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Review Article

A Brief Review on Immunology of Dental Caries and Caries Vaccine

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Abstract

Dental caries is an irreversible microbial disease of the calcified tissues of the teeth, characterized by demineralization of the inorganic portion and destruction of the organic substance of the tooth, which often leads to cavitation. Untreated dental caries in deciduous teeth was the tenth most widespread and the fourth most expensive chronic illness to treat condition among children worldwide, with prevalence peaking at the age of six. Individuals with active caries have an elevated serum antibody level for mutans streptococci. Findings also suggest that an increased antigenic load (bacteria from lesions) will give rise to elevated salivary antibody. Subjects with selective IgA deficiency without salivary antibody show markedly elevated levels of dental caries when compared to normal controls. IgA deficient subjects with IgM compensatory antibodies have significantly less caries than simply IgA deficient subjects. The immune system in secretions have been used to interfere with caries by stimulating salivary antibodies to appropriate antigens. The gingival crevicular fluid contributes IgG, which can also interfere with caries.
This review article emphasizes the comprehensive and contemporary idea about immunological aspect of dental caries along with overview on dental caries and immunity and recent advancements in the field of caries vaccine.

Keywords: ***Caries, Immunology, Vaccine, GTF, GBP***

Introduction

"Caries is defined as microbial disease of the calcified tissues of teeth that leads to demineralization of the inorganic components and the subsequent breakdown of the organic moieties of enamel and dentin" [1].

"Dental caries is an irreversible microbial disease of the calcified tissues of the teeth, characterized by demineralization of the inorganic portion and destruction of the organic substance of the tooth, which often leads to cavitation" [2].

The caries experience differs widely between nations and even within them. Caries prevalence is often low (0.5-1.7 DMF) in Asian and African nations, but high (12-18 DMF) among Americans and other Western countries [2].

Generally, highly industrialized nations have the highest caries indices, with decayed, missing, and filled teeth (DMFT) of around 4.5. However, across this wide group of nations, New Zealand, Australia, Brazil, and Argentina have an elevated caries pattern of more than 5.6 DMF [2].

Untreated dental caries in deciduous teeth was the tenth most widespread and the fourth most expensive chronic illness to treat condition among children worldwide, with prevalence peaking at the age of six [Petersen, 2008; Kassebaum et al., 2015]. The worldwide burden of dental caries study demonstrates significant discrepancies impacting disadvantaged and lower socioeconomic status groups, and it is larger in low- and middle-income nations [3].

When examining the geographical distribution of dental caries prevalence rates in India, western India has the highest prevalence (72%). However, this contradicts a meta-analysis by Janakiram et al., who discovered that the prevalence of dental caries was much greater in North India across all age groups than in other areas of India. This discrepancy in inter-regional estimations can be

attributed to the socioeconomic factors of the examined areas as well as the region's eating patterns [4].

Acid generation by oral microbes within tooth plaque is the most critical factor in the development of dental caries. Microorganisms readily transform simple carbohydrates into lactic acid [5].

Caries is now thought to be caused by four factors: oral bacteria, the oral environment, the host, and time. Excessive consumption of dietary carbohydrates causes the buildup of acid-producing and acid-resistant bacteria in the mouth [6].

The carbohydrate level of the diet is well recognized as one of the most critical elements in the dental caries process. Sucrose has been referred to as the "arch criminal" of dental caries due to its vulnerability to acidification by oral microbes [5].

Certain physical and chemical changes in the enamel might contribute to tooth sensitivity. These might include surface flaws (hypoplasia, deep pits, and fissures) that promote the growth of carbohydrates and bacteria. Alterations in tooth composition that predispose to destruction by cariogenic agents may occur prior to tooth eruption [5].

Carious lesions include a diverse range of bacteria, with Streptococcus mutans, Lactobacillus acidophilus, and Actinomyces viscosus being the most common pathogenic species implicated in the formation and progression of dental caries. S. mutans has been identified as the causal bacterium of dental caries. S. mutans includes seven different species isolated from animals and humans: Streptococcus cricetus, Streptococcus ferus, Streptococcus macacae, Streptococcus rattus, Streptococcus downey, S. mutans, and Streptococcus sobrinus. S. mutans and Streptococcus sobrinus are solely isolated from humans, with S. mutans being the most abundant species [7].

