Review Article

International Journal of Dental Research and Oral Health

Periodontal Vaccine: A Myth or Reality

Suman Kumari[1*], Labanya Biswas[2] and Abhijit Chakraborty[3]

[1]*Postgraduate Student, Department of Periodontics, Gurunanak Institute of dental sciences and research.*

[2]*Postgraduate Student, Department of Periodontics, Gurunanak Institute of dental sciences and research.*

[3]*Professor and Head, Department of Periodontics, Gurunanak Institute of dental sciences and research.*

***Correspondence authors**

Suman Kumari,
Postgraduate Student,
Department of Periodontics,
Gurunanak Institute of Dental Sciences and Research,
India

Submitted : 18 May 2024; Published : 8 June 2024

Citation : Kumari, S.et al. (2024). Periodontal Vaccine: A Myth or Reality. J Dental Oral Health., 5(1): 1-5.

Abstract

Periodontal disease represents a nuanced interplay of various factors, encompassing host-related elements, genetic predispositions, immune system irregularities, and environmental influences. While existing treatment approaches effectively impede disease advancement, they fall short of achieving complete eradication or preventing its reappearance. The pervasive prevalence of this condition has ignited innovative endeavors, particularly in the realm of vaccine development, to devise more comprehensive solutions.

Immunization stands as a cornerstone in applying immunological insights to enhance human well-being. The primary aim of a periodontal vaccine is to pinpoint the antigens implicated in the destructive cascade of periodontitis. By triggering antibody production against these antigens, the vaccine endeavors to provide protective immunity while also stimulating mucosal antibody responses.To date, no periodontal vaccine trials have met the stringent criteria set for an ideal periodontal vaccine. However, there is burgeoning potential for periodontal vaccines to complement mechanical therapy in the future. This paper aims to critically examine existing literature, focusing on the pivotal role that a primary periodontal vaccine could play in alleviating the global burden of periodontal disease and its associated human morbidity.

Keywords : Periodontal vaccination; Plantibodies; Synthetic peptides as antigens; Live viral vector vaccines Active immunization, Passive immunization.

Introduction

Periodontitis is a disease of multifactorial origin, "an inflammatory disease of the teeth caused by specific microorganisms or group of microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession or both. (Newman et al., 2006).

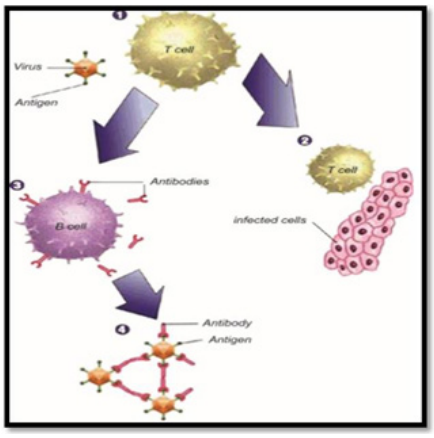
Pathogenesis of Periodontitis

The primary pathogens causing periodontitis are RED COMPLEX. These include :- (Newman et al., 2006; Gemmell et al., 1997).

Porphyromonas gingivalis
Aggregatibacter actinomycetemcomitans
Tannerela for sythensia

The diverse array of antigens generated by these bacteria elicits activation of pro-inflammatory cells, triggering the synthesis of an extensive range of cytokines. These antigens have the capacity to provoke either Th1 or Th2 cells. Subsequently, dendritic cells uptake these antigens and present them alongside major histocompatibility complex (MHC) antigens to CD-8 or CD-4 cells.

CD-8 cells → Th 1 response → CMI → Pro inflammatory
CD-4 cells → Th 2 response → Ab response → Protective



The host generates antibacterial substances like defensins, cathelicidins, and saposins. These substances serve as the initial defense, shielding host tissues from bacterial products. (Slots & Ting, 1999).

Requisite for Periodontal Vaccine

The overarching goal behind the implementation of a periodontal vaccine is the complete eradication of the pervasive burden posed by periodontal disease. Such a vaccine seeks to revolutionize oral health management by markedly enhancing maintenance protocols and preserving the integrity of natural dentition. Consequently, this advancement aims to mitigate the reliance on oral prosthetics, optimizing oral cavity function and overall quality of life.

Periodontal bacteria exhibit adeptness in circumventing host immune defenses and infiltrating tissues. Notably, these bacteria have the ability to enter systemic circulation; for instance, P. gingivalis can evade local gingival immune components by infiltrating epithelial cells. Moreover, it can further evade detection by escaping into systemic circulation through invasion of endothelial cells.

A. actinomycetemcomitans showcases a unique capability to invade both epithelial and endothelial cells, thereby facilitating its entry into circulation. This infiltration provides a platform from which it can disseminate to other tissues, establishing infection in diverse bodily sites.

