Journal of Advanced Medical and Dental Sciences Research

@Society of Scientific Research and Studies ***NLM ID:*** *101716117*

Journal home page: www.jamdsr.com doi: 10.21276/jamdsr Indian Citation Index (ICI) Index Copernicus value = 100

(e) ISSN Online: 2321-9599; (p) ISSN Print: 2348-6805

Review Article

Periodontal vaccine: Systematic review

[1]Hasan Mahdi Aldhafeeri, [2]Khalaf Mutheeb Al Mutairi, [3]Mohammed Ghanem M Aldhafeeri

[1,2,3]Dental Center, Ministry of Health, Hafar Al-Batin, Saudi Arabia, Eastern Province

ABSTRACT:

Aim: This systematic review aims to discuss the various immunization strategies related to periodontal diseases (PD) attempted so far. **Methodology:** An extensive literature Search was performed in electronic databases, such as PUBMED, Cochrane central register of controlled trials, Google scholar and science direct using various search terms such as "periodontal vaccines", "porphyromonas gingivalis", "chronic periodontitis", " genomic vaccine ", " recombinant vaccine", "immune response", " vaccination against periodontal bacteria". No limits and language restriction were applied during the electronic search to include all the possible animal studies, clinical trials in the potential relevant article search phase of the systematic review. **Results:** Forty eight studies were included in the present review. Out of which nine studies were done in Macaca fascicularis models and thirty nine studies were done in Murine models. Forty one immunization studies were done using various components of Porphyromonas gingivalis, four studies were done using Aggregatibacter actinomycetumcomitans and three studies were in other microorganisms. The studies have evaluated any of the three main parameters such as an increase in serum antibody titer, inhibition of pathogenic microflora and improvement in clinical parameters. Some studies have evaluated multiple outcome measures as well. A total of forty studies have evaluated an Increase in Serum Antibody Titres, fourteen studies evaluated the inhibition of pathogenic microflora and twenty studies have evaluated the improvement in clinical parameters. **Conclusion:** Studies evaluating Porphyromonas gingivalis are the most common and the structures showing the most potential as a vaccine candidate are Outer membrane proteins, fimbriae and gingipains, the structure having the least potential is Lipopolysaccharide.

Keywords: Periodontitis**;** Vaccine; Virulence; Porphyromonas gingivalis; Immune response; Animal studies.

Recieved: 12-08-2022 Revised: 05-09-2022 Accepted: 25-10-2022

Corresponding author: Hasan Mahdi Aldhafeeri, Dental Center, Ministry of Health, Hafar Al-Batin, Saudi Arabia, Eastern Province

This article may be cited as: Aldhafeeri HM, Mutairi KMAl, Aldhafeeri MGM. Periodontal vaccine: Systematic review. J Adv Med Dent Scie Res 2022;10(12):121-124.

INTRODUCTION

Periodontal diseases belong to a heterogeneous family of diseases, which demands a clear need for a better understanding of the etiology and pathogenesis behind formulation of a vaccine against the same. Both specific and nonspecific plaque hypothesis has its own merits and demerits.1, 2 However, epidemiological evidence indicates that host factors are likely to be of over-riding importance for the most severe forms. Specific inhibitors of virulence factors provide a logical approach, but their clinical application still demands improvement. Improvement of general health and resistance to disease by proper nutrition, the avoidance of intercurrent disease, and elimination of smoking and stress-induced risk are encouraged. The genetic basis of susceptibility to periodontitis is increasingly understood, and, while gene therapy is not likely to be a practicable approach to prevention, genetic markers of risk are emerging. The vaccine should also be investigated first in animal models like rodents, followed possibly by nonhuman primates, before being studied in human beings. Various bacterial strains being investigated are Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythia (previously T. forsythensis), Bacteroides macacae, Aggregatibacter actinomycetemcomitans (previously Actinobacillus actinomycetemcomitans) and Campylobacter rectus. These strains are used for periodontal vaccine preparation. The immunogens being tested included whole cells, sonicated cell walls, fimbriae and few purifiedproteins. Periodontal disease (PD) typically leads to halitosis, oral pain or discomfort, and periodontal damage which can result in tooth loss.3 Moreover, periodontitis may have a substantial effect on systemic health. Epidemiological, clinical interventional, and experimental studies have provided compelling evidence that periodontitis