Individuals with active caries have an elevated serum antibody level for mutans streptococci. Findings also suggest that an increased antigenic load (bacteria from lesions) will give rise to elevated salivary antibody. Subjects with selective IgA deficiency without salivary antibody show markedly elevated levels of dental caries when compared to normal controls. IgA deficient subjects with IgM compensatory antibodies have significantly less caries than simply IgA deficient subjects. The immune system in secretions have been used to interfere with caries by stimulating salivary antibodies to appropriate antigens. The gingival crevicular fluid contributes IgG, which can also interfere with caries [8].

Keeping this background knowledge in mind this article emphasizes the comprehensive and contemporary idea about immunological aspect of dental caries along with overview on dental caries and immunity.

Review

1. Immunology Of Oral Cavity

1.1 Humoral Immune Response

The human oral cavity is the location of initial encounter and primary immune response for many harmful pathogens. Both inductive and effector sites are involved in the elicitation of defense immunological responses. Most lymphocytes are activated and proliferate in inductive sites in response to antigen stimulation, and activated lymphocytes migrate and move to effector sites in order to mediate immune responses. The tonsils and proximal lymph nodes are the inductive sites in the oral mucosa, whereas the salivary glands, the lamina propria, and the epithelium are the effector sites.

T cells in the proximal related lymphoid tissues detect antigens collected at the oral mucosa. Specialized micropore (M) cells are located at the base of tonsillar crypts, which are incursions of the tonsillar stratified epithelium that significantly increase the epithelial surface. These cells help to carry these antigens into the tonsils. Dendritic cells (DCs) absorb antigens there and then deliver them to T helper cells and B cells, which make up the tonsil germinal centers [**Figure 1**].

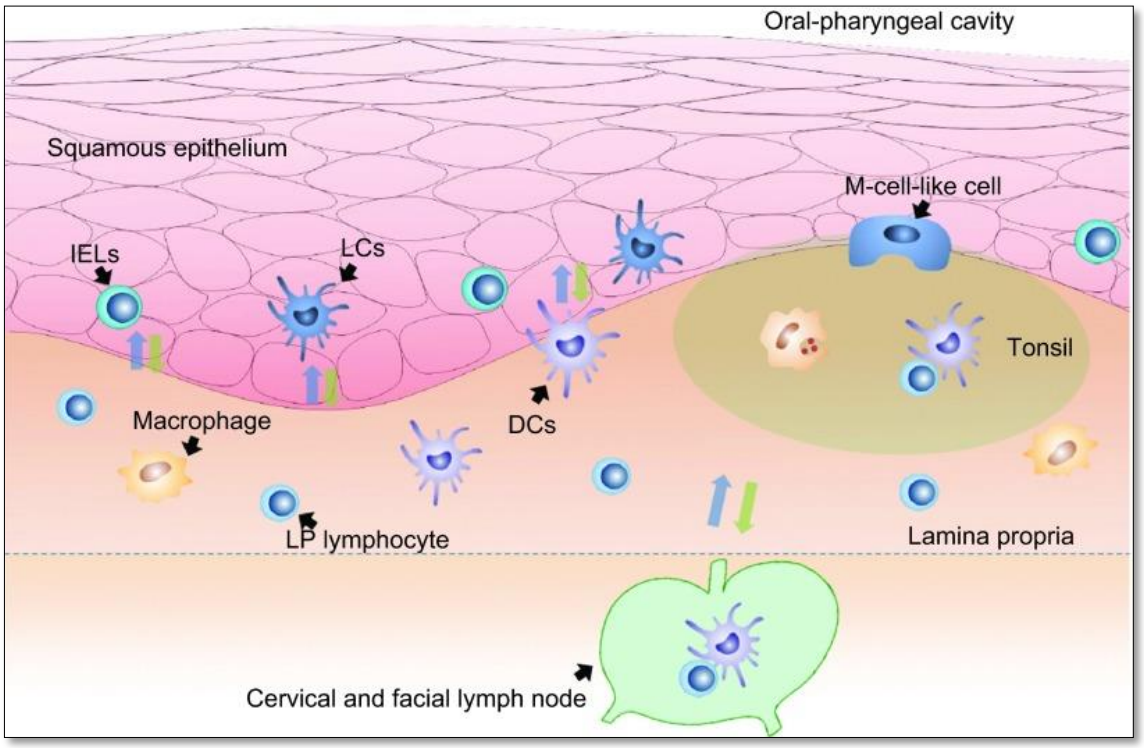

Fig 1: Picture depicting the structures and immune cells in the oral immune system.

