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Nanoparticles- The new age particles transforming treatment of periodontitis

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Abstract

Periodontal disease is an inflammatory and infectious disease that leads to breakdown of periodontal tissues and one of the recent advances in its treatment modality is nanotechnology. The aim of this review is to explore the new vistas of nanotechnology and silver nanoparticles in particular as an anti-inflammatory agent in the treatment of periodontitis exploring the host response aspect of the disease. Nano particles are clusters of atoms in the size range of 1- 100 nm while Nano technology is the study, design, creation, synthesis, manipulation, and application of materials, devices, and systems at the nanometre scale. Silver nanoparticles have the ability to anchor to the bacterial cell wall and subsequently penetrate it, thereby causing structural changes in cell wall affecting its permeability and hence, death of the cell. It can be used as a local drug delivery in the periodontal pocket in its nanoscale form to counter the inflammation of periodontitis. Considering the disadvantages of chemotherapeutic agents and increasing bacterial resistance, silver nanoparticles can be of advantage as non-surgical intervention to treat chronic periodontitis.

Keywords: Nano technology, Che mother a peutic, exploring

Introduction

Chronic Periodontitis has been commonly defined as "an infectious disease resulting in inflammation within the supporting tissues of the teeth, progressive attachment loss, and bone loss".[1] It is one of the most prevalent diseases demonstrating a rather slow progressing inflammatory nature. Children and adolescents both are known to be affected by it, but the predilection of the disease is seen with a higher percentage in adults, which

is usually in response to long standing plaque biofilm containing pathogenic bacteria and calculus accumulation observed in all alike.[2] The complexity of periodontal pathogenesis has multiple facets, highlighted by the shift in the composition of the plaque biofilm which can be displayed by certain parameters[3]. However, the importance of bacteria and other microbes in the etiopathogenesis of chronic periodontal disease cannot be underappreciated, but host related factors like genetics, immune response, smoking, systemic health, diet etc. are considered to be major determinants of disease.[4,5]

The current understanding of the effects of host related factors on the initiation and progression of the disease is scant, which causes the therapeutic interventions to be more directed towards means that help reduce the load of 'pathogenic' bacteria thought to be concerned with breaking up of host tissues.[6]

The elemental feature of the progression of periodontal disease is the presence of a periodontal pocket.[7] A pathologically deepened gingival sulcus around a tooth at the gingival margin,[8] is what is known as a periodontal pocket. The primary goal of periodontal therapy has been on the mechanical removal of plaque along with substantial aid of antibiotics and related compounds.[4,5] But it is also necessary to focus on the inflammation part of periodontitis while setting up a treatment plan for curing the disease.

Delivering the drug into the pocket provides a chance to deliver the drug into the local environment where the disease is primarily present and thus, enables the drug to act directly on the cells responsible for the destructive host response and the bacterial cells present in the periodontal pocket environment. The local delivery of the drug into the periodontal pocket also helps to avoid the systemic complications and the dose related effects of the drug that may occur when the drug is given systemically.

Nanotechnology is the new aspect that is being explored in the recent past in order to provide the advantages like direct contact with the target cells and also the smaller particle size provides for a larger surface area which come in contact with the cells in question. Nanotechnology is being used in a number of arenas like cosmetics, telecommunications, diagnostics so on and so forth. The oldest form of nanotechnology being used in dentistry is in the form of composite which is used as filling material. Nanotechnology and its role in dentistry still needs to be explored, especially in periodontics, wherein, their role as an anti-inflammatory can be explored in order to counter the host response aspect of periodontal disease. Silver has been known for its anti-bacterial properties. Its anti-inflammatory properties need further investigation, in particular its role in controlling inflammation in periodontitis.

Many authors have published reviews arguing the part nanotechnology can play in dentistry including new dental materials, but the role of silver nanoparticles in periodontitis has not been discussed so far.

