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Periodontal vaccines: Where we are now and where we can go

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ABSTRACT

Edward Jenner devised and established the notion of vaccination in the late 18th century, using the cross-protection offered by the cowpox virus, which is not dangerous to humans. In adults, periodontal diseases with their multi-microbial etiology are a leading cause of tooth loss. Current treatment approaches have only been able to stop the disease's progression; neither do they totally cure the condition nor stop it from returning. As a result, there is a need for more advanced therapeutic approaches, which may include vaccines that target potential periodontal bacteria. A boon to periodontics is the periodontal vaccination. No periodontal vaccine study has been able to fully meet all of the criteria for the ideal periodontal vaccine. The goal of the periodontal vaccination is to pinpoint the antigens implicated in the periodontitis damaging process that antibodies would be induced to guard against. In the future, periodontal vaccinations might become a supplement to mechanical therapy. To reduce the morbidity associated with periodontal disease in humans, eliminating the worldwide burden of periodontal disease would be the demanding primary function of any periodontal vaccination. This paper focuses on bringing to light the current approaches to periodontal vaccinations and what the future might have in store as far as this issue is concerned.

Keywords: Periodontal vaccine, *Porphyromonas gingivalis*, Periodontitis, Immunization, Periodontal diseases treatment, *Aggregatibacter actinomycetemcomitans*

INTRODUCTION

A chemical that is naturally dead or attenuated and delivered to the body with the goal of enhancing resistance to or curing a disease is referred to as a vaccine. The most well-known and significant application of immunological concepts to human health is vaccination. Vaccines are typically preventative, which means that they lessen the consequences of subsequent infections.[1]

There are three types of vaccinations, which we will talk about in this review –

a. Active immunization – A method of stimulating a person's immune system by giving them killed or live, attenuated products made of microorganisms.
b. Passive immunization – Immunization given passively, in which antibodies produced in one person are passed on to another.
c. DNA immunization – DNA vaccination involves giving a person DNA plasmids that include the genes needed to produce antigens.[1]

Periodontitis is a disease of the periodontium (the tissue supporting the tooth structure). It is one of the most common diseases of the oral cavity. The etiological factors are both local as well as systemic, and hence, in addition to prompt tooth loss, it also affects a patient's general health adversely.[2]

According to the current model of periodontal disease, the host-microbial interactions have a major role in determining the degree and severity of tissue loss, even if periodontal pathogens are crucial for disease start. Periodontal diseases are immunological inflammatory reactions brought on by dental plaque microorganisms that, when harbored in a vulnerable periodontium, cause tissue deterioration, bone loss, and, ultimately, tooth loss.

The cowpox vaccine was the world's first vaccine. Using the cross-protection offered by the cowpox virus, Edward Jenner devised and established the notion of vaccination in the late 18th century. French microbiologist Louis Pasteur created the first anti-rabies vaccine in 1885. Even Pasteur did not fully comprehend immunological memory or the role of the lymphocyte; these topics had to wait another 50 years. The main mechanism was finally identified with Burnet's clonal selections theory (1957) and the finding of T and B lymphocytes (1965).

It has been established that some chemicals signal periodontal tissue damage as the inflammatory response intensifies. They can be roughly categorized as (a) virulence factors for microorganisms and (b) those resulting from an inflammatory immune response in the host. Although bacteria are crucial because they initiate and maintain inflammation, host inflammatory mechanisms are responsible for the vast majority of tissue destruction. Lipopolysaccharides, bacterial enzymes, toxic compounds, microbial invasion techniques, fimbriae, bacterial deoxyribonucleic acid, and extracellular deoxyribonucleic acid are some examples of microbial virulence factors. The host-derived inflammatory mediators fall into three categories: Matrix metalloproteinases, prostaglandins, and cytokines.[3]

Major periodontopathogens are Gram-negative anaerobic bacteria, which include *Porphyromonas gingivalis*, *Tannerella forsythia*, *Aggregatibacter actinomycetemcomitans*, etc.

These bacteria create a wide range of antigens that excite cells that are pro-inflammatory and result in the release of several cytokines. Th1 or Th2 cells may be stimulated by certain antigens. Dendritic cells pick up antigens, which they then transmit to CD-8 or CD-4 cells along with major histocompatibility complex (MHC) antigens.

CD-8 cells → Response at Th 1 → Cell Mediated Immunity → Pro-inflammatory mediators

CD-4 cells → Response at Th 2 → Ab response → Protective mediators[4]

Three periodontal vaccinations were used in the early 20th century: Stock vaccines, autogenous vaccines, and pure cultures for *Streptococcus* and other pathogens. Examples include the Inava endocarp vaccine and the Vancott vaccination.