The adaptive immune response is triggered by the generation of antibodies in the germinal centers. Furthermore, it's possible that resident DCs move to the tonsils or proximal lymph nodes after collecting antigens in the non-keratinized areas of the oral mucosa to begin functioning immune responses there. Subsequently, B and T cells migrate to the effector sites (i.e., the epithelium, or, in the

case of B cells, different secretory structures such as immunoglobulin-producing plasma cells) [9].

Native oral bacteria are frequently linked to periodontal and dental caries, the two main oral ailments. These illnesses seem to arise from an imbalance in the resident microbiota of the mouth, which allows potentially harmful bacteria to proliferate.

Three main categories may be used to categorize the regulatory forces affecting the oral ecosystem: host-related, microbe-related, and external influences. Secretory immunoglobulin A (SIgA) is the primary specialized immune defense mechanism in saliva and is one of the host variables that may be crucial for maintaining the oral microbiota's equilibrium [10].

1.2 Secretory and Serum IgA

There are two kinds of IgA. Secretory IgA (SIgA) and serum IgA. Monomeric (7S) serum IgA molecules have a molecular weight of around 160,000. On the other hand, secretory IgA (SIgA) is present on mucosal surfaces and in secretions. It is a dimer made up of two monomer units connected at their carboxy terminals by a glycopeptide known as the J chain (J for joining) [**Figure 2**].

