.[10] Nanorobots could selectively and precisely occlude specific tubules within minutes. Ali Dabbagh et al. (2014) studied the capability of polyethylene glycol coated nanoparticles for treating dental hypersensitivity and found that these nanoparticles exhibited a significant potential for occluding dentinal tubules and decreasing dentinal hypersensitivity.[16]

Nanotechnology in Dental biofilm
Silver nanotechnology has been found to be effective on biofilm. Silver has high affinity towards negatively charged side groups like sulfhydryl, carboxyl and phosphate groups throughout the microbial cells. Silver inactivates membrane transport, cell wall synthesis and nucleic acid synthesis. Nano particles can carry and selectively release antimicrobial agents by the mechanism of smart release to kill bacteria and dismantle the biofilm matrix.[13] Silver nanoparticles are found to be effective against Escherichia coli, Staphylococcus aureus and Aspergillus niger.

Drug Delivery
Periodontitis can be managed by local drug delivery which does not have side effects of systemic drug delivery like antibiotic resistance, adverse drug reactions and high dosage.[7] Local drug delivery has the advantage of site-specific delivery, low dose requirement, bypass of first pass metabolism, reduction of gastrointestinal side effects and decreased dosing frequency.[7]A number of polymer-based delivery systems like films, chips, strips, fibers, microparticles, nanofibers, nanoparticles etc are available.[7] These systems have excellent mucoadhesive properties and are biocompatible and biodegradable.Pinon Segundo et al. (2005) developed a new drug delivery system containing nanospheres which was composed of biodegradable polymer.[17] Nanoparticles were prepared using poly d lactide, Coglycoside,Poly D L Lactide,cellulose acetate phthalate and poly vinyl alcohol as stabilizer.[18]A preliminary in vivo study using the nanoparticles was performed in dogs with only the gingival index (GI) and bleeding on probing being determined. With respect to the gingival index (GI), at days 1 and 8, it was found that a severe inflammation was detected in control sites compared to experimental sites. It was concluded that triclosan nanoparticles were able to effect a reduction of the inflammation of the experimental sites.[19]

Tetracycline has been incorporated into microspheres for drug delivery by local means and used in a periodontal pocket.[20] In the near future drug delivery systems such as hollow spheres, nanotubes and nano composites could be used in periodontal treatment. Curcumin loaded nanoparticles locally injected in an experimental periodontal disease model showed significant reduction in the loss of alveolar bone.[49]

The Potential advantages in nano-drug delivery compared to emulsion-based carriers and microparticles are:
1. Controlled release characteristics, enhanced stability and dissolution in aqueous medium
2. Increased transportation across the cell membrane which reduces clearance and enhances bioavailability
3. Improved drug loading ability due to increased surface area per unit mass and higher surface reactivity[20,21]

1) Nanospheres and Nanocapsules
Nanospheres consists of a dense polymeric matrix and nanocapsules are made of an oil core enclosed by a polymeric membrane.[22] These are polymerosomes, and this contribute to the most relevant class of nanoparticles for drug delivery.[23,24] A polymer-protein conjugate results in better biological and clinical efficacy due to the extended plasma circulation period by altering the proteolytic degradation.[25] The antibacterial agent is incorporated into nanospheres. The gradual disintegration of the nanospheres results in the controlled release of the drug and shows site-specific drug delivery.

Nanocapsules made up of poly(lactic-co-glycolic acid), PLGA, cause photo destruction of plaque biofilm and enhance drug delivery.[26] An intrapocket drug delivery system containing polymeric nanoparticles loaded with triclosan has been used effectively.[17] PLGA nanoparticles combined with polyethylene glycol nanoparticles incorporating minocycline have shown to exhibit better antibacterial action than the free drug.[27] The enhanced antibacterial activity of the active drug is due to the bio-adhesive nature of biopolymers, which binds to the bacterial cell wall and thus prolongs the drug action.