The need for vaccine development was brought on by bacteria that are capable of evading host immune responses and invading tissues, like *P. gingivalis*, which produces protease that not only provides peptides needed for its propagation but also breaks down serum-antibacterial components and immune cell-derived peptides, allowing it to hide from the components of the local gingival immune system by invading epithelial cells. Then, by penetrating endothelial cells, it might get out and into the bloodstream generally. To reduce the prevalence of systemic diseases linked to periodontal disease, patients must pay for periodontal therapy.[5]

Periodontal disease does not yet have a preventative strategy, and available care is palliative. The availability of a periodontal vaccination would not only prevent or slow the progression of periodontal illnesses but also improve the standard of living for those who cannot easily access periodontal therapy.

MATERIAL AND METHODS

Since the topic has the potential to bring about a necessary change, a great amount of information could be found. Initially, Google Scholar was used to document a sample of the articles available for this review, after that databases such as Science Direct, ADA, FDI, and PubMed for articles published up to May 2023. We found nine peer-reviewed articles on the topic. The Internet, since it has a vast array of information, was used to gather the required insights into the topic. The sources on the Internet, written by professionals and published on reliable websites and journals, have been mentioned in the references.

TYPES OF PERIODONTAL VACCINATION

Active immunization	Passive immunization	Genetic immunization
Whole bacterial cells	Murine monoclonal antibody	Plasmid vaccines
Subunit vaccines	Plantibodies	Live, viral vector vaccines
Synthetic peptides as antigens		

Active immunization

Whole cells

To achieve active immunization, the entire cell and all of its constituent parts are injected into the host.

In rats immunized with *P. gingivalis* cells, Klausen *et al*. found that the serum antibody levels to both whole cells and partially purified fimbriae from the pathogen were increased, and the activities of collagenase and cysteine proteases

in gingival tissues as well as periodontal tissue loss were decreased.

Immunization of squirrel monkeys with *P. gingivalis* strain 1–372 whole cells led to a rise in anti-*P. gingivalis* immunoglobulin G (IgG) antibody levels in serum and a marked decrease in gingival crevice colonization.[6]

Subunit vaccines

The ability of *P. gingivalis* to enter the gingiva's epithelial cells, which guard against humoral immune factors, has been demonstrated *in vitro* investigations. *P. gingivalis* interacts with many immune system facets. The formation of active immunization uses its virulence factors as components, and this includes –

I) Outer membrane protein (OMP) – The coaggregation of *P. gingivalis* and *Streptococcus gondonii* was seen to be prevented by transcutaneous injection of OMP of 40 kDa. It can also be applied to the creation of vaccines for passive immunization.[7]
II) Gingipains – These are cysteine proteinases known as arginine gingipain (Rgp) and lysine gingipain (Kgp), respectively, that cleave both synthetic and natural substrates following arginine or lysine residues.

The main tools used to assault the periodontal region are cysteine proteinases. They are visible on the *P. gingivalis* outer membrane. The growth and pathogenicity of *P. gingivalis* are significantly influenced by Rgp and Kgp.

Therefore, it is possible that Rgp and Kgp can be inactivated by proteinase inhibitors of antibodies specific to Rgp and Kgp, thus decreasing the virulence of *P. gingivalis*.[6]

III) Fimbriae – The functions of fimbriae are the following:
    i) Host adherence
    ii) Release of TNF and interleukins
    iii) Invasion into oral epithelium.

In an animal study, it was observed that subcutaneous injection with a highly purified 43 kDa fimbrial protein elicited Fim A-specific antibodies in serum and saliva that conferred protection against *P. gingivalis*-induced alveolar bone loss.[8]

Synthetic peptides as antigens

In vitro, synthetic peptides based on the fimbrillin protein structure prevent *P. gingivalis* from adhering to saliva-coated hydroxyapatite crystals.

Passive immunization

Murine monoclonal antibody

Antigens are inoculated into mice and the antibodies, thus obtained, are injected into the host to bring about passive immunity. Topical application of a murine monoclonal antibody to *P gingivalis*, showed prevention in the recolonization of deep pockets by *P gingivalis* and other periodontopathic microorganisms.[1]

Plantibodies

Molecular biological methods to express bacterial or viral antigens in plants, which could be utilized as oral vaccines, are a very recent approach to immunization strategies.[1,4]

Genetic immunization

Plasmid vaccines

Plasmids have the capacity to grow, whereas DNA does not. Plasmids can fuse with the DNA of a particular pathogen of interest thanks to this property, and they are then administered to an animal to induce the formation of antibodies. This is then given to the host to immunize them. Plasmid vaccinations have the drawback of occasionally causing oncogenesis.[6]

Live, viral vector vaccines

The proteins of disease-producing organisms are designed to express in a variety of infectious but non-disease-generating DNA or RNA viruses or bacteria. These vectors enter body cells, generate proteins, and activate the cellular or humoral immune system.

