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A Memorandum Entry Into The Nano World Of Periodontology

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Abstract:
*Nanotechnology means creating and utilizing the materials, devices and systems through the control of matter on the nanometer length scale (10^{-9})**.** The studies on tooth structure provided a basis for nanotechnology-based dental treatments known as 'nanodentistry'. Periodontal diseases are caused by dental plaque that leads to an immune and inflammatory response in the adjacent tissues. Nanotechnology provides the fabrication of new systems that can be incorporated into an active anti-infective part of the periodontal treatment by using nano delivery systems. It is believed that nanotechnology could be applied in various fields of dentistry to maintain good oral health in all possible means.*

Key words: *Nanotechnology, Nanomaterials, Periodontal tissue engineering, Periodontal drug delivery, Bone regeneration, Dental implants*

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I. Introduction

The creation and utilization of materials, devices and systems through the control of matter on the nanometer length scale is called Nanotechnology. Nanometer is a billionth of a meter (10^{-9}) which is at the level of atoms, molecules and supramolecular structures. **[1]** The potential applications of nanotechnology in medicine are vast. These include imaging and diagnostics, targeted drug delivery, Nano-enabled therapies, and tissue engineering. **[2]** The studies on tooth structure provided a basis for nanotechnology-based dental treatments known as 'nanodentistry'. Nanodentistry simulates the architecture of both soft and hard natural tissues, by adapting novel biomaterials for exclusive restoration of the tissues that has been lost due to disease and enables antibacterial activity. Therefore, it is believed that nanodentistry could help in maintaining the oral health with the usage of biotechnology, nanomaterials and nanorobotics. **[3]**

Applications of nanotechnology in dentistry includes local anesthesia, cure for hypersensitivity, nanorobotics dentrifice, antibacterial adhesives used for orthodontic treatment, photosensitizers and carriers, diagnosis and treatment of oral cancers. Periodontal diseases are caused by dental plaque that leads to an immune and inflammatory response in the adjacent tissues. Nanotechnology provides the fabrication of new systems that can be incorporated into an active anti-infective part of the periodontal treatment by using nano delivery systems such as quaternary ammonium poly (ethylene imine) antimicrobial nanoparticles (NPs), colloidal carriers or liposomes that could breach the hydrophobic barrier of oral biofilm and better penetrate inflamed tissues. **[3]** This review of literature will highlight the plausible applications of nanotechnology and the usage of nanomaterials in Periodontics.

II. Review of literature

History

The term "Nano" is derived from a Greek word which means 'dwarf'. **[4] James Clerk Maxwell** in the year **1867** put forward a hypothesis, a tiny entity known as 'Maxwell's Demon'. That was the first time that the concepts of nanotechnology have come to lights. In the first decade of the 20th century, the Nano-particle sizes were observed and measured. **Richard Adolf Zsigmondy** studied gold sols and other nanomaterials sizing ≤10 nm and published a book in 1914. He utilized dark field ultramicroscope for viewing particles that sized less than the wavelength of light.

Moreover, Zsigmondy was the first to use nanometer specifically for characterizing particle size. He represented the nanometer as 1/1,000,000 of a millimeter. He also introduced a classification system depending on the particle size in the nanometer range. Later, on December 29, 1959, Nanotechnology topic was started again by a talk ''There's Plenty of Room at the Bottom,'' by physicist **Richard Feynman** at an American Physical Society meeting at Caltech. Since then, nanotechnology has been part of mainstream scientific theory with potential medical and dental applications. **[5]** A Japanese scientist **Norio Taniguchi** of the Tokyo University of Science was the first who employed the term "nano-technology" in **1974**. **[1]**

However, the term "nanotechnology" in contrast with "nano-technology" was given by **Prof. Kevie E. Drexler** in his **1986** book titled "Engines of Creation: The Coming Era of Nanotechnology". **[1]** Later in the year 2000, **R.A. Freitas Jr.,** formally presented the term "nanodentistry". He envisaged the usage of nanorobots for orthodontics, dentition regeneration, nanomaterials, and robots in dentifrices which they called dentifrobots. In **2002, Ishiyama et al.** at Tohoku University established magnetically driven spinning screws which can travel through veins and carry drugs to the target site or to get into tumors and destroy producing heat. Gordon's group at the University of Manitoba introduced magnetically controlled 'cytorobots' and 'karyorobots' that can perform wireless surgeries intracellular and intranuclear. **[6]**