The aim of this review is to explore the new vistas of nano technology as a treatment modality and silver nanoparticles in particular as an anti-inflammatory agent in the treatment of periodontitis exploring the host response aspect of the disease.

New paradigm in the treatment

Until the year 1960, bacteria seen to be causative in periodontitis was not affirmed.[9] Then the discovery of specific association of different complexes of bacteria via their detailed characterization with specific bacterial species led to today's antimicrobial approaches towards the prevention and treatment of periodontitis, which also reflected its cause and effect with health and disease.

The contemporary concept of periodontal disease that is known today, is the contribution of the pioneering work of Socransky,[10] who refined Koch's postulates in respect to periodontal disease. A cleansable environment is of utmost importance when area of concern is the maintenance of plaque- free areas.[11] Both invasive and non-invasive contribute towards this goal. Numerous adjuncts either systemic or local agents like antibiotics, films and strips with these antibiotics have been used to further aid the mechanical methods to enhance the elimination of bacteria with considerable success.[12] Notwithstanding, the health burden of periodontal disease on the susceptible population, continues to rise.[13]

A while ago, it was believed that the extent of periodontitis in the modern world could be reduced with effective plaque controls and only population with limited access to oral healthcare in the developing nations would show signs of significant disease. However, in the current times it has been recorded that diseases that are associated with aging, including periodontitis, are influenced to a large extent in a negative way by vices of the modern world, like obesity, smoking etc. and also that there are associations between periodontitis and diseases of aging, including type 2 diabetes and cardiovascular diseases.[14,15,16] The need of the hour is to understand the role of host-response in periodontal susceptibility which is strongly suggested by the consortium of periodontitis with major non-infectious diseases.[17]

A natural reservoir which is readily obtainable for the introduction of a delivery device is a periodontal pocket.[18] The GCF present in the periodontal pocket provides a medium which helps in the release of drugs from the dosage form and it further distributes it all over the pocket.[19] The above-mentioned features coupled with the attribute that the periodontal diseases are confined to the immediate habitat of the pocket, make the periodontal pocket a natural site for therapy with local drug delivery.[20] The nature and location of the pocket is such that its accessibility makes the local drug delivery systems partially successful in the treatment.

For the treatment of periodontitis, the major challenge that is faced by the scientists involved with the formulation of nanoproducts is delivering drugs to the gingival epithelium as the anatomy of the route and contours of the lesion is complex which causes the drug to penetrate poorly to the area.[21] The most recent form of drug delivery system that is being extensively researched in periodontics is nano technology.

Nanotechnology- dawn of a new era

Nanotechnology is the study, design, creation, synthesis, manipulation, and application of materials, devices, and systems at the nanometre scale (one meter consists of 1 billion nanometres).[22] Nanotechnology is spearheading one of the most important engineering revolutions since the industrial age.

In the field of nanotechnology, K Eric Drexler was the first to develop guidelines pertaining to it. He published the book "Engine of Creation" which opened the doors to the science of nanotechnology to the public.[23] The United National Human Genome Research Institute proposed a new approach to the development process of new technology which is nanotechnology.[24] This could be accomplished by addressing the ethical, legal and social implications before the marketing of the nano-products so that the any modification and adjustment can be easily made in the early stages of production.[25,26]

The unique properties of nanomaterials is the reason for the extensive research being done in the realm of nanotechnology.[24] Atoms are what build a biologic tissue and these can be measured using the nanoscale.[24] The biologic molecules interact with these nanosized

particles are a more molecular level in comparison with micro or macro-sized particles.[27]

The physical attribute of nanoparticles that makes them unique is their high surface to core ratio which implies that the number of atoms on the surface are significantly higher than the ones present deep within the core.[24] This provides an advantage as the ones on the surface have greater unbound surfaces which is in contrast to the core atoms which allows the creation of new and strong bonds, which renders these nanoparticles more reactive than micro and macro particles.[28]

