INTRODUCTION

Dental caries, one of the most commonly found diseases in human beings, is multifactorial caused by host, agent and environmental factors. According to Shafer, dental caries is defined as “An irreversible, microbial disease of the calcified tissues of the tooth, characterized by demineralization of the inorganic portion and destruction of the organic matrix of the tooth which often leads to cavitation” (Shafer, 2016). Sturdevant defined dental caries as “An infectious microbiologic disease of teeth that results in localized dissolution and destruction of the calcified tissues” (Roberson & Gopikrishna, 2013). The word dental caries is derived from Latin word meaning rot or decay. It is similar to Greek word ker meaning death (Nikiforuk, 1985). The term is in accordance with the clinical picture of a carious lesion that depicts decaying tissue. In Japanese, dental caries is mush – ha (mush – room; ha – tooth) meaning hollow tooth and in Chinese, the word for hollow tooth is Chung choo.

Dental caries because of its uniqueness remains one of man’s most common, oldest and single costliest ailment. As huge amount of money and time is spent on treating dental caries, the prime aim is to prevent this condition for public health betterment (Shivkumar et al., 2009). Many studies have been performed over several decades demonstrating the feasibility of immunization over rodents and primates for treating dental caries. Although these vaccines are still in early stages, they have become a hope for many.

Text

Dental Caries

Dental caries, also known as tooth decay or a cavity, is an infection, usually bacterial in origin that utilizes sugar in the diet for the production of acid. The acid produced by hydrolysis of the food debris accumulated on the tooth surface causes demineralization of the hard tissues (enamel, dentin and cementum) and destruction of the organic matter of the tooth.

Causes

The two contributing factors that cause tooth decay are bacteria and diet rich in sugars and starch (Shafer, 2016). In modern times, because of consumption of refined sugars rich diet, dental caries has reached epidemic proportions. The bacteria present in the mouth combines with food and saliva to form a sticky substance called plaque, which aids in adhering the bacteria to the tooth surface. Foods rich in starch also add to the stickiness of plaque, which after a couple of days begins to become hard and gets converted to tartar or calculus. Bacteria present in the plaque also convert sugars into acids that results in dissolution of tooth structure leading to holes or cavities.

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Since these two contributing factors play an important role, dental caries has been aptly described as “dietobacterial” disease.

According to W.D. Miller, the three factors involved in caries process are
1. Oral microorganisms
2. Carbohydrate substrate
3. Acid which causes dissolution of tooth minerals.

Role of carbohydrates: The presence of readily fermentable carbohydrates has been thought to be responsible for the loss of caries resistance. The cariogenicity of a dietary carbohydrate varies with the frequency of ingestion (Newburn, 1983), physical forms (Lenander et al, 2000), chemical compositions (Geddes, 1994), route of administration and presence of other food constituents (Shafer, 2016). The various forms of carbohydrates that lead to dental caries are shown in Figure 1.

Role of microorganisms: A wide group of microorganisms capable of inducing carious lesions includes Strep Mutans, Strep salivarius, Strep mitior, Strep milleri, Strep oralis, Strep sanguis, Lactobacillus acidophilus, Lactobacillus casei, and Actinomyces viscosus. Available data strongly suggest that Strep Mutans, Lactobacillus and Actinomyces viscosus play an important role in the initiation and development of dental caries (Krithika et al, 2004; Russel et al, 2004).

Role of Acids: Bacteria breakdown dietary starch to form acid. The starch present in the diet is broken down by enzymes present in bacteria to form acids (Flowchart 2). Homfermentative organisms such as Streptococci and Lactobacillus forms 90% or more lactic acid and Heterofermentative organisms produce mixture of metabolites such as propionic acid, butyric acid, succinic acid and ethanol (Newburn, 1983).

Streptococcus was first isolated in carious lesion by Clarke in 1924 and because of its varying morphology termed it as Streptococcus Mutans. They are facultative anaerobic, non-motile, catalase –ve, gram +ve cocci, non-haemolytic acidogenic organisms, occur in short or medium chains (Goody & Hicks, 2008) and produces extracellular and intracellular polysaccharides (Newburn, 1983). Streptococcus Mutans shows virulence factors (Table 1) and fulfils Koch’s postulates as a cause of dental caries (Table 2).