adversely impacts systemic health in humans. However, clear confirmation that successful treatment of PD can reduce the risk or incidence of PD-associated conditions like atherosclerosis and type 2 diabetes mellitus is lacking.4,5 This injudicious use of antibiotics is alarming, especially considering the ubiquity of PD and the extra-oral distribution of systemic antibiotics, as this contributes to the development of antimicrobial resistance.6 Antimicrobial resistance has evolved as one of the most urgent threats to public health, causing treatment failures, prolonged hospital admissions, and increases in healthcare costs.7 Since the host inflammatory response acts as main driver of tissue destruction and simultaneously exacerbates dysbiosis, it can be reasoned that adjuncts to mechanical debridement should not rely on nonspecific bacterial clearance by systemic antibiotics, but rather on the alteration of host immune responses. periodontal vaccines may contribute to long-term prophylaxis, by preventing the subversion of the immune system by keystone PD pathogens, avoiding and reverting dysbiosis, and averting destructive hyperinflammation.8 In addition, periodontal vaccines might discourage the use of antibiotics.6 Efficacious periodontal vaccines will need to elicit protective antibody responses in the oral cavity that are specific for PD inducing bacteria. Local antibody responses in the oral cavity rely on both systemic (IgG) and mucosal immunity (secretory IgA, SIgA). IgG within the oral cavity mainly originates from the blood circulation by passive leakage via the gingival crevicular epithelium, while the SIgA is locally produced in the salivary glands by activated B cells that migrated from the mucosa associated lymphoid tissues (MALT).9 Hence, effective periodontal vaccines must induce both systemic and mucosal immunity in the oral cavity, which has proved difficult with traditional vaccination strategies. This is evident by the current lack of a human periodontal vaccine, while the first vaccines against PD, including the Inava Endocorps vaccine, were already developed in the early twentieth century.10 Reviews so far conducted have stressed on the need for preventive therapy for periodontal disease because of its worldwide prevalence, systemic disease linkage, and the failure of traditional periodontal therapy to regenerate the lost periodontium or to eliminate the disease.

AIM OF THE PRESENT STUDY

This systematic review aims to discuss the various immunization strategies related to periodontal diseases (PD) attempted so far.