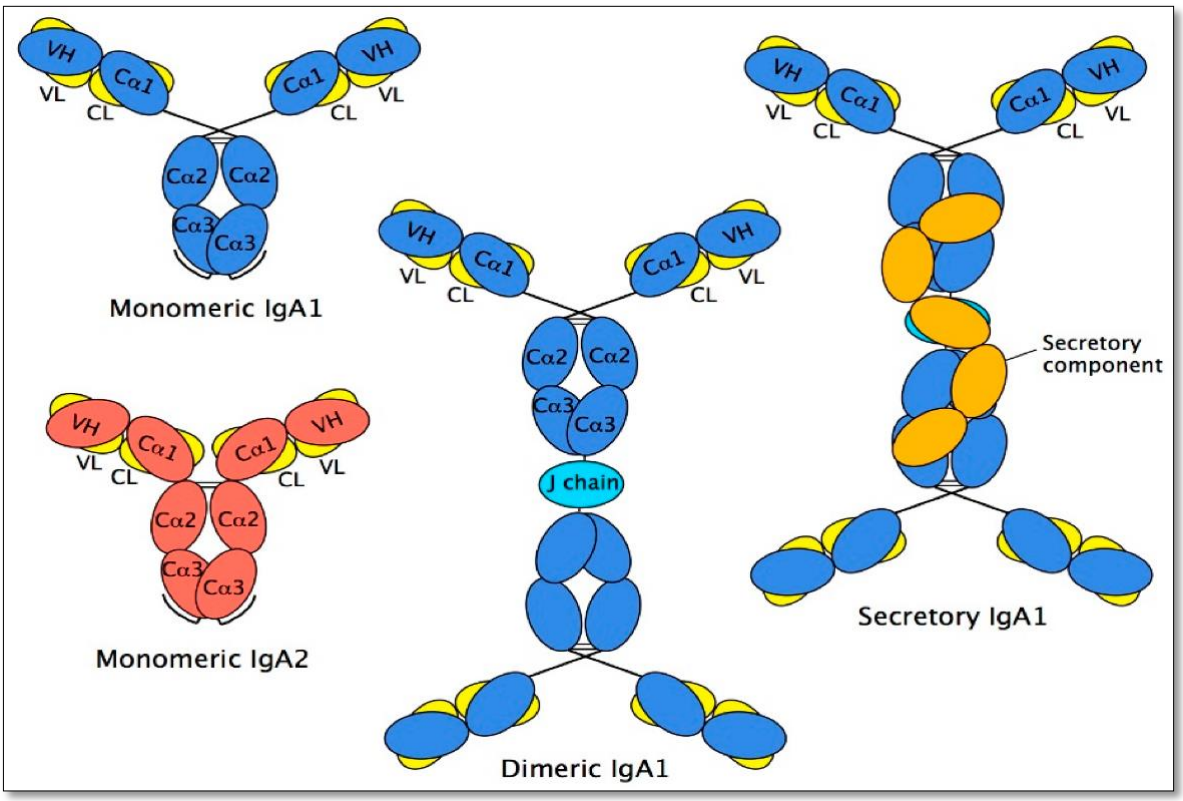

Fig 2: Picture showing structures of different types of Immunoglobulin A

The dimeric form of IgA known as secretory IgA (SIgA) is the more significant form. Plasma cells located in close proximity to the mucosal or glandular epithelium produce dimeric SIgA. J chains can also be seen in IgM and other polymeric immunoglobulins. Another glycine-rich polypeptide known as the secretory component or secretory piece is found in secretory IgA (SIgA). This is generated by mucosal or glandular epithelial cells rather than lymphoid cells. Mature B cells known as plasma cells produce dimeric IgA molecules, which subsequently attach to a receptor on the basal membranes of nearby epithelial cells. The poly-Ig receptor is the name given to this receptor.

Tightly attaching to IgA dimers, this receptor transfers them to extracellular fluids like the mucus in the digestive and respiratory systems via the epithelial cells. The poly-Ig receptor is cleaved when the poly-Ig receptor-lgA dimer complex reaches the mucosal cell's outer membrane. The secretory piece, also known as the secretory (S) component, is the area of the receptor that remains bonded to the IgA dimer. The secretory component is not easily broken down by the enzymes involved in digestion. In environments with a diverse and abundant bacterial flora, like the intestinal mucosa, the secretory piece is thought to shield IgA from denaturation by bacterial proteases. Serum IgA is significantly smaller than SIgA [11].

1.3 Cellular Immune Response

The immunology of caries is not directly influenced by the cellular immune response. Firstly, cellular immune processes often do not manage immunization against germs until they are chronic and persistent; secondly, because oral immune cells have difficulty operating in mouth environment. The majority of bacterial infections are treated via the antibody-complement-neutrophil axis (IgG) or secretory immunity (secretory IgA). The effectiveness of the latter approach does not necessarily depend on the neutrophil. By using T cells as both helpers and suppressors, they alter the humoral immune response. They lead to gingival tissue irritation, which increases gingival fluid flow and makes it easier for Polymorphonuclear leukocytes (PMNLs) and IgA to enter the mouth [12].

2. Mechanism of Action of Dental Caries Vaccine

Vaccines against dental caries are designed to specifically target antigenic elements of S. mutans, such as adhesins, glutamyl transferase, glucan binding protein, and dextranases [**Figure 3**].

