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Nanotechnology: The Gateway of Revolution in Dentistry

Swati Singh[1], Sanjay Kumar[2], Amit Kumar[3], A K Sharma[4]

[1]Senior resident, Department of Dentistry, Indira Gandhi Institute of Medical Sciences, Patna, India

[2]Additional Professor, Department of Dentistry, Indira Gandhi Institute of Medical Sciences, Patna, India

[3]Senior resident, Department of Dentistry, All India Institute of Medical Sciences, Patna, India

[4]Professor and head, Department of Dentistry, Indira Gandhi Institute of Medical Sciences, Patna, India

Abstract: ***Nanotechnology has tremendous potential to provide a comprehensive oral health care with advanced devices and tools for better diagnosis, cure and prevention of oral diseases.Its effectiveness is also been seen in field of medicine, engineering and our day to day life. Research is going on to reduce the cost and improve the quality of medical technology by making advances in field of nanotechnology, so that we can address the prevalent medical conditions and reduce human sufferings. Thus, the aim and objectives of this review is to elaborate, the recent development and trends and the far-reaching impact of nanotechnology on clinical dental practice and its future implications.***

Keywords: Nano dentistry, diagnostic nano technology, preventive nano technology, therapeutic nano technology, nanorobots

1. Introduction

Imagination is the soil that brings dreams to life. Nanotechnology, a 21st-century frontier, was born out of such dreams[1]. The word "nano" derives from the latin word "*nanus*" that indicates a person of very low height, i.e. a dwarf[2].The impact of this technology is expected to exceed the impact that the electronics revolution had on our lives[3].Nanoscience is a convergence of physics, materials science and biology, which deal with manipulation of materials at atomic and molecular scales; whereas nanotechnology is the ability to observe measure, manipulate, assemble, control, and manufacture matter at the nanometer scale[4].The National Nanotechnology Initiative (NNI) in the United States define Nanotechnology as "a science, engineering, and technology conducted at the nanoscale (1 to 100 nm), where unique phenomena enable novel applications in a wide range of fields, from chemistry, physics and biology, to medicine, engineering andelectronics"[5]. Both the terms nanoscience and nanotechnology have their own meaning.

Robert Freitas Jr. was the first scientist who described the medical applications of nanotechnology and nanorobots.He also introduced the concept of nano dentistry, which he defines as the science and technology that "will makepossible the maintenance of near-perfect oralhealth through the use of nanomaterials, biotechnology, including tissue engineering and nanorobotics"[6].Norio Taniguchi, a Japanese scientist was the first to use and define the term "nanotechnology" in 1974 as: The understanding and control of matter at dimensions between 1 and 100 nm where unique phenomena enable novel applications[7].Over the last years, nanotechnology has been introduced in our daily routine. Drexler in 1991 used the terms "nanobots" or "assemblers" for nano processes in medicine applications and then the famous term "nanomedicine" was also used for the first time by him[8].

The aim and objectives of this review is to elaborate, the recent development and trends and the far-reaching impact of nanotechnology on clinical dental practice and its future implications.

A computerized search was done through goggle scholar by using the following key term: Nanotechnology in dentistry. The searched articles were collected and relevant reference articleswere retrievedand compiled to write this review article with objective of elaboratingthe recent development and trends and the far-reaching impact of nanotechnology on clinical dental practice and its future implications.

There are two approaches of Nano dentistry[9]:

1) Bottom up approach: This approach arranges smaller components into more complex assemblies. For example, synthetic DNA fabrication and replication by pairing nucleic acids of nano size dimensions.
2) Top down approach: This approach creates smaller devices by using larger ones to direct their assembly.Typical examples of top down processes are milling machining, lithography, coatings of medical implants and start using CVD technology to enhance blood flow and biocompatibility.

Application in Field of Dentistry:

Arbitrarily application of nanotechnology could be dealt under three categories:

- Diagnostic nanotechnology
- Preventive nanotechnology
- Therapeutic nanotechnology

I) Diagnostic nanotechnology

Nanotechnology has shown great impact in field of drug delivery system and fabrication of novel material and designs of implants and tissue engineering field.Most of the contributions in dentistry have been made in three fields:

atomic force microscopy (AFM), imaging contrast enhancers, and biochips[10].