METHODOLOGY

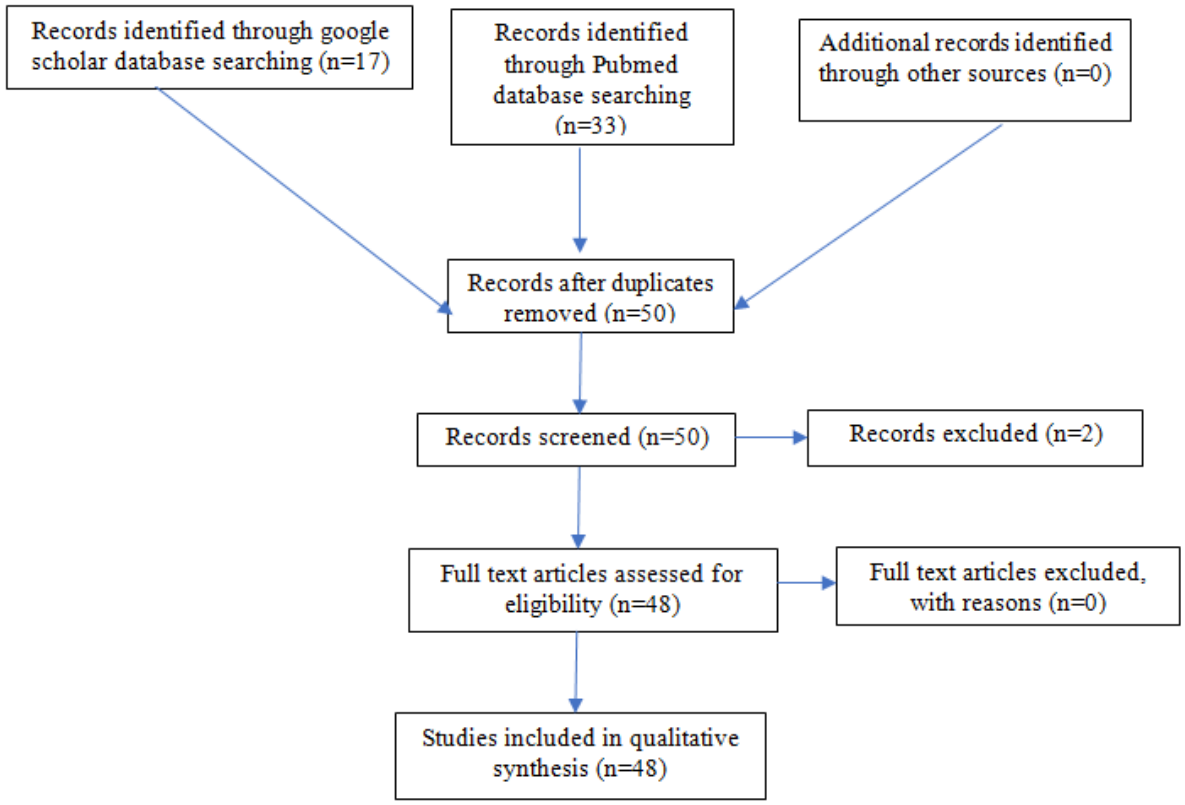
A Search was performed in electronic databases, such as PUBMED, Cochrane central register of controlled trials, google scholar, science direct using various search terms such as chronic periodontitis, aggressive periodontitis, experimentally induced periodontal disease, adult periodontitis, adult periodontitis, acute suppurative periodontitis, apical periodontitis, chronic periodontitis, circumpubertal periodontitis, animal model, animal study, preclinical study, monkey study, rat study, dog study, rabbit study, animal studies for periodontal vaccine, periodontal vaccine using non-human primates, periodontal vaccine using murine models, Immunization, vaccination, immune response, genomic vaccine, recombinant vaccine, subunit vaccine, adjuvant, periodontal vaccine, human periodontal vaccine, active immunization, passive immunization, DNA vaccine, acellular vaccine, autogenous vaccine, attenuated vaccine, bacterial vaccine, booster immunization, gene gun DNA immunization. No limits and language restriction were applied during the electronic search to include all the possible clinical trials in the potential relevant article search phase of the systematic review.

RESULTS

A total of forty eight studies were included in the present review. (Table 1) Out of which nine studies were done in Macaca fascicularis models and thirty nine studies were done in Murine models. Forty one immunization studies were done using various components of Porphyromonas gingivalis, four studies were done using Aggregatibacter actinomycetumcomitans and three studies were in other microorganisms. The studies have evaluated any of the three main parameters such as an increase in serum antibody titer, inhibition of pathogenic microflora and improvement in clinical parameters. Some studies have evaluated multiple outcome measures as well. A total of forty studies have evaluated an Increase in Serum Antibody Titres, fourteen studies evaluated the inhibition of pathogenic microflora and twenty studies have evaluated the improvement in clinical parameters. Among the forty one studies done in P.gingivalis, three studies have used whole cell as an antigen, four studies have used capsular antigen, seven studies were done on fimbriae, one using lipopolysccharide, seven studies on outer membrane proteins, five studies on hemagglutinins, twelve studies using gingipain, one using heat shock protein and one using the genomic DNA respectively. A study by Choi et al. in a murine model, immunization with a conjugate vaccine consisting of Porphyromonas gingivalis capsular polysaccharide and Fimbriae led to an increased serum antibody titre of Immunoglobulin G.11 However, it was not known whether capsule of Porphyromonas gingivalis was capable of eliciting the immune response on its own as P. gingivalis Fimbriae was also a part of the conjugate vaccine administered. Later on, Gonzalez et al. in his study went on to demonstrate that capsule as such was capable of eliciting an increase in titers of IgG and IgM and also provided protection against P.gingivalis induced alveolar bone loss. Based on the studies by Chen et al. and Elkins et al.12, 13 LPS as a vaccine did not show any induction of serum