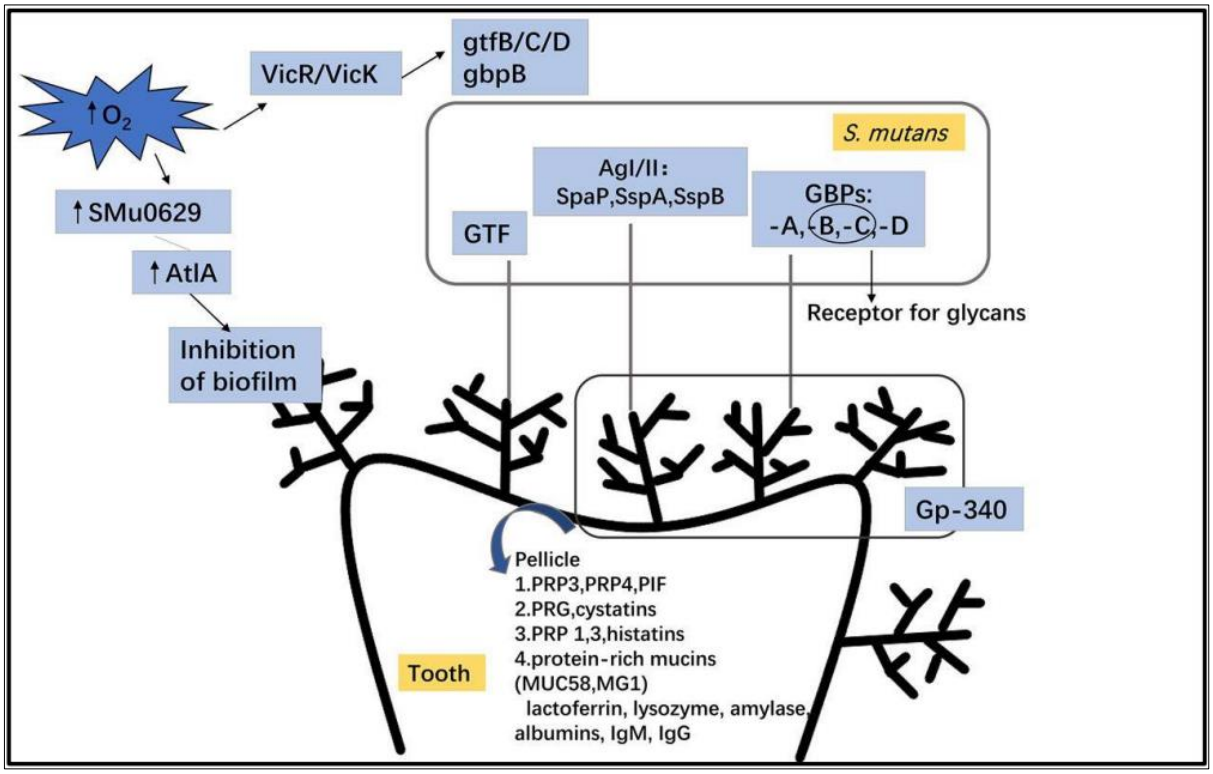

Fig 3. Antigens produced by S. mutans and inhibition of biofilm

2.1 Adhesins

These are entire protein polypeptides that were extracted from S. mutans and S. sobrinus. Research reveals that tooth caries and bacterial adhesion can be hampered by antibodies that are specific to S. mutans Ag I/II or S. sobrinus. Humans are protected against S. mutans-caused dental caries by either passive vaccination with antibodies or active immunization with intact antigen I/II.

2.2. Glucosyl transferase (GTF)

Lactic acid is the main acid that most acidogenic bacteria make, and it helps demineralize enamel. Caries is linked to two lactic acid generating bacteria: Lactobacillus and Streptococcus. Whereas streptococcus is more common in enamel caries, lactobacillus is linked to dentinal caries. These lactic acid bacteria also have the ability to use the enzyme glucosyltransferase to convert extracellular sucrose into extracellular glucose polymers, or glucans. Animal illness cannot be caused by S. mutans that are unable to make GTF. It has been demonstrated that antibodies against GTF obstruct the enzyme's synthesis activity as well as the development of plaque in vitro. S. mutans and S. sobrinus are the two main cariogenic streptococcal species in humans.

2.3. Glucan binding protein (GBP)

Glucan Binding Proteins are proteins which S. mutans secretes that are connected to the bacterial cell. They attach to extracellular glucans in the dental biofilm, which encourages S. mutans cells to aggregate. The S. mutans itself produced these glucans by enzymatic synthesis. GbpA, GbpB, and GbpC are the three unique glucan-binding proteins that S. mutans secretes. Out of the trio, a protective immune response against dental caries has only been demonstrated by antibodies to GbpB. Therefore, it can be applied mucosally by the intranasal route or by subcutaneous injection of GbpB in the area of the salivary glands.

2.4 Dextranases

In order for bacteria to readily infiltrate early dental plaque that is high in dextran, dextran is a crucial component of that plaque. One significant enzyme that S. mutans produces is called dextranase, which breaks down dextran. When employed as an antigen, dextranase can stop the bacterium from colonizing early dental plaque [12].

3. The Human Application of Immunization

3.1 Routes of Vaccine Administration

The oral approach was previously tried, but it did not work since the inductive sites were far away and the stomach acidity had a marked effect on the antigen. The nasal associated lymphoid tissues are the target of the intranasal route. A protection might be shown using the S. mutans antigen, AgI/II12, and the glucan-binding domain, GTF-B11. An IgA response may be elicited by the tonsillar vaccination. Rabbits' major and minor salivary glands can produce IgA in response to the tonsillar administration of a specific antigen.