Efforts have been made continuously to make advancements in field of diagnosis. Biosensors were introduced incorporating nanotubes, nanowires, and nano-dots to improve the biorecognition process and overall performance of the sensing assembly. Nano biosensors are mechanically compliant and has high level of sensitivity i.e. gold nanoparticle modified DNA bioreceptor detects an analyte at a concentration as low as 0.05 nm; carbon nanotubes were utilized for the detection of circulating cancer cells in the body[11].

Atomic force microscopy (AFM) helps in characterization of bacteria's and their binding to substrates[12], real- time scanning of live bacteria's[13], provides information regarding cell membrane elasticity and membrane-molecules' properties[14], it also reveals the pattern of binding of bacteria to tooth surfaces or dental implants and helps us visualize the way antibacterial drugs bind to the bacterial cell wall; thus helps in treating drug- resistant species[15].

In dentistry near-infrared (NIR) luminescent quantum dots (QDs) is the latest advancement which helps in detection of tumors. The luminescence of QDs is photostable with narrow, symmetric emission spectra which is very effective for labeling biological species in vivo[16].QDs also helps in early detection of oral squamous cell carcinoma which is one of the most common types of cancer in oral oncology and has also been used in the case of common dental ailments such as dental caries and periodontal diseases where biofilms and bacterial infections play an important role[17].

Biochips are very small devices (less than a few millimeters) on which a collection of miniaturized test sites (microarrays) are arranged.Main advantage over traditional diagnostic approach is that it can performmany testssimultaneously. First work on biochips was initiated in field of dentistry in 2002 by National Institute of Dental and Craniofacial Research. They developed a salivary diagnostic test micro fluidics and micro-electromechanical systems (MEMS). This technology helps in measuring DNA, gene transcripts (mRNA), proteins, electrolytes, small molecules in saliva and helps us correlate these findings with systemic diseases[18].

Wong in 2008 developed the oral fluid nano-sensor test, which enables simultaneous and rapid detection of multiple salivary protein and nucleic acid targets. It can be used for detection of salivary biomarkers for oral cancer[19].Yoshizawa and Wong in 2013 reviewed another profiling technique for detecting miRNA expression levels. The presence of miRNAs in saliva can be a potential biomarker for early detection of oral squamous cell carcinoma (OSCC)[20].

Weigum et al.2013 initiated a work on the development of a diagnostic cytology-on-a-chip technique that rapidly detects premalignant and malignant cells with high sensitivity and specificity[21].

Christodoulides et al.2007 have developed an electronic microchip-assay to detect C-reactive protein (CRP), which is a biomarker for inflammation associated with periodontal disease at the picogram per milliliter level[22].CRP is also classified as a systemic marker of inflammation that has been shown to significantly increase in other conditions, including myocardial infarction, atherosclerosis, and arthritis[23].

Integrated microfluidic platform for oral diagnostics was developed by Herr et al.2007 to perform immunological assays in less than 10 minutes. This device is able to detect proteins in the picomolar range for tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) that have been spiked into saliva[24].

II) Preventive Nanotechnology

Modern era of dentistry deals with more of conservation of tooth structure, that can be better achieved by prevention of oral diseases, particularly dental caries and periodontal diseases.

The approaches of nanotechnology in caries prevention are as follows:

- Anti-bacterial nanotherapy
- Remineralization of lost tooth structure
- Development of vaccines for caries

Antibacterial nanotherapy

Dental composites and adhesives have been modified by addition of antibacterial nanoparticles e.g. silver, zinc oxide and polyethylenimine[25].These particles act by several mechanism like disrupting bacterial cell membrane, generation of reactive oxygen species and prevention of DNA replication[26].Studies have shown reduced count of S. mutantsand Lactobacillus acidophilus in biofilms in an in vitro model[27].