2) Nanofibers

Nanofibers are rigid or flexible in nature. They are around 100 nm in diameter. They are manufactured by electrospinning, laser spinning, or phase separation utilizing natural, synthetic or hybrid polymers.[28,29] Poly(caprolactone), poly(p-dioxanone) and chitosan are the most used polymers for its fabrication. Several biomolecules such as tetracycline, ciprofloxacin, metronidazole are being incorporated into nanofibers. Poly (caprolactone) nanofibers incorporated with metronidazole, ciprofloxacin and a combination of both exhibit potent antimicrobial properties against micro-organisms associated with periodontal disease, namely Porphyromonas gingivalis, Fusobacterium nucleatum and Aggregatibacter actinomycetemcomitans.[30]

The use of nanofibers for drug delivery in periodontal treatment resulted in the burst release of the antimicrobial agent. This drawback was overcome by using multilayer constructs. These were designed to increase the drug retention ability in the nanofibers. In addition to delivering antimicrobial agents, nanofibers have the capability for bone tissue regeneration in periodontal therapy.

3) Nanogels/ Nanocomposites

Nanocomposite hydrogels have gained considerable attention for drug delivery. They are made of a blend of various components such as nanoparticles, a matrix system gel and a suitable antimicrobial agent. The nanoparticles thus incorporated in the hydrogel matrix form a new drug delivery device for the management of periodontal disease. An antimicrobial release system of chitosan nanocomposites incorporating copper nanoparticles exhibited potent in vitro antimicrobial activity against A.actinomycetemcomitans and has appeared to be a promising tool in periodontal therapies.[31]

4) Dendrimers

Dendrimers are hyperbranched nanoparticulate structures made up of unimolecular micelles having a unique architecture. They possess an outer hydrophilic and inner hydrophobic structure and are composed of three layers: the core, building blocks and numerous functional groups at its periphery.[32] They are called cascade polymers or arboroles.

The central core encapsulates the active chemical ingredient. The building blocks with its repeating units in the internal layers are arranged in a geometrical fashion, that forms concentric layers called generations.[33] The active molecules either get conjugated onto the surface or encapsulated into the dendrimer architecture. Hyperbranched structure and enhanced mucoadhesivity make them a superior drug delivery vehicle for the management of periodontal disease. An antimicrobial agent like triclosan (TCN) encapsulated into the dendrimer results in the solubilization of TCN, that results in slow release of the drug and improved efficacy.[34]

5) Liposomes

They are self-assembled nanoparticles composed of lipid bilayers.[35] Liposomes are spherical vesicles composed of an inner aqueous core and outer chemically active one to several concentric lipid bilayers. The lipid bilayers engage hydrophilic heads and hydrophobic hydrocarbon tails encapsulating the aqueous spaces.[36] They acquire the ability to stabilize and encapsulate hydrophilic molecules in its aqueous core and hydrophobic molecules in the lipid bilayers. They consist of either natural phospholipids or non-ionic surfactant components. Due to their lipid nature, they fuse with the bacterial cell membrane and destroy them.

The nanoscale version of liposomes is called nanoliposomes with a diameter ranging from 50-150nm. Nanoliposomes have all the benefits of nanocarrier system. The doxycycline incorporated nano-liposome slow-release gel for the treatment of rat periodontitis showed an improvement in the condition by decreasing matrix metalloproteinase.[37] The unique, versatile feature of liposomes makes them an attractive drug delivery system.

Bone replacement materials

Various hydroxyapatite nanoparticles have been tried out to treat periodontal bone defects with promising results. They have shown to help periodontal regeneration by proliferation and osteogenic differentiation of periodontal ligament cells. Nanohydroxyapatite (NHA) is a highly biodegradable and biocompatible material. The synthetic

NHA that have been used in osseous defects are Ostim (Osartis GmbH, Germany) HA, VITOSS® (Orthovita, Inc., USA) HA + TCP, and NanOss™ (Angstrom Medica, USA) HA.[7]

Ostim, available as a paste, when applied to bone defect is initially osseously interweaved, resorbed as it heals and finally replaced by natural bone. A study using autogenous bone graft and Ostim in the management of human intrabony periodontal defects have shown complete resorption of the NHA after 12th week.[47]

Vitoss is a highly porous material (90% pore space) resembling human cancellous bone. Animal studies using Vitoss show new cancellous bone which reached density and structure of existing cancellous bone by 12 weeks.[6]

NanOss bioactive mimics the composition, structure and size of bone and provides induction of natural bone.[48]

GTR Membrane

Chitosan, a copolymer of N-acetyl- glucosamine and N-glucosamine units is a natural biopolymer and is biocompatible. The wide biologic properties of chitosan are under study for use as bone substitute in periodontal surgeries.[38,39] Carbon fiber, which is a type of nanofiber, has shown enhanced osteoblastic cell adhesion which is vital for dental implants.[40]