After applying GTF topically to the smaller salivary glands, the proportion of native and total streptococcal flora in the saliva decreased throughout the course of the next six weeks. Salivary IgA reactions to the S. mutans antigen, such as GTF, are distantly induced by the rectal route. Adjuvants such as liposomes, microparticles, macroparticles, and heat-sensitive enterotoxins from E. Coli and cholera aid in the delivery of the dental caries vaccine [13].

3.1.1 Oral Route

According to the authors of earlier research, oral feeding, gastric intubation, or vaccination with capsules or lysosomes were the methods used to apply the antigen and induce oral immunity in the GALT.

Salivary IgA antibodies were likewise elevated after oral vaccination with a capsule containing 500 mg of GTF from S. mutans [12].

3.1.2 Intra Nasal Route

To create immunity to streptococcal antigens, intranasal delivery of the antigen, which targets the nasal associated lymphoid tissue (NALT), has been employed. Rats might be made to develop protective immunity against cariogenic mutans streptococci by

administering S. mutans antigens intranasally. Ag I/II and GbpB from S. mutans, either alone or in combination with mucosal adjuvants, might be used to demonstrate protection [12].

3.1.3 Systemic Route

It has been effectively demonstrated that entire dead S. mutans administered subcutaneously to monkeys may induce serum IgG, IgM, and IgA antibodies. Through gingival crevicular fluid, the antibodies enter the oral cavity and provide protection against dental caries. Elevation of serum IgG antibodies was mostly linked to protection against caries [12].

3.1.4 Active Gingivo-Salivary Route

Increased IgG and IgA levels have been linked to the utilization of the gingival crevicular fluid as a delivery system. A) Injecting lysozyme into rabbit gingiva resulted in the production of local antibodies from cell response b) Applying live S. mutans to rhesus monkeys' gingiva, which was unsuccessful in eliciting the production of antibodies. c) Using Streptococci antigen with a lower molecular weight, which improved immune function presumably because of improved penetration [12].

3.2 Passive Immunization

Passive immunization can be achieved by:

a) When murine monoclonal IgG antibodies 13 specific for S. mutans' antigens were applied topically to monkey gingiva, over the course of a year, there was no dental caries and S. mutans colonization was reduced, in contrast to control animals [12].
b) Passive immunization has also been accomplished through the use of egg yolk antibodies. In order to acquire egg yolks enhanced with IgG antibodies for GTF, chickens were immunized with the GTF antigens. When this antibody-enriched egg yolk was fed to rats in an experiment, dental cavities was reduced by 50% [12].
c) Another approach is to use whey and milk from immune-compromised cows. IgG antibodies were produced in the serum and milk whey of cows that were given a vaccine derived from entire mutans streptococcal cells by systemic vaccination. In a pilot human study, using a mouthwash made of bovine milk whey containing antibodies against mutans 14 streptococci for 14 days reduced the amount of S. mutans in the group compared to the control [12].
d) Transgenic plant antibodies: Secretary IgA, a colorless and tasteless vaccination that can be applied to teeth, was recently created by crossing four tobacco plants. This antibody, which is the first vaccine generated from plants, has demonstrated efficacy against S. mutans and the ability to agglutinate cells [12].

3.3 Active Immunization

Active immunization can be achieved by:

a) Consumption of complete S. mutans in the form of capsules, which did not open until they got to Peyer's patches, 15 which triggered an antibody response
b) Rats given an oral vaccination with synthetic peptides derived from the S. mutans GTF enzyme have demonstrated efficient inhibition of the enzyme's action.
c) When S. mutans antigens and cholera toxin subunits were combined, it was possible to limit S. mutans colonization, increase the pace of caries reduction, and provide a good immune response.
d) Using S. mutans genes fused to pathogenic salmonella was another technique. It is becoming increasingly clear that attenuated salmonella is a successful vaccination method [12].

4. Recent Studies

The target antigen is the S sobrinus recombinant enolase, or rEnolase. Rats' mouths were given enolase together with an alum adjuvant. Salivary IgA and IgG antibodies that were particular to this recombinant protein rose in response to it. These findings suggested that rEnolase would be a safe and viable option to be used in human dental caries vaccination studies. Healthy young individuals were tested for the suppressive effects of lozenges containing egg yolk antibodies (immunoglobulin Y [IgY]) against the Streptococcus mutans cell-associated glucosyltransferase (CA-gtf). The study's findings demonstrated that in young, healthy people, lozenges containing anti-CA-gtf IgY might prevent mutant Streptococci from colonizing their oral cavities. All vaccinations appear to pose no dangers as long as they are produced and administered correctly.