Remineralization of lost tooth structure

Calcium carbonate nanoparticles has good retention on tooth surface;thus, it acts as a delivery vehicle for slow continuous release of high concentrations of calcium ions into the surrounding oral fluids (saliva and dental plaque). These nanoparticles havepotential of increasing the ph. of surrounding fluid and are effective in remineralizing incipient enamel lesions when incorporated into an experimental tooth dentifrice[28].

Nanosized Calcium Flouride (CaF_2) rinse could potentially be used as an anticaries agent by increasing the F-concentration in oral fluids and thus enhancing tooth remineralization.Dental nanocomposites with different forms of nano calcium phosphates were used as fillers, e.g., dicalcium phosphate anhydrous, tetracalcium phosphate for their remineralizing action[29].

Development of vaccines for caries

DNA vaccines are safe and effective strategy for prevention of dental caries, but these vaccines are still under trial for example Examples pcDNA3-Pac, pCIA-P,pGJGLU/VAX, and pGLUA-P[30]. DNA vaccines have shown poor immunogenicity in large animals and human beings. So, to overcome this nanotechnology has been employed to tailor

delivery vehicles (e.g., anionic liposomes in chitosan/DNA nanoparticle complex was used as a delivery vehicle) to enhance the immunogenicity of anticaries DNA vaccine[31].

III) Therapeutic nanotechnology

Nanotechnology in Dental Materials[32]

Autopolymerisedresin mixed with 2% or 5 wt.% zirconium oxide nano particles improved the physical properties and strength of denture base.To inhibit the fungal growth in dental silicones commonly used as denture soft liners and obturators, solutions of chlorhexidine mixed with sodium triphosphate (TP), trimetaphosphate (TMP) or hexametaphosphate (HMP) nanoparticles were investigated. The solution was found to be effective in inhibiting the growth of candida albicans.

Luting cements impregnated with nanoparticles has been found to be effective in increasing the bond strength to enamel and dentin, when compared to conventional luting cements. For e.g. nano hydroxyapatite/fluoroapatite particles added to glass ionomer cements and ZnO and MgO nanoparticles added to zinc poly carboxylate cement has shown to improve the physical and mechanical strength of both the cements.

Newly introduced resin nano-ceramic computer-aided design and computer-aided manufacturing (CAD/CAM) blocks has showed superior aesthetics, durability, and fracture resistance e.g. Lava^{TM}ultimate resin nano ceramic blocks.

Vinylpolysiloxanes impression material impregnated with nanofillers improves the flow, hydrophilic properties and enhances the precision detaile.g. Nanotech elite H-D.

Nanotechnology in Conservative and aesthetic dentistry[32,33]

There are two types of nano composites named as nanofills and nanohybrids. These nano composites served two purposes, one improving the translucency and thus improving esthetics; second increasing the wear resistance.
Recently, a smart material nano-amorphous calcium phosphate (nACP) filled composite resin has been developed which improves remineralization properties of composite and inhibits the initiation of secondary caries. Application of a nanocomposite coating consisting of lactose-modified chitosan (Chitlac) with silver nanoparticles (nAg) has been helpful in preventing initiation and progression of secondary caries. Incorporating cross linked quaternised polyethyleneimine (QPEI) nanoparticles in resin composites was also reported to have antibacterial effects against various oral pathogens, such as Enterococcus faecalis, Streptococcus mutans, Actinomyces viscousus, Lactobaciluscasei, and whole saliva.

Calcium peroxide nanoparticles were added to tooth whitening agents as its deeper penetration into the tooth structure allows for a longer action time and ultimately a significant improvement in aesthetics.

Nanotechnology in Endodontics

A bioceramicbased nanomaterial sealer was developed recently (EndoSequence BC Sealer - Brasseler USA) consisting of nanosized particles of calcium silicate, calciumhydroxide, CaP, zirconia in addition to a thickening agent. These nanomaterial sealers provide excellent seal and gives dimensional stability even in irregular dentinal surfaces.

Nanosilver particle mixed with calcium hydroxide intracanal medicament has been seen to be effective against entrococcus faecalis for short term[34].Nanodiamond particle impregnated gutta percha points has improved endodontic filling potential as it has better adaptation to the canal with less void formation. These gutta percha points also has superior physical and chemical properties.