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<th>Table 2 Koch’s postulates for S. Mutans</th>
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The structure and antigenic composition of Streptococcus Mutans are responsible for the immune responses to this organism. The immunogenicity of the microorganism is due to surface antigen of cell wall that includes adhesions, Glycosyl
transferase (GFT) and glucan binding protein (GBP). The other major protein antigens present in Streptococcus Mutans are termed as Streptococcal antigens I, II, I/II, III. The other component present is dextranases and lipoteichoic acid (LTA). The matrix of cell wall is made up of cross-linked peptidoglycan that is composed of N–acetyl amino sugars, N–acetyl muramic acid and numerous peptides (Lehner, 1992). Dextran is responsible for the adhesion of Streptococcus Mutans to the tooth surface. LTA is derived from protoplast membrane and has a carbohydrate component glycerol phosphate which produces a backbone common to gram +ve bacteria and also responsible for cross reaction between LTA (Kilian & Bratthall, 1986).

**Adhesins:** It forms the 2 most important human pathogens identified as antigen I/II & Pac or P1 in Streptococcus Mutans and Spa – A or Pag in Streptococcus sobrinus (Shanmugan et al, 2013). The adhesin activity of antigen I/II is related to the alanine–rich repeating region in the N–terminal and proline–rich region in the centre of the molecule (Lehner et al, 1992). Studies in mice have shown that immunization may be achieved by directing antibodies to the intact Ag I/II molecule or to its salivary binding domain, thus blocking the colonization of S. Mutans on the tooth surface (Bowen, 1996; Smith & Taubman, 2002).

**Proteins:** GTF exist in 3 forms: GTF 1, GTF – S - 1, GTF – S and the genes coding for the 3 forms are GTF – B, GTF – C & GTF – D (Shivkumar et al, 2009). GTF is the enzyme that converts sucrose into glucan and aids in the adhesion of S. Mutans to the tooth surface. Studies have shown that immunization with GTF can protect against caries in experimental animals (Smith & Taubman, 1997).

**Glucan Binding Protein (GBP):** It exist in 3 forms in S. Mutans – GBP – A, GBP – B and GBP – C. Immunization with GBP – B has shown to induce a protective immune response to dental caries in experimental animals (Smith & Taubman, 1997) and in young children, induction of natural immunity is related to IgA Ab to GBP – B (Sato et al, 1997).

**Polysaccharides**

**Extracellular dextran (Glucan):** It is synthesized by the action of GTF on sucrose. Predominantly α 1, 3 water insoluble dextran termed mutan is synthesized by S. Mutans and α 1, 6 linked water-soluble dextran is synthesized by S. Sanguis (Newburn, 1983; Jespergaard et al, 1999).

**Extracellular Levan (Fructan):** It is less synthesized by S. Mutans and more quantities by S. Salivarius and Actinomyces viscosus (Nikiforuk, 1985).

**Intracellular Amylopectin:** It may be responsible for acid production inside the plaque by being metabolized to lactic acid when the carbohydrate source is depleted (Nishikawara et al, 2006; Newman & Nisengard, 1993). It is found in S. Mutans and dental plaque.

**Metabolism of S. Mutans & Its Role in Cariogenesis**

The most important substrate for the involvement of S. Mutans in the caries process is the disaccharide sucrose. The different pathway by which S. Mutans may dissiplate sucrose is shown in Flowchart 3.
Secretory IgA antibodies (Flowchart 5)

- Direct immunization of GALT
- Sensitized B cells activated
- Stimulates salivary glands
- Produce secretory IgA antibodies
- Prevent adhesion of S. Mutans to enamel surface + inhibit GTF activity
- Dextran formation prevented

FLOWCHART 5: Role of Secretory IgA Antibodies

Gingival crevicular mechanism (Flowchart 6)

- GCF contains humoral immunoglobulin’s (IgM and IgG)
  - Cellular components (lymphocytes, PMN’s, macrophages)
- Subcutaneous immunization with S MUTANS
  - Organism is phagocytized & undergoes antigen processing by macrophages
  - T and B lymphocytes sensitized by macrophage prevent antigen HLA CLASS 2 COMPLEX & releases IL 1
  - Induces CD4 and CD8 cells with release of IL 2
  - Cells interaction important for modulation of immunoglobulin’s + B lymphocytes