Self-assembly in nanomaterials

A primary feature of the nano-sized materials is the development of self-assembly.[29] An independent organization of components into patterns or structure without human intervention occurs.[30] The entire process of development can be modified and arranged through the appropriate setting of conditions.[31,32] The most important concept to understand in the context of self-assembly is that self-assembly is naturally present in cells and tissues and essentially understanding that life requires an understanding of self-assembly.[31] The crucial aspect of nanotechnology is the knowledge of making conglomerations of nanostructures by the means of self-assembly.[29]

Implications of nanotechnology

Nano technology is being assimilated into regular life at a very fast pace in respect to healthcare, diagnostics, cosmetics, tele communication and a plenty of different fields. Hence, it is imperative to understand its implications on health and society in general. A moral quandary is faced by the dentists due to the uncertainty of nanomaterials when faced with a choice between a large range of materials to choose from such as hybrid or micro-filled composite resins and Nano-filled composite resins that are attractive in theory and also supported by short term studies.[24] The reactions of various nanomaterials are essentially dependent on the size i.e., 100nm sized particle being non-toxic could be drastically modified into a toxic particle when its size is reduced to 1 nm and vice-versa. A non-toxic nanomaterial could derelict or agglomerate thus trans forming into toxic nanoparticles.[29]

Nano medicine, a subsidiary of nano technology is a distinct medical intervention at the molecular level for curing disease or restoring damaged tissues, such as bone, muscle or nerve. Drug delivery, both in-vivo and in-vitro diagnostics and manufacturing of upgraded biocompatible materials are the applications expected in nano medicine.[33] Drug delivery is the process of releasing a bioactive agent at a specific rate using a suitable carrier.[34]

Drug delivery by nanomaterials

Nanoparticles are the materials that find abundant use in medicine. Nanoparticles are those whose size is known to be $\leq$ 100 nm making them microscopic particles.[34] What makes these particles so luminous for the medical field is their desirable properties like their surface to mass ratio that is significantly greater than that of other particles, quantum properties and also their propensity to adsorb and carry other compounds like drug, proteins etc.[35] The definition states that the size of nanoparticles to be less than 0.1 m or 100 nm, but it is speculated that the particle size say larger than 100 nm may prove to be more beneficial as it would allow substantial amount of drug to be loaded onto particles.[34]

The hiccups with conventional drugs usually seen are poor solubility, low bioavailability and early elimination from the body by the reticuloendothelial system. Also, drug resistance at the target level owing to physiological barriers or cellular mechanisms is also experienced.[35] Therefore, reducing the size of the delivery system to

become smaller than their targets assists in exact drug release into highly precise targets.[36] Individual cells should be targeted by an ideal drug delivery system not just specific tissues or organs. This archetypal vehicle would be biocompatible and virtually completely dependable, when the desired target cells are the only site where the drug molecules are being directly delivered so that the unwanted side effects are effectively eliminated.[37]

Recent studies have show that this gap can be fulfilled to a great extent by the means of nanotechnology-based drug delivery systems and the performance of the presently available drugs also been shown to improve considerably.[35,37] Nanotechnology has provided the opportunity for materials like liposomes, polymer or even a metallic nanoparticle to be reduced to a size in the nanoscale and be used as a delivery system, in order to evade the body's defence mechanism.[35]

Advantages

The advantage that is obtained is the reduction in the frequency of administration and subsequent uniformity in the distribution of the drug over a prolonged period of time.[29] In addition, nanotechnology can also be used to formulate the drug on a nanoscale and not just be used to manufacture nano-sized particles to function as carriers. This will therefore allow the drug to function as its own carrier.[34]

Disadvantages

The agendas that nano drug delivery cannot achieve are specific drug targeting and delivery, reducing drug toxicity while maintaining the desired therapeutic effects, pronounced safety and biocompatibility and production of new safer medicines.[34] Numerous materials that find use as nanodrug delivery devices are liposomes, lipid nanocarriers, polymeric nano-particles, dendrimers, nano-capsules, ceramic nanoparticles, polymeric micelles, metallic nanoparticles etc.[38]