The implementation of periodontal vaccination is crucial for mitigating the incidence of systemic diseases linked to periodontal issues. By addressing periodontal disease, which leads to heightened systemic inflammation markers, vaccination can help prevent conditions such as myocardial infarction, cerebrovascular stroke (Van Dyke & Starr, 2013), and adverse birth outcomes like preterm birth and low birth weight infants. (Jacob & Nath, 2014).

Ideal Properties of Vaccine

- Safety
- Protectivity
- The ability to provide sustained protection
- The ability to produce neutralizing antibodies
- Stimulation of protective T-cells which provides cell mediated immunity.

History of Periodontal Vaccine

The term "vaccine" generally refers to a substance, often containing either deactivated or weakened forms of live infectious agents, that is introduced into the body. Its purpose is to bolster the body's immune response, empowering it to better defend against or eradicate a particular disease. (Roderich, 2004).

In early 20th century three periodontal vaccine were employed:

1. Pure cultures for streptococcus and other microorganism.
2. Autogenous Vaccines.
3. Stock vaccines.

Examples include: Vancott's vaccine, Goldenberg's vaccine or Inava endocarp vaccine.

Types of Periodontal Immunization

Active immunization

- Whole bacterial cells
- Sub unit vaccines
- Synthetic peptides as antigens

Passive Immunization

- Murine monoclonal antibody
- Plantibodies.

Genetic Immunization

- Plasmid vaccines
- Live, viral vector vaccines

Active Immunization

Whole bacterial cells: Active immunization involves introducing the entire cell, along with its constituent components, into a host organism. This process stimulates the host's immune system to mount a response, thereby achieving immunization against the pathogen.

Klausen's research in 1991 revealed that rats injected with P. gingivalis cells showed heightened levels of serum antibodies against both intact cells and partially purified fimbriae from the bacterium.(Lamont & Jenkinson, 1998).

In 1992, Kesavalu conducted experiments using a mouse chamber model and found that immunization with either killed heterologous invasive or noninvasive strains of P. gingivalis resulted in protection against invasion but not colonization by the bacterium. While the immune response to whole cells or specific envelope components did not fully prevent lesions, it did eliminate mortality. (Kesavalu, 1992).

P. gingivalis is increasingly recognized as the principal pathogen implicated in the progression of chronic periodontitis. It is classified as a gram-negative coccobacillus, lacking spores, motility, and saccharolytic activity, and requiring anaerobic conditions for growth. (Micael et al., 2006).

The components of P. gingivalis utilized as subunits for active immunization development include: (O'Brien-Simpson et al., 2004).

- Outer membrane protein
- Gingipains
- Fimbriae
- Heat shock protein

Outer Membrane Protein

Researchers have observed that the transcutaneous injection of the 40kDa outer membrane protein (OMP) effectively prevents the coaggregation of P. gingivalis with Streptococcus gordonii. Furthermore, this method presents potential for vaccine development targeting passive immunization. Studies have demonstrated that polyclonal antibodies directed against the 40 kDa OMP exhibit a protective effect, possibly mediated by

complement, resulting in bactericidal activity. (Katoh et al., 2000).

Gingipains

Termed by Travis and colleagues, these are cysteine proteinases capable of cleaving both synthetic and natural substrates following arginine or lysine residues. They are known as arginine gingipain (Rgp) and lysine gingipain (Kgp), respectively.

Expressed on the outer membrane of P. gingivalis, Rgp and Kgp play pivotal roles in the bacterium's growth and virulence. (Marawar et al., 2004).

Gingipains vaccines predominantly utilize DNA vaccines, which are capable of eliciting both humoral and cellular immune responses. (Moritz et al., 1998).

Fimbriae

Fimbriae serve additional functions such as:

- Facilitating colonization by adhering to host surfaces.
- Promoting invasion of oral epithelial cells and fibroblasts.
- Influencing inflammation by releasing interleukins and tumor necrosis factor (TNF), thus modulating the host immune response. (Person, 2005).

The classification of P. gingivalis into five fimbrial types (I-V) based on antigenicity is well established. However, vaccines targeting a single fimbrial type may lack effectiveness against other strains of P. gingivalis possessing different fimbrial types. This strain-specificity poses a challenge in developing broadly effective vaccines against P. gingivalis infections.

Heat Shock Protein

Rats that received immunization with P. gingivalis HSP60 experienced a reduction in bone loss caused by infection with multiple periodontopathic bacteria. Additionally, there is a notable association between the concentration of HSP90 and microbial colonization. (Lopatin et al., 1999).

Sub unit vaccine: Immunization involves utilizing a segment of the bacterial cell, commonly either its outer component or fimbriae, to trigger an immune response.