In **2003**, "MR-sub" project of **Martel's** group at The Nanorobotics laboratory of Ecole polytechnique in Montreal, tested using variable MRI magnetic fields to generate forces on an untreated microrobot containing ferromagnetic particles, developing sufficient propulsive power to direct the small device through the human body. **[7]** In **2005, Brad Nelson's team**, at the Swiss Federal Institute of Technology in Zurich fabricated a microscopic robot which is as tiny to be injected into the body using a syringe. **[8]** Subsequently, nanotechnology has come into practice in various fields including dental diagnosis, material and therapeutics.

Nanomaterials

Nanomaterials are classified into one-dimensional, two-dimensional and three-dimensional nanostructures.

ONE DIMENSIONAL- The smallest possible crystalline wires with cross-section as small as a single atom can be engineered in cylindrical confinement. This provides mechanical stabilization and prevents linear atomic chains from disintegration. **[9]**

TWO DIMENSIONAL-They are crystalline materials consisting of a two-dimensional single layer of atoms. Thin films with nanoscale thicknesses are considered nanostructures, but are sometimes not considered nanomaterials because they do not exist separately from the substrate. **[9]**

THREE DIMENSIONAL- Some bulk materials contain nanostructure in a multilayer system of parallel hollow Nano channels located along the surface and having quadrangular cross-section. The thickness of the channel walls is approximately equal to 1 nm. The typical width of channel facets makes about 25 nm. **[9]**

There are various forms of nanomaterials incorporated in dentistry. They are Nanoparticles, Nanorods, Nanospheres, Nanotubes, Nanofibers, Nanopores, Dendrimers and Dendritic copolymers, Nanocomposites, Nanocapsules, Nanoclays.

Applications of nanotechnology in periodontics

The application of nanotechnology in the periodontal management was put forward by **Kong et al 2006. [10]** Nanotechnology is employed in various fields in periodontics.

i. *Nanotechnology in local anesthesia*

Nano-sized stainless-steel crystals are assimilated into suture needles. The gingiva of the patient is instilled with a colloidal suspension containing active micron-sized dental robots that respond according to the dentist. Nanorobots then can reach the pulp via the gingival sulcus, lamina propria or dentinal tubules. Once the nanorobots reaches the dentin, they enter the dentinal tubular holes which are 1-4 µm in diameter and moves further towards the pulp. This movement is leaded by numerous chemical gradients, controlled by nano-computer which in turn is directed by the dentist. Nanorobots enters the pulp chamber in approximately 100 seconds.

When nanorobots pass through the enamel, dentin, and the pulp, they are controlled by the dentist to occlude the nerve endings in the specific tooth requiring treatment. As soon as the nanorobot receives signals from the dentist who guides it using handheld controlled display monitor, it anesthetizes the targeted tooth immediately. The movement of nanorobot is facilitated by the increased diameter of tubules near the pulp. **[11]**

Finally, after the dental treatment gets over, the nanorobots are guided again by the dentist in the same acoustic data links to return back from the tooth through the same path after restoring all the blocked senses. This completely reversible usage of nanorobots in anesthesia seems to increase patient compliance by reducing anxiety due to the fear of needle pricks and also has very minimal side effects and complications. **[12]**

ii. *Nanotechnology in the treatment of dentinal hypersensitivity*

Dentin hypersensitivity is another pathological phenomenon that may be amenable to nanodental treatment. Numerous therapeutic agents could be used to treat this painful condition, however, reconstructive dental nanorobots, that use native biomaterials, holds the capacity to occlude targeted dentinal tubules precisely within few minutes, that can cure the symptoms quickly and permanently. **[12]** Nanomaterials that has small size, larger surface area, high surface energy, and large proportional of surface atoms that owes to the development of demineralization agents into dentinal tubules. The size and reactivity of nanoparticles (NPs) may allow them to be delivered further into dentinal tubules, with an enhanced potential for decontamination, remineralisation and reduced sensitization compared with contemporary treatment regimens.