Nanotechnology in Orthodontics

During orthodontic treatment higher forces are applied to overcome friction which was major factor affecting the alignment or retraction of teeth during orthodontic treatment. Applying too much force led to anchorage loss, to avoid such problems nano coated arch wires and brackets were introduced recently. Nanoparticles of tungsten disulfide (WS2) and nickel-phosphorous were used for coating the wires[35].

Nanotechnology in Periodontics and Implant

Tissue engineering: The nanofibrous scaffolds have been widely developed as the matrices for regeneration of dental tissues, including dentin–pulp complex, enamel, PDL, cementum, alveolar bone, and temporomandibular joint. Stimulation of odontogenic differentiation in human dental pulp stem cells has been exhibited by nanofibrous scaffolds made of poly-l-lactide acid (PLLA). Attempt has been made to regenerate enamel my using nanomaterial structure which contain high amounts of Arg-Gly-Asp (RGD) sequences. This structure showed the abilityto induce proliferation and differentiation of ameloblasts, which were able to synthesize, organize, and biomineralize enamel nodules. Surface of nanofibers of poly (lactic-co-glycolic acid) (PLGA) or gelatin coated with silica or HA nanoparticles has shown to improve adhesion of periodontal ligament fibroblastcells. The nanohydroxyapatite/ polyamide nano composite scaffolds have shown regeneration of alveolar bone defects. Nanosized β-tricalcium phosphate within a collagen matrix has also been studied and has shown enhanced boneregeneration when implanted along withmesenchymal stem cells[10].

Bone graft material: Nanobone mimics natural bone and is composed ofnanocrystals with nanopores situated between these crystals. The surfaces of the pores are modified by adding silicon molecules, which then helps in adsorption of the protein. Two promising materials which are used for treatment of bone defects are nanophase hydroxyapatite (HA) and nanophase carbon. Commonly used materials are Vitosso (Orthovita, Inc, USA), HA + tri-calcium- phosphate (tri CaP), and Ostim HA (Osartis GmbH, Germany).

Laser plasma application in periodontics: Titanium dioxide (TiO_2) based nanoparticles coupled with laser irradiation exhibit excellent properties and effects-like shock wave, micro abrasion, and stimulation of collagen production. These properties can be beneficial in treatment of gingival

depigmentation, periodontal pocket therapy and soft tissue incisions.

Local drug delivery: Local drug delivery reduces the unwanted systemic side effects of drugs and also provides increased concentration of drug in confined area. Utilizing nanoparticles to deliver therapeutic molecules has been explored for periodontal regeneration. Minocycline (Arestin) encapsulated in PLGA nanoparticles has antibacterial effect and has shown substantive release of drug for one week. A more osteoconductive vehicle for the delivery of tetracycline was developed using calcium-deficient HA nanoparticles showing sustained release of up to 88% over a period of 5 days and considerable antibacterial effect[36]. Growth factors are now widely used for dental regeneration, bone morphogenetic protein (BMP) encapsulated in glycidyl methacrylate and gelatin nanoparticles has showed a sustained release of more than 12 days. Nano diamonds, which are carbon nanoparticles of 4–5 nm, have also been used as a growth-factor carrier for the alveolar ridge augmentation.

Nanotechnology in dental implants: Nanotechnology can be utilized for surface modification of dental implants i.e. roughness and chemistry of surface by use of nano particles coating which improves adhesion and integration to surrounding tissues.

Nanotechnology in surgical field[37]

Nanocoated surgical blades: Diamond nanolayers has been applied on blades which shows chemical/biological inertness and are less adhesive to material or tissues. These properties enhance the cutting efficiency and reduces trauma to tissues. Trephines with nanocarbon coating and ophthalmic blades has also been used.

Nanoneedles and optical tweezers: Stainless steel incorporating nanosize particles (1– 10 nm quasicrystals) has been applied for plastic and ophthalmic surgeries. These newly developed blades have excellent cutting efficiency, ductility and corrosion resistance.

Optical tweezers are a powerful technique for non-invasive manipulation of single biological molecules within cells. These are electric force driven tweezers developed by attaching carbon nanotubes to the end of electrodes.