The most dangerous concern is that certain rheumatic fever patients' sera exhibit a serological cross-reactivity between specific haemolytic streptococci antigens and cardiac tissue antigens. It has been observed that normal rabbit and human cardiac tissues cross-react with antisera obtained from rabbits vaccinated with S. mutans whole cells and with a high molecular weight protein. Streptococcus ratti and S. mutans cell membranes contain polypeptides that are immunologically cross-reactive with both human heart tissue and the myosin from rabbit skeletal muscles.

The indications of carcinogenic Streptococci colonization and proliferation in dental biofilms may aid in the development of more sophisticated and knowledgeable methods to "lock out" harmful bacteria. The consumption of whole S. mutans causes the selective production of S-IgA in gnotobiotic rats. There was a correlation between the emergence of S-IgA and a lower incidence of the caries vaccination. The main strategy used in the majority of the studies has been to implant the same organism in the animals' mouths and feed them a diet high in sucrose after first immunizing them with an adjuvant containing S. mutans antigen as often as required to achieve high antibody levels.

Since dental caries meets the requirements for an infectious illness, efforts have been made to prevent it by immunization. The theory behind this is that by immunizing against S. mutans, an immune response should be elicited, perhaps blocking the organism from colonizing the tooth surface and avoiding decay. The vaccine may be administered concurrently with the tetanus and diphtheria vaccinations. After that, the immunity might be periodically increased to offer lifetime protection [13].

Rats and mice are the most common animal models used in anticaries vaccination trials. Although successful in rats, these findings cannot be applied to people due to the short period of time that caries develops in these animals, in addition to the fact that, in contrast to humans, S. sobrinus has a higher cariogenic potential in these animals than S. mutans. Furthermore, compared to humans, rats and mice have distinct dental morphologies and caries criteria [14].

Conclusions

Dental caries is an irreversible microbial disease. The primary aetiologic agents for dental caries are Streptococci mutans,

S.sobrinus and Lactobacillus. Through adhesions, S.mutans attaches to the dental pellicle and through the formation of GTF and then glucan, more organisms colonize and lactic acid formation is initiated, thus causing dental caries. An immune intervention can be undertaken by blocking the receptors which are necessary for the colonization of these bacteria or by inactivating GTF. Through these measures, the immunization against dental caries can be achieved. This may help greatly in improving the oral health in the developing countries. Despite the promising laboratory advances, anticaries vaccines are still far from being a current reality, since most studies are done in small animals, making it difficult to extrapolate to humans. Despite the large number of laboratory studies with experimental animals and the evidence of vaccines' efficacy, there is no marketability for human use. The vaccine production requires large-scale investments, largely burdening their cost, which is not feasible and advantageous for public health systems. In addition, some challenges must be overcome through further research, as the residence time of the vaccine with appropriate concentration in the oral cavity, best route of administration, as well as a reduction in the possibility of cross-reactions. Still, it should be pointed out that dental caries is a multifactorial disease, which can be prevented and controlled by other simple means and with lower costs, such as proper hygiene and use of fluorides, which are already established in the literature. Therefore, elimination of caries is the main objective of the health professionals. Still more clinical trials are needed to evaluate the safety of these vaccines so that potential risks are eliminated.

Ethics approval and consent to participate

"Not applicable"

List of abbreviations

Glucosyl transferase: GTF
Immunoglobulin A: IgA
Immunoglobulin G: IgG
Decayed, Missing, and Filled Teeth: DMFT
Dentritic Cells: DCs
Secretory immunoglobulin A: SIgA
Polymorphonuclear Leucocytes: PMNLs
nasal associated lymphoid tissue: NALT
immunoglobulin Y: IgY
Streptococcus mutans cell-associated glucosyltransferase: CA-gtf

Conflicts of Interest

"The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper."

Authors' contributions

RG Wrote the paper and contributed significantly in designing and language.
SG Drafted the article or revised it critically for important intellectual content.
SM Contributed data or analysis tools
SD Conceived and designed the format for writing
MP Agreed to be accountable for all aspects of the work and supervised over all work.

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Picture References

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