iii. *Nanotechnology in oral hygiene practice*

1. Chlorhexidine mouth rinse

Nano-CHX is a new blend of mesoporous silica nanoparticle (MSN) when encapsulated with a pure non-salt form of CHX. The antimicrobial properties of Nano-CHX were evaluated in both planktonic and biofilm modes of representative oral pathogenic bacteria. The Nano-CHX demonstrated potent antibacterial effects on planktonic bacteria and mono-species biofilms at the concentrations of 50–200 µg/mL up to 72 h. **[12]**

2. Chitosan

Astriandari and Safitri, 2013 obtained Chitosan from shrimp shells and specially processed and modified physically and chemically in order to obtain NP chitosan. The NP chitosan, due to its antibacterial substance and with superior properties, is applied to obtain desired results in dentistry. The physical modification of chitosan as antibacterial agents is utilized as NPs in mouthwash. Utilization of nanochitosan is found to be more effective than chitosan since it has a low molecular weight and spills particles around the bacterial cell. Therefore, nanochitosan is used instead of alcohol-based mouth rinse and with its nanocalcium component it strengthens the tooth against acid attack. **[13]**

3. Dentifrice

Nakashima, S et al, 2009 incorporated Nanosized calcium carbonate (NC) into a test dentifrice and studied its effectiveness on enamel lesion remineralisation. The test dentifrice showed a statistically substantial mineral surge demonstrating enamel lesion remineralisation. An increased calcium concentration in the remineralizing solution was also detected after a single usage with the test dentifrice. The study signifies the possible remineralisation potential of incipient enamel lesions due to the unique properties of NC, later releasing calcium ions into oral fluids. **[14]**

4. Hydroxyapatite(ha) as surface defect filler

Pepla, E et al, 2014 incorporated the nanoform of Hydroxyapatite, which the enamel of a tooth is mainly composed of, in a toothpaste (nanosynthesized HA). This addition of nanosynthesized HA to toothpaste could fill any microscopic fissures/cracks/voids that are present on the enamel surface of tooth. It also forms a protective layer on the enamel to prevent from mechanical damage. The results suggested that the Nano-hydroxyapatite has significant remineralizing effects on initial enamel lesions, certainly superior to conventional fluoride, and good results on the sensitivity of the teeth. The nano-HA has also been used as an additive material, in order to improve already existing and widely used dental materials, in the restorative field. **[15]**

iv. *Nanotechnology in periodontal drug delivery*

Periodontal therapy requires local delivery of drugs for more predictable results of treatment. In the treatment of periodontal infections, where vascularity is compromised, obtaining effective local antibiotic concentrations by parenteral administration is difficult, thus the delivery of an active antimicrobial agent directly to the site of infection represents a viable alternative treatment. **[16]**

The primary goals of nano-drug delivery system include:

- More specific drug targeting and delivery
- Reduction in toxicity while maintaining therapeutic effects
- Greater safety and biocompatibility
- Faster development of new safe medicines

There is a general opinion that when the size of a particular material becomes nanoscopic, the properties of the material such as its electronic properties, melting point and optical properties might change. This fact has brought up attraction towards nanomaterials. The evolution of nanopharmaceuticals, nanosensors, nanoswitches, and nanodelivery systems started having pivotal roles in local, or targeted drug delivery.

v. *Nanotechnology in bone regeneration*

Transplantation of bone requires 3D porous scaffolds for support and guidance to bone formation. In spite of having many developments in porous materials, the regeneration of bone by itself is still facing troubles. The following elements are essential in bone regeneration,

✓ Osteoconductive matrix (scaffold)

✓ Osteoconductive signals

- ✓ Osteogenic cells that can respond to these signals
- ✓ Adequate blood supply

There are new systems brought up by the nanotechnology to plan the internal surfaces of scaffold and construct drug delivery system with controlled spatial deliveries. The cells are distributed in the scaffold either by getting attached to its internal surface or held together with the help of a gel- like vehicle.

