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RESEARCH ARTICLE

NANODENTISTRY – PROBLEMS AND CHALLENGES IN RESEARCH

*,[1]Suresh Mitthra, [2]Venkatappan Sujatha and [2]Sekar Mahalaxmi

[1]Department of Conservative Dentistry and Endodontics, Sree Balaji Dental College and Hospital, Bharath University, Narayanapuram, Pallikaranai, Chennai-600100, Tamilnadu State, India
[2]Department of Conservative Dentistry and Endodontics, SRM Dental College and Hospital, SRM University, Ramapuram, Chennai-600089, Tamilnadu State, India

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ABSTRACT

Nanotechnology entered dentistry with the advancements in dental materials mainly composites and bonding agents. The development of nanodentistry will alter the focus to more specific diagnosis and treatment modalities for the maintenance of perfect oral health. Many studies have demonstrated that nanomaterials can exhibit inflammatory responses and promote DNA damage through direct or indirect mechanisms. The key point is that different nanomaterials exhibit a variety of toxicity depending upon the type of living organism. Future research must be based on the development of methodologies for nanomaterials control and to minimize nanomaterial hazard. This review provides an overview of the challenges faced by nanodentistry and related toxicology issues.

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INTRODUCTION

Nanodentistry aims at designing more biocompatible dental materials with maximum patient safety and reduced risk of occupational hazard. The advancements in the field of nanodentistry will revolutionise dentistry with the application of nanodiagnosis, nanorobotics, nanomaterials, nanosolutions, nanosurgery and nanodrugs (Rita Chandki *et al.*, 2012). As with any new technical advancement, the associated risks and ethical issues are the same with regards to research in Nanodentistry (DuoxiYao *et al.*, 2013). Applications of nanotechnology in dentistry are multi-fold, some of which include- nanorobotic, carbon nanotube or nano-needle based drug delivery; nanofillers in composite resins, Glass Ionomer Cement and vinylpolysiloxane impression materials; nanorobotic administration of local anaesthesia; nanosolution based bonding agents for composite resin; nanobrushes for interproximal gingival tissue cleansing and endodontic debridement; gold nanoparticles or nanorobotic based dentinal hypersensitivity cure; nanorobotic dentrifice; tooth repair and repositioning with orthodontic nanorobots and nano-hydroxyapatite; nanodiagnosis with stem cell imaging & tracking for the treatment of oral cancer (Malathi Suresh *et al.*, 2014; Abiodun-Solanke *et al.*, 2014). The use of nanotechnology has its own merits and demerits. Nanoscience can be used to create miniature nanorobots on the molecular level that could kill oral bacteria and viruses. However as an adverse effect, this could lead to toxicity and damage to the healthy oral tissues (Mantri and Mantri, 2013). Researchers have proved that nano-machines have the ability to self-replicate. In this way it is not necessary to produce multiple machines one by one, thus reducing manufacturing costs. But the world will be endangered if the process goes out of control. Imagine a world filled with billions of nanorobots! These self replicating machines would immediately start to replicate themselves upon exposure to the natural environment (Robert, 2005).

Corresponding author: **Suresh Mitthra,**
Department of Conservative Dentistry and Endodontics, Sree Balaji Dental College and Hospital, Bharath University, Narayapuram, Pallikaranai,Chennai-600100, Tamilnadu State, India.

Issues faced by nanodentistry

Scientists have invented microscopic devices to render dental treatment (that are normally done by the dentist or with the use of extensive dental instruments). These devices are called nano-assemblers that are controlled by computer to perform specialized jobs. The size of these nano-assemblers is less than that of a cell nucleus, enabling them to reach and occupy locations that are inaccessible by hand or with conventional equipments. They are bacteriocidal to cariogenic bacteria in the oral cavity and even reconstruct sites of caries on natural teeth. Nanodentistry has enormous potential but social issues of people acceptance, ethical concern, biomedical-regulation and human safety must be clarified before nano-assembler nanodentistry can provide high quality dental care to the world's lower economic population that currently receives less or no dental care. With the successful manufacture of new innovative nanomaterials, there is an greater concern of risk of environmental exposure (Sujatha *et al.,* 2011). Nanomaterial properties differ from other materials due to two reasons: the increase in surface area and quantum effects. Nanoparticles due to their nano size (10^{-9}m) have an increased surface area per unit mass compared to larger particles. In addition, quantum effects become more dominant at the nanoscale. All properties, including electrical, optical and magnetic are altered (Kanaparthy and Kanaparthy, 2011).