Modified catheters: Catheters are small tube-like devices used for injecting or draining fluid from body, the major side effect is thrombus formation on the surface of these devices. These catheters have been modified by coating with silver nanoparticle for anti-bacterial effect; carbon nanotubes have been added to increase the flexibility, strength and reduce thrombogenic effect.

Other applications: A nano porous silver powder has been developed which has antibacterial effect and is less toxic. This powder has been applied as coatings on medical devices i.e. implants, indwelling catheters, wound dressings, and for burns and other chronic wounds.

Smart instruments embedded with sensors gives insight of internal condition of tissues to surgeons, self-assembling nanofibers for hemostasis, conduits for nerve repair are some of the approaches which are been studied widely for future application.

Nanorobots*: the upcoming warriors*

Nanorobots are minuscule devices that do precision work at the atomic or molecular scale, defined as being 1-100 nanometers in at least one dimension. This field is still evolving and will be implemented in near future. According to their application they are classified as below[38]:

- **Pharmacyte:** used for drug delivery at target area.
- **Diagnosis and Imaging:** microchips are used which helps in early detection of disease.
- **Respirocyte:** nanorobots as artificial oxygen carrier to cells.
- **Microbivores:** nanorobots as phagocytic agents.
- **Clottocytes:** nanorobots with a unique biological capability: "instant" hemostasis using artificial mechanical platelets.
- **Chromallocyte:** nanorobots replacing entire chromosomes in individual cells thus reversing the effects of genetic diseases.

Applications of nanorobots in dentistry

Treatment of gingival and periodontal diseases: Nanorobots designed for specific area would destroy the pathogenic bacteria specific to the disease without harming the beneficial bacterial flora, thus maintain a healthy ecosystem.

Maintenance of oral hygiene: Nanorobots incorporated in dentifrices has ability to swim and reach the surfaces beyond bristles of tooth brush or floss. They destroy the pathogenic bacteria present in supra and sub gingival calculus and acts as a barrier to halitosis.

Treating dentinal hypersensitivity: Dental nanorobots could provide quick and long-lasting relief from sensitivity within minutes by selectively and precisely occluding the dentinal tubules. E.g. acclaim toothpaste, trucare toothpaste.

Orthodontic tooth movement: In near future nanorobots will be used for rapid and painless orthodontic tooth movements i.e. straightening, rotational and vertical repositioning movements in few minutes to hours by directly manipulating the periodontal tissues, including gingivae, periodontal ligament, cementum and alveolar bone

Natural biomineralization: Nanorobots would be able to create and mimic natural hardest structure, the enamelby using highly organized micro architectural units of nano-rod like calcium hydroxyapatite crystals arranged parallel to each other.

Inducing local anesthesia: A colloidal suspension containing millions of active analgesicmicron-size dental robots will be instilled on the patient's gingiva with the help of nano-computer. These dental robots may be commanded by the dentist to shut down all the sensitivity in any particular tooth that requires the treatment.

Nanotoxicity and hazards: Nanotoxicology aims at studying the interaction between nanomaterial and its effect on the biological system. Rise in use of nanomaterial is a matter of health and safety concern due to following reasons: a) compared to other molecular analogues in solvents or in condensed phase nanomaterial is much more reactive; b) smaller particle size allows them to easily migrate to biological system; c) may cross the biological membranes in the lung, gut, and even brain causing damage to intracellular structures and cellular functions.

The U.S. Environmental Protection Agency (EPA) has made the control of manufacture of nanomaterial under the general Toxic Substance Control Act (TSCA). The final regulation was issued on 11 January 2017, and titled "Chemical substances when manufactured or processed as nanoscale materials: TSCA reporting and recordkeeping requirements". This rule focuses on keeping record of new chemical produced or processed at the nanoscale, which provides the information about chemical identity and volume produced, the possible effects on health and environment and the nature of personnel and environmental exposure.

2. Conclusion

Nanotechnology is a new ray of hope in field of oral health care. The field is still getting explored and in near future will revolutionaries' various fields including general and dental care, biomedicine,food, and agriculture. Risk needs to be balanced with benefit to maximize its application in field of medicine.

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