vii. *Nanomaterials for periodontal tissue engineering*

Tissue engineering for periodontal regeneration are focused on the utilization of synthetic scaffolds for cell delivery purposes. Self-assembling biologic systems are those which automatically undergo pre specified assemblies much in line with known biologic systems associated with cells and tissues. Using these principles, it is possible to construct systems on a nanoscale. The clinical utility of these nano-constructed self-assembling materials is their capacity to be developed into nanodomains or nanophases, leading to unique nanobuilding blocks with inbuilt nanocontrol and nanodelivery capabilities. Polymer scaffolds for cell seeding, growth factor delivery and tissue engineering purposes are also created. **[10]**

- ✓ Nanoparticles that offer to the Tissue the use of their Chemical Components and their Bioactivity: Calciophosphatic particles are added to the filling nanopowders or carried by hydrogel in the bone healing sites, with other components, in order to promote remineralisation. The nano-Hydroxyapatite has shown excellent biological performances compared to conventional Hydroxyapatite. It also showed biocompatibility and bioactivity in respect of bone components, probably as a result of its similarity with the chemical component and mineral structure of bone tissue. Due to their small size and large specific surface, they promote ion exchange within a physiological environment, increases the protein absorption and cellular response.
- ✓ Nanostructured Materials for Drug or Signaling Molecules Delivery: These are nanomaterials that incorporate molecules which, once released, enhance the regenerative capacities of the tissues. They are often useful in Tissue engineering and are bioactive nanocarriers represented by nanospheres, nanotubes, and nanofibers.
- ✓ Nanostructured Materials to Build Scaffolds: Many methods have been developed to shape scaffolds for tissue-engineering applications and the conventional techniques include emulsion freeze-drying, phase separation, gel casting, precipitation, and solvent casting/salt leaching. **[17]**

viii. *Nanotechnology in photodynamic therapy*

Antimicrobial photodynamic therapy (aPDT) has been defined as a aid for removing or controlling the infections wherein a photosensitizer or dye having a light source of a specific wavelength, by way of illustration, toluidine blue excited with a wavelength of 630 nm is applied. The photoinactivation of Gram (+) and Gram (-) bacteria is based on the concept that some photosensitizers can be accumulated in significant quantities on the plasma membrane, a critical target to induce irreversible damage in bacteria. Neutral or anionic photosensitizer molecules are efficiently bound to Gram (+) bacteria and may photodynamically inactivate them. In Gram (-) bacterial cells, these photosensitizer molecules are bound only to the outer membrane, and cannot inactivate bacterial cells after illumination. This is related to the differences in bacterial membrane composition. The peptidoglycan layer in the Gram (+) bacteria is porous with a single lipid bilayer, whereas in Gram (-) bacteria, the peptidoglycan layer is between a double lipid bilayer, with lipopolysaccharides (LPS) at the outer surface of the bacterial membrane. As a result, photosensitizers' ability to penetrate the bacterial membrane and reach the cytoplasm is more challenging in Gram (-) than Gram (+) bacteria.

Inorder to overcome these challenges, Nanostructure materials have been used to serve as carriers to improve the delivery and penetration of therapeutic agents. The physicochemical characteristics of nanoparticles can shape specific properties related to solubility and adsorption of drugs, besides their protection against degradation and delivery in specific sites that can be supportive of an enhanced antibacterial outcome against oral pathogenic biofilm.

ix. *Nanotechnology in dental implants*

The idea of using titanium implants in dentistry began in early 80s and was based on Branemark's definition of 'Osseointegration 'as direct contact of a living bone with functionally loaded oral implants. Nanotechnology enhances the surface topography and stability of implants which are imporatant for the osseointegration and success of implants.

Nano HA and nano calcium phosphate particles aids in osteoblast formation on implant surface. These nano coated implants integrate well to the adjacent tissues. Also titanium oxide nanotubes with silver nanoparticles acts as anti- infective agents, there by improving the life of implants. Nanotechnology brings a variety of new high surface area biocompatible nanomaterials and coatings to increase the adhesion, durability, and life span of implants. Nanostructure modifcation of dental implants improves osseointegration through enhanced biomimicry of host structures. Ceramic materials such as calcium phosphate (hydroxyapatite or HA) and calcium carbonate are the available calcium derivative nanoparticles. **[3]**

Future aspects of nanotechnology in periodontics

Nanotechnology brings innovations to cell based treatments for regeneration and medications that are used to reduce inflammation and pain.