Synthetic peptides: These antigens demand the synthesis of linear and branched polymers consisting of 3-10 amino acids, which are constructed based on known sequences of microbial antigens. While they possess low immunogenicity on their own, they must be linked to larger proteins to provoke an effective antibody response.

Two approaches for creating synthetic peptide vaccines include:

1. Deduction from RNA sequence data: Researchers analyze RNA sequences to determine the protein sequence of microbial antigens. This method allows for the identification of potential vaccine candidates based on genetic information.
2. Testing overlapping peptides and mutational analysis: Synthetic peptides overlapping different regions of the target antigen are synthesized and tested for immunogenicity. Mutational analysis involves introducing mutations into the peptide sequences to identify critical epitopes responsible for inducing immune responses.

In 1992, Genco observed that synthetic peptides designed from the protein composition of fimbrillin effectively hinder the attachment of Pg to hydroxyapatite crystals coated with saliva during in vitro experiments. (Evans, 1992).

Passive Immunization

Passive immunization is short lived because host does not respond to immunization and protection lasts only as long as injected antibody persists.

Murine monoclonal antibodies: The antigens are first introduced into mice through inoculation. Following this, they are extracted from the mice and administered via injection into the host organism. (Gupta et al., 1996).

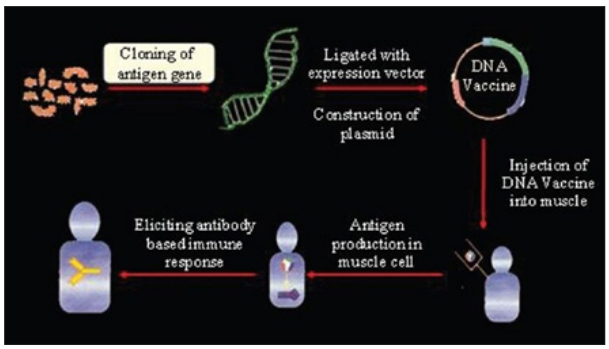
Booth et al. (1996) successfully developed a murine monoclonal antibody targeting P. gingivalis. Their research demonstrated that this antibody effectively prevented the recolonization of deep pockets by the pathogen in patients diagnosed with periodontitis.

Plantibodies: Molecular biological techniques are utilized to express bacterial or viral antigens within plants, facilitating the creation of vaccines that can be administered orally. (Teughels et al., 2008).

Genetic Immunization

Gene therapy entails the insertion of genes into the cells and tissues of an individual to address a disease. This approach relies on genetic engineering or recombinant DNA technology.

Plasmid Vaccines: DNA itself does not possess the capacity to grow, whereas plasmids, due to their nature as extrachromosomal DNA elements, have the capability to replicate. Plasmids are often engineered by integrating DNA fragments from pathogens of interest. These modified plasmids are then introduced into animals to stimulate the production of antibodies. Subsequently, they are transferred to the host organism for immunization. (Kudyar et al., 2011).



Live, viral vector vaccines: Non-pathogenic DNA or RNA viruses or bacteria have been genetically modified to express proteins from disease-causing organisms. These modified vectors are introduced into the body's cells, where they produce the desired proteins. This process triggers either humoral or cellular immune responses, effectively priming the immune system against the targeted disease. (Kudyar et al., 2011).

Limitation Of Periodontal Vaccine:- (McArthur & Clark, 1993).

1. The array of periodontal diseases presents intricate challenges due to their diverse nature and uncertain outcomes.
2. Accurately distinguishing between primary colonizers and secondary invaders poses a significant challenge in understanding periodontal disease progression.
3. Cultivating and identifying disease-associated microorganisms is hindered by their elusive nature, compounded by variations in plaque composition among individuals and even within the same individual.
4. While presumptive periodontal pathogens are common in human subgingival bacterial flora, they are not naturally present in rodent flora, complicating research translation.
5. Periodontal diseases vary in severity and chronicity, adding complexity to their diagnosis and treatment.
6. The clinical detection and quantification of active periodontal disease remain challenging tasks.
7. The unique location of the gingival sulcus, situated between systemic and local immune systems, presents complexities in understanding the immune response in periodontal disease.
8. Although periodontal disease itself is not typically fatal, its systemic implications underscore the importance of effective management and treatment.

Conclusion

The emergence of DNA vaccines, within the last five years, has propelled them into Phase I clinical trials among healthy human subjects. Despite their success in animal models, numerous obstacles persist on the path to realizing a viable periodontal vaccine for humans. Challenges include the intricate and variable nature of periodontal diseases, the difficulty in distinguishing between primary and secondary microbial agents, and the complexities associated with cultivating and identifying disease-associated microorganisms. Moreover, the considerable diversity in plaque composition among individuals further complicates vaccine development. Although our understanding of periodontal vaccines remains incomplete, ongoing and robust research efforts offer promising prospects for the eventual realization of an effective solution.

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