The issues faced by Nanodentistry

1. Engineering issues
   - Difficulty in manufacturing nano based dental materials on a mass scale.
   - Accurate positioning and assembly of molecular scale parts of dental nanorobots.
   - Manipulating and co-ordinating activities of large numbers of independent microscale nanorobots simultaneously inside the oral cavity.
2. Biological issues
   - Developing biocompatible dental nanomaterials.
   - Ensuring compatibility with all intricate parts of the oral cavity.
3. Social challenges-
   - Ethical issues.
   - Public awareness, cost factor of manufacture & nanotechnology based dental treatment.
   - Bio-regulation and human safety.

Ethical and social issues

Traditionally, dental ethics is patient and treatment centred rather than research and oral disease centred. In other words most medical ethics is focussed on clinician-patient relationships, life decisions, resource allocation, treatment options, informed patient consent etc. Biomedical research becomes significant only when it enters clinical trials. While the removal of the cause of disease is generally preferable to symptomatic treatments, it does not appear to matter whether diseases are addressed at a molecular / cellular or whole organ level. Since the applications of nanodentistry is not limited to its use only in the science of dental materials but as it is extended to life sciences, it becomes mandatory to address all the ethical issues of this new technology. The nano-dental research programme raises issues that aim to expand the boundaries of dental ethics. This concerns for example the recognition of nanodrugs, mode of drug delivery and acknowledgment of the limits of knowledge and control. Nano-dental research raises questions of distributive justice and global equity as major public investments are directed at oral cancer treatments and thus at attempts to reduce mortality in developing countries. Drug companies are still striving to increase the success rate of their products as well as to increase the production of dental nanomaterials and to reduce the manufacturing costs, including the time for development. Nanotechnology can revolutionize the drug industry by enhancing the drug discovery process via miniaturization, automization and reliability of treatment. It will also reduce the cost of nanodiagnosis, drug delivery and nano drug design with the use of inexpensive DNA sequences, nanorobots, nanoneedles, carbon nanotubes etc (Bhardwaj *et al.,* 2014; Vicki Brower, 2006). Ethical questions of many kinds arise in the general area of research, manufacturing and applications of nanotechnology. It is impossible to subject all distinguishable kinds of nanomaterials to extensive testing. Thus, direct empirical research is required to determine the impacts of representative nanomaterials, research that can be the basis for comparison of similar materials that are not tested so intensively. Risk assessment for nanomaterials covers four related steps- hazard identification, hazard characterization, exposure assessment and risk calculation (Luther *et al.,* 2004) (Karluss Thomas, 2005). Research and development hazards differ from those in manufacturing, in the use of the product and in the disposal when the product is no longer serviceable. Hazards may be higher in cases of accidents or misuse. For example nanoscale engineered substances designed to hold hydrogen in fuel tanks of future hydrogen powered automobiles might be entirely contained and safe in normal use, but they might pose a risk in severe accidents when the fuel tank ruptures. Some critics argue that the benefits of nanotechnology themselves raise ethical issues, because they may not be available to everyone.

The development of a deontological code is needed to prevent nanodentistry from progressing in the wrong direction with the core interests of safety and non-invasion of the human body. Ethical & safety guidelines to standardize research procedures are necessary to bridge the gap between science and ethics. The greatest ethical concerns are to foetuses, children, terminally sick, elderly and disabled belonging to the lower socio-economic groups in the neighbourhood (Neenu Singh, 2009). Since the command and controlled manipulation of the human cell and genetic signature embedded in the DNA of each individual has become possible in nanotechnology including the use of stem cells for research, a guideline for establishing limits to the exploration of the human being has become a necessity. Anyways, none of these guidelines should prevent the growth of nanodentistry aimed towards the progress of the human race (Howard and Debra, 2005).