Silver nanoparticles as anti-inflammatory agent

Burns and other wounds have long been treated using compounds of silver like silver nitrate or silver sulfadiazine exploiting the anti-bacterial properties it possesses.[39] Silver nanoparticles have started to gain prime focus among the emerging nanoproducts due to the unique properties and increasing utilization of silver for several applications in the field of nanomedicine.[40] It is seen that nanotechnology provides Silver in the pure form. Of all the commercially available nanoproducts Silver nanoproducts make up almost 1/4th of that catalogue.[24] Reducing the size of Silver to the nanoscale furnishes it with physiochemical properties and biologic activities that are different from those possessed by the Silver salts.[41,42]

Since time immemorial, Silver has been known for its therapeutic attributes, but these Silver nanoproducts as mentioned due to their size now possess these physiochemical and biologic properties which proffers it a wider range of applications like anti-bacterial, anti-viral and anti-inflammatory effects.[43-46] The antibacterial activity of the silver ions is understood in a great aspect and has thus led to its use in the field of medicine. Silver acts by blocking the respiratory enzyme pathways and also alters the microbial DNA and the cell wall thus, making it anti-bacerial.[47]

However, the anti-inflammatory aspect of Silver has not been understood fully. The effects on the inflammatory markers are not understood well, but there are some studies that have reported the anti-inflammatory effect of Silver nanoparticles by diminishing cytokine production in postoperative adhesion or burn wound models and in stimulated human peripheral blood mononuclear cells.[48-51] In one of the studies done to investigate the anti-

inflammatory action of Silver nanoparticles by Tian et al (2007),[50] they observed that Silver nanoparticles modulate the cytokine production and thus, bring about reduction in inflammation. Therefore, the role of Silver nanoparticles in wound healing can be considered extensive.[50]

Bhol et al (2007) in an ulcerative colitis model study demonstrated that the Silver nanoparticles suppressed the pro-inflammatory cytokines like TNF-α, IL-1β AND MMP-9. They concluded that administered intra-colonically or orally may have therapeutic potential for treatment of IBD.[48] Neutrophil apoptosis, decreased MMP activity as part of the action of Silver may further enhance the overall reduction in the inflammatory response and as a result, may induce an increased rate of wound healing.[48]

Periodontitis as is known is a bacterial infection but the host response plays a major role in the manifestation of the disease. Silver nanoparticles can be used as a local drug delivery in the periodontal pocket to counter the inflammation of periodontitis. Shawky et al (2015) conducted a study using silver nanoparticles, delivering it in the periodontal pocket, and they observed that the clinical attachment level and pocket depth were improved due to the application.[52]

Due to the limited number of studies conducted on the anti-inflammatory aspect of silver nanoparticles as drugs delivered locally in the treatment of chronic periodontitis it still has to be seen whether the drug can be used in the periodontal pocket to reduce the inflammation.

The precise mechanism of action of silver nanoparticles also needs to be researched more.

Conclusion

Chronic periodontitis is a bacterial infection which is caused by a host microorganism. But periodontitis is a multifactorial disease and other factors like smoking, diet, genetics and stress, systemic health and social factors impact the host response and thus, the manifestation of the disease. Nanotechnology has provided a number of advantages in the delivery of drugs and has thus impacted the treatment of various diseases. Since, nanotechnology involves reducing a drug to the nanoscale it can used to deliver drugs into the periodontal pocket thus, increasing the bioavailability of the drug. One such material that is being extensively researched in medicine as a nanodrug is silver nanoparticle. The antibacterial effect of silver is widely known and has been utilized for various purposes in a number of treatment modalities. The anti-inflammatory effect is also known, but it has to be researched further in order use it in the treatment of chronic periodontitis as a local drug delivery agent.

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