OTHER ROUTES OF VACCINE ADMINISTRATION

Mucosal vaccination

Since mucosal vaccines are typically more successful at simultaneously producing IgG and salivary immunoglobulin A (IgA) in the oral cavity than systemic immunizations, they are more likely to provide protection against periodontitis. In fact, compared to systemic immunization, all 11 of the preclinical studies that assessed this found that mucosal vaccination increased dual immunity in the oral cavity. In addition, some investigations revealed that mucosal immunization provided defense against experimental periodontitis-related bone loss or gingival swelling.[9]

Oral vaccination

Oral vaccinations have made a significant contribution to the global fight against infectious illnesses. After receiving an oral vaccine against antigens from human periodontal infections, several studies discovered strong antigen-specific antibody responses in the serum and saliva of mice, rats, and hamsters. In comparison to subcutaneous and intramuscular

immunization, oral gavage or intragastric intubation often led to larger levels of salivary IgA and antibody-producing cells in mucosa-associated tissues. In three investigations, the clinical impact of these immunizations on periodontal health was also examined. Results showed protection against *P. gingivalis*-induced alveolar bone loss or decreased gingival swelling in a mouse gingival abscess model.[10]

Intranasal vaccination

Intranasal delivery has advantages over oral immunization in that it prevents the gastrointestinal breakdown of oral vaccinations. Variable levels of antigen-specific antibody responses were found in the serum and saliva of mice, rats, and dogs in the intranasal periodontitis immunization studies that were examined. *In vitro* protective effects of the generated antibodies were also seen in eight of these trials, including decreased bacterial invasion of epithelial cells, biofilm formation, and pathogen survival.[11]

Sublingual vaccination

A few studies evaluated sublingual immunization against periodontitis in mouse models and found that blood IgG levels were considerably lower after sublingual immunization than after intranasal immunization, despite salivary IgA levels being equal. In addition, Puth *et al*. discovered that sublingual immunization against this cornerstone pathogen significantly reduced the amount of *P. gingivalis*[9] induced alveolar bone loss in mice, even though an even greater level of protection was discovered after intranasal delivery of the same vaccine.[12]

Periodontal vaccines against *A. actinomycetemcomitans*

A. actinomycetemcomitans is thought to be a significant pathogen in aggressive periodontitis and other human periodontal diseases. Based on the amino acid sequence of *A. actinomycetemcomitans* fimbriae, a synthetic oligopeptide was created, and it proved successful in inhibiting adhesion and subsequent colonization in a rabbit model.[13]

Following a challenge with live *A. actinomycetemcomitans*, mice who had received immunization with anti-surface associated material from *A. actinomycetemcomitans* showed a higher protective opsonic antibody response and quick healing of the main lesions.[14]

LIMITATIONS OF PERIODONTAL VACCINES

- Periodontal disease is complex and multifactorial
- Sustaining sufficient antibody levels over an extended time is a challenge
- Contamination of vaccines may be possible
- Toxic responses to fully inactivated vaccinations may occur.

FUTURE OF PERIODONTAL VACCINES

- Human trials of the conducted *in vitro* studies are a challenge currently
- A pan-gene approach is required to be undertaken, rather than focusing on only one at a time so that multiple representatives of the same gene can be included
- The future would be bright if research and development were focused toward the involvement of all pathogens rather than just one.

DISCUSSION

The multitude of pathogenic microorganisms suggests that the creation of a vaccination for periodontitis could be quite difficult, which is one of the main hurdles. The antigenic factors of bacteria may have an elevated likelihood of cross-reaction with human equivalents; hence, bacterial whole cells or a crude extract preparation for immunization is not preferred. Additional vaccines could contain undesirable proteins, poisons, or even live viruses, which would be dangerous for everyone but hypersensitive people. Attenuated vaccines may return to the wild kind;[15] purportedly killed vaccines might not have been safely and properly destroyed. An immunocompromised recipient may have major worries about this. With the restriction of antigens displayed by antigen presentation cells, which hides immunomodulatory epitopes, animal models used for vaccine trials may reveal contradictions with human models in the MHC.

CONCLUSION

The present method of treating periodontitis is non-specific and focuses on the elimination of plaque using mechanical debridement, often requiring surgery. This continuous therapy is expensive, uncomfortable, and has a shaky prognosis because of low patient compliance.

The requirement for ongoing therapy to avoid the pathogen's reestablishment restricts the usage of antibiotics. Vaccination may be a crucial supplementary therapy to mechanical debridement in people to prevent perio-pathogen colonization, but further study in this area may hold the key to the creation of periodontal vaccines. Against periodontitis and periodontitis-induced systemic illnesses, a complex vaccine design approach focusing on several pathogenic species is unquestionably required.

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Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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