Nanotoxicology

According to Howard Kipen and Debra Laskin (2005) "Smaller is not always better: nanotechnology yields nanotoxicology!". The dental implications of nanotechnology are limited due to concerns about genotoxicity. Genetic alterations may occur due to exposure to nanomaterials (Sujatha *et al.,* 2011) that include chromosomal mutations, DNA fragmentation and changes in gene expression profiles. DNA damage occurs due to direct and indirect mechanisms when nanomaterials gain access into the human body via lungs, skin or oral routes. After penetrating the cell membrane, the nanomaterials diffuse across the nuclear membrane, integrates with the nucleus following mitosis and transforms each daughter cell. These nanoparticles disrupt the genetic material via direct DNA interaction. Geiser. M & researchers (2005), Liu.L & co-workers (2007) proved that titanium dioxide and silica nanoparticles cause prevention of replication, transcription and cell proliferation via the formation of intra-nuclear protein aggregates. Quantum dots penetrate the nuclear membrane (Nabiev et al 2007), and subsequently target and interact with histone proteins (Robert, 2005). The key reason for the nanomaterial genotoxicity is the enormous intracellular generation of reactive oxygen species (ROS) and reduced level of anti-oxidants. Toyokuni & his researchers (1998) concluded that carcinogenesis is promoted by ROS that can alter intracellular homeostasis by reacting unfavourably with DNA, proteins and lipids (Solaiman and Al Hadlaq, 2006). Protective inflammatory mediators secreted in response to tissue injury such as cytokines, interleukins (IL), tumour necrosis factor (TNF), migration inhibition factors, reactive nitrogen species and ROS cause DNA fragmentations and mutations. Nanomaterials with their miniature size and greater surface area promote inflammation. In vivo studies conducted by Oberdorster G, Li. (1998) has shown that intra-tracheal instillation of ultrafine carbon black and TiO_2 nanoparticles into rats lungs produced chronic inflammatory response. But, the particle size and composition influences the degree of this response. Park *et al.* (2008) concluded that inflammatory reactions were not observed after nickel and iron oxide nanoparticle exposure in vitro, whereas exposure to cobalt, silica, TiO_2 and zinc oxide nanoparticles induced inflammatory response in decreasing order respectively. Thus, nanomaterials clearly produce oxidative DNA damage by excessive formation of ROS; promote corrosion causing liberation of metal ions, and chronic inflammatory responses. Hence oxidative stress triggers specific signalling pathways including mitogen activated protein kinase (MAPK) and NF-kB (Bonavallot *et al.,* 2001), which together with the reduction of antioxidant defences, lead to the release of pro-inflammatory cytokines, triggering inflammation, by ROS release from inflammatory cells (e.g. neutrophils) (Xia *et al.,* 2008; Malathi Suresh *et al.,* 2014).

Zeni (2008), Worle (2006), Brown DM (2007) & other researchers have proved that exposure to single walled carbon nanotubes (SWCNT) and multi walled carbon nanotubes (MWCNT) produces chromosomal damage and point mutations due to the asbestos fibres in CNT. SWCNT & MWCNT localised in the nucleus, leads to the formation of granulomas in vivo following intraperitoneal administration, promoting the development of mesothelioma in long-term administration. These studies therefore confirm that CNTs have carcinogenic potential, but the underlying mechanism has not been investigated and remains a mystery (Abou Neel *et al.,* 2015).

Role of dentist in practicing nanodentistry

When nanodentistry basically deals with the therapeutic use of nanorobots under computer control, the role of the dentist in this scenario becomes questionable. However significant success has been achieved in the development of restorative dental materials incorporating nanoparticles that widely ranges from synthesis of nanoparticles and its incorporation into dental materials, designing an in vivo functional dental nanorobot to the use of various newly developed nanomaterials such as nanoneedles, nanosolutions, nanotite (nano coated implants). Cases of simple neglect will become fewer and patients of rare diseases and esthetic concern will become more important. Treatment option will be more exacting and dentists will be able to arrive at a diagnosis with patient preference and his genetic makeup in mind. All this will demand even more than today, the best technical abilities, professional judgement and strong doctor-patient interpersonal skills that is the hallmark of a contemporary dentist (Neetha *et al.,* 2013; Mitsiadis *et al.,* 2012).

Conclusion

The potential implications of scientific and nanotechnological innovations is the realm of the future applications. Developments are at the horizons of dental sciences are not completed comprehended and needs further exploration. Nanomaterials and nanodevices have the capacity to uplift the current situation of nanodentistry. Nano-robots fabricated to nanometre precision will allow the dentist to execute curative and reconstructive procedures in the oral cavity at the cellular and molecular levels. Nanodentists of the near future will make good use of the natural healing, immune powers and homeostatic mechanisms and dental treatment will be customized to match the genetics of each patient. It is hoped that one day we will be able to use nano-hydroxyapatite to rebuild bone that has receded over time after tooth extraction, making implants the last option. A longer term hope is that self-replicating dentifrobots could repair and rebuild decayed teeth and oral tissues completely. As with all emerging technologies, a successful future for nanodentistry will be achieved through open sharing of ideas and research finding, through testing and frank discussion. In short, “Future is coming, it will be amazing!”. Funding, accessibility to nanomaterials, time, equipments available for research and treatment needs will determine which prospects become reality. The promise of nanodentistry is certainly high, but it should be able to break the barriers of ethical, social implications, genotoxicity concerns to become a true reality! (Mitsiadis *et al.,* 2012; Tanwer and Nanodentistry, 2015).

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