Antibody Titres or protection against P.gingivalis induced alveolar bone loss. Therefore, LPS based vaccines may not confer any potential benefits as a vaccine candidate. In a study by Katz et al. subcutaneous immunization of rats with recombinant Hemagglutinin B (HagB) derived from P.gingivalis 381 showed an enhanced serum IgG response.14 Page et al. found that subcutaneous immunization of Macaca fascicularis with purified cysteine protease from P. gingivalis resulted in a high induction of serum IgG titres and reduction of P.gingivalis in subgingival plaque and reduced alveolar bone loss.15 After P.gingivalis, Aggregatibacter actinomycetumcomitans is considered an important pathogen in progression of periodontal disease. Takamatsu et al. in their study found that subcutaneous and intranasal immunization of mice with capsular serotype b specific polysaccharide antigen produced a specific antibody which efficiently opsonized Aggregatibacter actinomycetumcomitans serotype b.16 Prevotella intermedia or a combination of cell wall antigens with CEA of Campylobacter rectus, F.nucleatum and Actinomyces viscosus lead to a significant increase in serum IgG, IgM and IgA antibody levels. There are no human clinical trials until now. Longitudinal studies of human periodontal diseases present limitations in assessing the mechanisms of disease becausethere are numerous variables that are difficult to control among patients, including activity level, susceptibility, progression, and duration of the disease.17 Aukhil et al. (1988), Kohyama et al. (1989) and Sjostrom et al. (1994) in their longitudinal studies measured the reduction in serum IgG titers to different periodontal pathogens like P. gingivalis, T. denticola, A. actinomycetemcomitans and F. nucleatum following initial periodontal therapy [30,32]. Craig et al. in 2002, measured the serum IgG antibody response to six periodontal pathogens among three different population groups and found a positive correlation.18

Table 1: Prisma flowchart of the present study



DISCUSSION

Based on the results obtained from this systematic review, the organism which has been investigated the most in formulating a periodontal vaccine is Porphyromonas gingivalis, the least promising vaccine candidate could be the lipopolysaccharide. Studies on LPS did not show induction of any antibody response or significant clinical or microbiological improvements. The most promising vaccine candidates could be outer membrane proteins, fimbriae and gingipains. Individually each of the components were able to stimulate a heightened immune response. A candidate vaccine combining these factors could prove effective against Porphyromonas gingivalis mediated destruction. One more observation was that, even though studies on capsule have shown promising results, they were among the least investigated components so far. Until now, the development of Vaccines for Human usage has always relied on conventional approaches that are

time consuming and requires the pathogen to be cultured in laboratory conditions and could identify only the abundant antigens. However, with the rapid advancements in bioinformatics, it is possible to study the complete genome sequence of an organism. Vaccine candidates can be identified from this method called “reverse vaccinology”.19, 20 This approach was first used to develop a vaccine against serogroup B meningococcus by identifying the antigens that could be used as potential candidates.21 This approach has been tried against Porphyromonas gingivalis as well. Very recently, Huang et al. have used a novel technique of cell free protein synthesis as a platform to produce vaccine candidates. They were able to recombinantly generate a cocktail of P.gingivalis proteins that were capable of eliciting a high serum IgG response as well as were capable of protecting the mice from progressive bone loss.22

CONCLUSION

There are numerous studies in animal models that have yielded good results in terms of improvements in serum Antibody titres, reduction in bone loss. However, none have been able to identify a sole or complete vaccine candidate suitable for human usage yet. A candidate vaccine combining various components of the microbe could be one of the best solutions that could prevent periodontal disease as such.

ACKNOWLEDGMENT

This work was carried out in collaboration among all the authors. All authors read and approved the final manuscript.