FLOWCHART 6: Role of Gingival crevicular mechanism

Routes of Administration

Currently, the following strategies that are being under consideration in caries research studies includes the following (Sato et al., 1997):

- ✔ Common mucosal immune system
- ✔ Systemic (subcutaneous)
- ✔ Acute gingiva – salivary
- ✔ Passive immunization with topical application of antibodies

Common Mucosal Immune System

Oral: It relied on oral induction of immunity in the GALT. Antigen was applied by oral feeding, gastric intubation, or in vaccine containing capsules or liposomes. Experiments have shown that there was an increase in secretory IgA antibodies in saliva when killed S. Mutans was given to germ free rats in drinking water followed by live S. Mutans, thus concluding that in comparison to subcutaneous immunization oral immunization does not reduce caries significantly.

Intranasal: Administration of the antigen intranasally stimulates nasal associated lymphoid tissue (NALT). This has been utilized to boost immunity to the antigen associated with S. Mutans colonization and accumulation (Nikiforuk, 1985).

Tonsillar: Fukuizumi & co-workers (1999) have been shown that repeated application of a particulate antigen in the tonsillar area (palatine tonsil & naso – pharyngeal tonsil) stimulates IgA antibody producing cells to the effector sites such as the salivary glands (Smith & Taubman, 1997).

Minor salivary gland: The minor salivary glands are mainly located in the lips, cheeks, and soft palate. The ducts of these glands facilitate retrograde access of bacteria and also associated with lymphoid tissue aggregates. This forms the basis of these glands to form a potential route for the mucosal induction of salivary immune response. Experiments have further supported that the labial application of GTF had significantly lowered S. Mutans flora in the whole saliva (Smith & Taubman, 1997).

Subcutaneous

The antibodies IgA, IgM, IgG via crevicular fluid enter the oral cavity and thus provide a protection against dental caries. Out of the three antibodies, IgG protects against dental caries. This is further supported by experiments performed successfully in monkeys where subcutaneous administration of S. Mutans elicits serum IgG & IgM antibodies (Lehner, 1992).

Acute Gingival Salivary route

Another route that can be used for vaccine administration is gingival crevicular fluid (GCF). This route has 2 benefits: First, it excludes any side effects of using the vaccine with the other routes. Second, it localizes immune response to the oral cavity. Increased level of IgG & IgA level is associated with GCF, further strengthening its protective role (Tandon, 2008).

Passive immunization

Passive immunization involves passive or administration of readymade antibodies externally. This is used when there is high risk of infection and body has insufficient time to develop its own immune response. This carries the drawback of repeated applications, as the immunity provided is temporary (Smith & Taubman, 2002; Nikiforuk, 1985). Several approaches tried were:

- ✔ Monoclonal antibodies
- ✔ Bovine milk & Whey
- ✔ Egg – yolk antibodies
- ✔ Transgenic plants

Newer Methods

These new methods that are under clinical trials are being used to boost immune response to stimulate antibodies production that may provide a protective mechanism. The various new methods are:

1. New Fusion Anti-caries DNA Vaccine
2. Adjuvants and Delivery Systems for the Vaccine like:
   a. Synthetic peptides
   b. Coupling with Cholera and E. coli toxin subunits
   c. Recombinant vaccines with salmonella strains
   d. Liposomes
   e. Microcapsules and microparticles
   f. Conjugate vaccines.
CONCLUSION

With studies in progress and researches still going on regarding this ‘wonder vaccine’, we can hypothetically at present consider that the dental caries vaccines would be the first non-living vaccine to be applied by any mucosal route during the first three years of life and much more research will be necessary before a caries vaccine becomes available to the general public. Also, understanding the signals for colonization and growth of cariogenic streptococci in dental Biofilm may help us devise more refined and informed techniques to abandon those bacteria that can cause us harm. Regardless of the mechanism by which immune protection against dental caries is achieved, further advances to make immunization against caries practicable will depend upon clinical trials aimed at establishing whether the findings from animal experiments can be transferred to humans. And for that we can only wait for a perfect impact that will be created by this “wonder vaccine” on dental caries.

References


How to cite this article:

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