Atomic force microscopy (AFM)

AFM, with its capability to directly interact with and image live cells without any disruption of their morphology and properties, offers a breakthrough in characterization of bacteria as well as measurement of their adhesion to different substrates.[41,42] The way by which bacteria adhere to tooth surfaces or dental implants has been revealed using AFM. A study using 8.5% doxycycline nanosphere gel prepared from 2% w/v Carbopol by Botelho, Martins 2010 with atomic force microscopy(AFM) image analysis on topography and surface roughness has shown increased periodontal healing by preventing bone loss.[4]

Gene Therapy

Gene delivery systems use viral, nonviral vectors, and gene guns.[43] Nanotechnology, in the process of substituting the repaired gene employs nanosize gene carriers that are less immunogenic instead of viral vectors. In an in-vitro study, calcium phosphate nanoparticles were used as nanovectors to deliver platelet derived growth factor, PDGF-B gene delivery in fibroblasts, the target gene for periodontal regeneration.[44]

Disease diagnosis

Nanosized quantum dots based on immunofluorescence can be used for labelling specific bacteria and thus ease their identification and removal.

Nanotechnology in Implants

Dental implant is the most blooming field in dentistry. The most important challenge in implants is to achieve and maintain osseointegration. An intimate junction of the gingival tissue with the neck of dental implants prevents bacterial colonization leading to peri-implantitis while direct bone bonding ensures a biomechanical anchoring of the artificial dental root. Nanoscale features have the ability to induce the differentiation of stem cells along the osteogenic pathway that contributes to the mimicry of a cellular environment that favours the process of rapid bone gain for the improvement of the bone forming activity at the bone-implant interface.

Nanophase hydroxy apatite (HA)is the main component present in the hard tissues of the body which represents a promising class of maxillofacial implant formulations that has greater osseo integrative properties.[45] Using nanotechnology, the surface roughness of dental implants can be modified to provide the necessary desired bone-to-implant contact. Coating titanium dental implant surface with nanocrystalline HA powders can improve performance. New coating technologies for applying nanoparticles of HA and related calcium phosphates (CaP) onto the surface of implants have shown to provide an osteoconductive surface.[46] Chemical and physical processes are used to create nanofeatures on dental implant surfaces. This can alter the cellular and tissue responses that promote osseointegration.
Three nanostructured implant coatings have been developed.
1)Nanostructured Diamond
2)Nanostructured Hydroxyapatite Coatings
3 Nanostructured Metallo-Ceramic Coatings

Studies have shown that Nano hydroxyapatite modified surfaces exhibited antibacterial activity against S. aureus and Escherichia coli and induced no cytotoxic effect towards human bone marrow cells.[1]

Peri-implantitis

In periimplantitis, the affected parts become covered by an infected smear layer. Treatment of periimplantitis include complete removal of the infected biofilm and the smear-like layer, resulting in complete exposure of the roughened titanium implant surface. After this procedure, a clot-blended graft adhesion to the implant surface through application of a graft material with a particle size smaller than that of the implant surface pores should be done. The mechanical integration thus obtained will reduce the possibility of the implant bone micro-gap, a factor that could ensure complete protection of the underlying defect-filled regenerative materials or blood clot. Particle size is thought to be an important factor that optimize the adhesion of particles to the exposed implant surface, thus retarding the apical migration of the epithelial attachment and enhancing re-osseointegration.[7]

Conclusion:-

Nanotechnology is the future in the field of Periodontics and is inevitable in the management of an individual's oral health under microscopic level. Ethical considerations, social acceptance and human safety are mandatory to provide the world's 80% population with a high standard of dental treatment. The 21st century nanomedical physicians will be able to use the goodness of the natural healing power of the human body. The expanding field of nanotechnology increases the number of sources for human exposures to nanoparticles by different routes like inhalation (respiratory tract), ingestion (gastrointestinal tract), dermal (skin) and injection (blood circulation). Research must be done in the field of nanoparticles for its application in various aspects like drug delivery and gene therapy, in the development of nano-tweezers for cell surgery, in detection and modification of molecular signaling and for patient-specific treatment. All the research activities in this promising field are at the initial stage. However, results obtained so far show a strong potential for nanomaterials to revolutionize the diagnosis and treatment planning as well as tissue regenerative materials for improving aesthetics in dental field. More studies on development and application of nanomaterials and nanodevices are required to achieve great results in the field of Periodontics.

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