REFERENCES

1. Loesche WJ. Chemotherapy of dental plaque infections. Oral Sci Rev 1976;9:65.
2. Loesche WJ. Ecology of the oral flora. In: Nisengard RJ, Newman MG (Eds). Oral microbiology and immunology. Philadelphia: Saunders 1988:307.
3. Armitage GC. Periodontal Diagnoses and Classification of Periodontal Diseases. Periodontol (2000) 2004:34:9–21. doi: 10.1046/j.0906-6713.2002.003421.x
4. Hajishengallis G, Chavakis T. Local and Systemic Mechanisms Linking Periodontal Disease and Inflammatory Comorbidities. Nat Rev Immunol (2021) 21(7):426–40. doi: 10.1038/s41577-020-00488-6
5. Liccardo D, Cannavo A, Spagnuolo G, Ferrara N, Cittadini A, Rengo C, et al. Periodontal Disease: A Risk Factor for Diabetes and Cardiovascular Disease. Int J Mol Sci (2019) 20(6):1414. doi: 10.3390/ijms20061414
6. Jepsen K, Jepsen S. Antibiotics/antimicrobials: Systemic and Local Administration in the Therapy of Mild to Moderately Advanced Periodontitis. Periodontol (2016) 71(1):82–112. doi: 10.1111/prd.12121
7. Dadgostar P. Antimicrobial Resistance: Implications and Costs. Infect Drug Resist (2019) 12:3903–10. doi: 10.2147/IDR.S234610
8. Hajishengallis G, Chavakis T, Lambris JD. Current Understanding of Periodontal Disease Pathogenesis and Targets for Host-Modulation Therapy. Periodontol 2000 (2020) 84(1):14–34. doi: 10.1111/prd.12331
9. Brandtzaeg P. Secretory Immunity With Special Reference to the Oral Cavity. J Oral Microbiol (2013) 5(1):20401. doi: 10.3402/jom.v5i0.20401
10. Hirschfeld I. An Investigation of Inava Endocorps Vaccine**Report of the Committee on Scientific Research. Read Before the American Academy of Periodontology, Louisville, Ky., Sept. 18, 1925. J Am Dent Assoc (1926) 13 (11):1613–24.
11. Maeba S, Otake S, Namikoshi J, Shibata Y, Hayakawa M, Abiko Y, et al. Transcutaneous immunization with a 40-kDa outer membrane protein of Porphyromonas gingivalis induces specific antibodies which inhibit coaggregation by P. gingivalis. Vaccine. 2005 Mar 31;23(19):2513-21
12. Chen PB, Davern LB, Schifferle R, Zambon JJ. Protective immunization against experimental Bacteroides (Porphyromonas) gingivalis infection. Infect Immun. 1990 Oct;58(10):3394-400.
13. Elkins KL, Stashak PW, Baker PJ. Prior exposure to subimmunogenic amounts of some bacterial lipopolysaccharides induces specific immunological unresponsiveness. Infect Immun. 1987 Dec;55(12):3085-92
14. Katz J, Black KP, Michalek SM. Host responses to recombinant hemagglutinin B of Porphyromonas gingivalis in an experimental rat model. Infect Immun. 1999 Sep;67(9):4352-9.
15. Page RC, Lantz MS, Darveau R, Jeffcoat M, Mancl L, Houston L, et al. Immunization of Macaca fascicularis against experimental periodontitis using a vaccine containing cysteine proteases purified from Porphyromonas gingivalis. Oral Microbiol Immunol. 2007 Jun;22(3):162-8.
16. Takamatsu-Matsushita N, Yamaguchi N, Kawasaki M, Yamashita Y, Takehara T, Koga T. Immunogenicity of Actinobacillus actinomycetemcomitans serotype b-specific polysaccharide-protein conjugate. Oral Microbiol Immunol. 1996 Aug;11(4):220-5.
17. Dumitrescu AL, Abd-El-Aleem S, Morales-Aza B, Donaldson LF. A model of periodontitis in the rat: effect of lipopolysaccharide on bone resorption, osteoclast activity, and local peptidergic innervation. J Clin Periodontol. 2004 Aug;31(8):596-603
18. Craig RG, Boylan R, Yip J, Mijares D, Imam M, Socransky SS, et al. Serum IgG antibody responses to periodontal pathogens in minority populations: Relationship to periodontal disease status and progression. J Periodont Res 2002;37:132-46
19. Rappuoli R. Reverse vaccinology. Curr Opin Microbiol 2000;3:445–450
20. Rappuoli R. Reverse vaccinology, a genome-based approach to vaccine development. Vaccine. 2001 Mar 21;19(17-19):2688-91
21. Huang N, Shimomura E, Yin G, Tran C, Sato A, Steiner A, et al. Immunization with cell-free-generated vaccine protects from Porphyromonas gingivalis induced alveolar bone loss. J Clin Periodontol. 2019 Feb;46(2):197-205. doi: 10.1111/jcpe.13047