Nanodevices holds significant advantages by improving health, using natural resources and lowers pollution. [**11]** Some of the potential benefits of medical nanomaterials include improved drug delivery, antibacterial coatings of medical devices, reduced inflammation, better surgical tissue healing, and detection of circulating cancer cells. **[18]**

The growing interest in nanodentistry may lead to nanotechnologic improvements creating micron-sized dental robots called nanorobots. These nanoscaled robots may be controlled by a dentist using a computer transmitting orders with local sensors or acoustic signals. These nanorobots with cell penetration ability may be used in local anesthesia and analgesia by affecting the sense transfer on the nerve; in dentin hypersensitivity by occluding dentinal tubules with native logical nanomaterials; as a dentifrice patrolling all over the tooth surface; for metabolizing dental biofilm into harmless and odorless together with calculus debridement; as a part of a targeted releasing system delivering novel vaccines, antibiotics, and drugs with reduced side effects. **[19]**

Hazards of nanotechnology

Potential adverse effects should be investigated with regard to functionality and esthetic outcome. Conventional materials used in dentistry may have an adverse effect on both, soft tissue and/or surrounding bone. The classic example of such a scenario is amalgam fillings which contain nonprecious metals which by oxidative products may induce discoloration of surrounding gingiva, commonly known as 'amalgam tattoo'. Such bluish-black discolorations may also be caused by other dental metallic materials such as orthodontic wires or brackets. They have to be differentiated with melanoma, and in some cases require surgical or laser-assisted removal.

Interactions between nanoparticles and gingival fibroblasts results in increased cell oxidative stress, inflammation and apoptosis. Also, direct DNA damage through internalization of NPs and intracellular ions release was observed in fibroblast cell lines in the study of **Jiravova et al, 2016**. **[20]**

The toxic effects of NPs are resorption of bone around teeth or dental implants, gingival discolorations, irritations and genotoxicity and mutagenicity. The large scale usage of nanomaterials comprehensively could possess health and environmental risks. The brief exposure to the uplifted nano particles could lead to acute cardiovascular mortality, as reported by American Health Association.

On the contrary, **Heravi et al, 2013**, in an invitro study revealed that orthodontic adhesive containing Ti02 nanoparticles indicated comparable or even lower toxicity than its nanoparticle free counterpart. It was concluded that incorporation of 1% by weight of Ti02 nanoparticles to the composite structure does not result in additional health hazards compared to that occurring with pure adhesive. **[21]**

Despite high antibacterial properties of nanoparticles, they may induce cytotoxic effect to selected cells and tissues. They may also induce apoptosis and necrosis in osteoblast cell lines in a concentration- and time-dependent manner and are related to increase of inducible nitric oxide synthase, inducible nitric oxide synthase protein and generation of increased amounts of NO. It can be assumed that nanoparticles may interfere with all cell involved in bone metabolism such as pre- and osteoclasts, osteoblasts and their precursors and osteocytes as well. **[22]**

III. Summary and conclusion

Nanotechnology is applied in various fields including medicine and dentistry. The usage of Nanoparticles in dentistry is efficient in action when compared to the conventional materials, because of the difference in their sizes. Much smaller size of the nanoparticles than the conventional materials allows easier penetration of the former into human tissues. In a timeframe of approximately half a century, nanotechnology has become the foundation for remarkable industrial applications and exponential growth. **[18]**

Despite of having the fact that the above mentioned wonders that nanotechnology could bring sounds unfeasible, the researchers are aiming to make nanotechnology possible in all means. However, nanotechnology also carries risk of mishandling and abuse. The outcomes of nanomaterials are encouraging to future clinical studies that will permit the therapeutic value of nanotechnology-based restorative materials to be established. However, social issues concerned with public acceptance, ethical issues, government regulatory guidelines, and human safety must be discussed before molecular nanotechnology can be realized as the possibility of providing high-quality dental care in routine clinical practice and to society.

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