ISSN No: 2582-0559

REVIEW ARTICLE

THE ORAL BIOTOME AND EFFECTS OF RECENT TOPICAL FLUORIDE THERAPIES – A REVIEW

Dr. B N Rangeeth, Dr. Priyaa Rangeeth* ,

Department of Pedodontics, Thai Moogambigai Dental College, Chennai, Tamilnadu, India.

*Chief Consultant, Gums to Crowns Laser and Implant Dental Clinic, Chennai, Tamilnadu, India.

DOI: 10.37841/jidam_2022_V9_I1_02

Address for Correspondence

Dr. B N Rangeeth, MDS,

Department of Pedodontics

Professor, Thai Moogambigai Dental College

Email: dr_rangeeth@yahoo.com

Received : 18.07.2021 **Accepted : 02.03.2022**

First Published: 05.03.2022 **Published : 30.03.2022**

ABSTRACT

The oral cavity has an extremely diverse and complex microflora that include bacteria, fungi and viruses. Understanding this is the primary aim in prevention of oral diseases and also a major role in diagnosis and treatment of systemic diseases. Considering the oral cavity as a mirror of the human body newer genomic therapies have improved the detection as well as discovery of newer flora. Though the oral microbes are quite diverse there seems to be simple means to control as well as manage the oral diseases and in this regard, fluorides seem to play a major role in the control and this article intends to discuss the same.

KEWORDS: Oral Microflora, Streptococcus species, Fluoride therapy, Dental Caries

INTRODUCTION

The oral cavity is an extremely diverse, dynamic and unique ecosystem in the human body with a characteristic feature being the instability of its ecological conditions with many anatomical sites that constitute separate ecological niches promoting the development of microorganisms, with each niche having a distinctive microbiome[1]. With the microbial load of the oral cavity the importance of fluoride and its effect on the dentition has been noted as early as even 1951[2] with a note on its non-toxic concentrations in drinking water and its conservative nature in managing caries in molars. There have been substantial changes and new formulations and methods are discovered for a healthier dentition by understanding its method of action in the oral cavity. There was an increased interest in the nature of the physiological actions of fluoride ions on bacterial cells considering their anti-cariogenic effect which was due to their direct inhibition of metabolism of the plaque bacteria. The effect of fluoride by autolysis of bacteria prompted more research as considering fluoride as an anti-microbial agent, which is a contributing factor to the anti-cariogenic effect[3].

Fluoride the 13th most abundant element and due to its anti-caries effect is added to drinking water, food, dentifrices and preventive therapeutic products. The basic form of action is through incorporation into the mineral of teeth forming fluoroapatite that is less susceptible to action of acids, the effect termed remineralization that is increased in fluoride is available in micro-molar levels. Dental caries is an infectious disease and the acids produced by cariogenic bacteria are found beneath the plaque pellicle leading to demineralization of the mineral content. Therefore the effect of fluoride must be concentrated towards the plaque pellicle in preventing demineralization, therefore makes it a lifelong necessity to have an exposure to fluoride rather than only during the formation and eruption of the dentition[4].

ORAL BIOTOME

The oral environment is quite complex and transforms especially with age and other factors. Considering the age there is a major transformation where during the first three months period there is colonization of the mucosal surfaces and later colonization of the hard surfaces of the dentition of the deciduous followed by the permanent dentition even on artificial materials like orthodontic mechanisms, prosthesis, restorations, etc. The biofilm on the tooth surface which colonizes the oral microflora are of two types depending on the location namely, supra and sub gingival plaque that are significantly different. The subgingival bacteria predominantly bearing gram negative flora including *Prophyromonas gingivalis, Actinobacillus* etc. The cause of dental caries is usually the supragingival microbiome. Research also indicates that other microorganisms present in dental plaque that have been considered to be non-cariogenic upto now, such as *Bifidobacterium, Propionibacterium, Streptococcus salivarius, Streptococcus oralis, Streptococcus milleri, Enterococcus faecalis, Actinomyces naeslundi and Actinomyces viscosus*, may also result in dental caries[1].

Around 700 species of bacteria have been detected by DNA analysis in the oral cavity. The colonization normally begins with transmission from the birth canal where streptococci, lactobacilli, bifidobacteria include the initial colonizing ones, and the growth of which are supported by the components of the mother's milk and in the case of Caesarian deliveries the colonization of *Streptococcus mutans* can be delayed by a year. Around 6 weeks of age streptococci and V*eillonella* species are abundant and the bacterial count dependent on physiological changes including eruption and exfoliation of the dentition. S*treptococci* and l*actobacillu*s are primarily responsible for acid production where the mutans streptococci and *S sorbinus* are able to transform sucrose to lactate making it more cariogenic[5]. Streptococcus was the predominant genus in infant saliva. *Veillonella, Neisseria, Rothia, Haemophilus, Gemella, Granulicatella, Leptotrichia* and *Fusobacterium* were also predominant genera in infant samples, while *Haemophilus, Neisseria, Veillonella, Fuso bacterium, Oribacterium, Rothia, Treponema and Actinomyces* were predominant in adults[6]. The application of molecular techniques was especially useful in determining microbial zones within the oral cavity and identifying the change due to age and diseases.

ANTIMICROBIAL EFFECT OF FLUORIDE

In general, fluoride acts primarily in remineralization and the antibacterial activity plays a very important role such as the effect on bacterial enzymes. Basically fluoride in acidic plaque that cariogenic exists in also in an acidic pH as HF. This easily moves across the bacterial cell membrane then there is disassociation of the HF into F^- and H^+ in the cytoplasm providing the availability of F ions and binds to various cell structures, mainly the proteins[4].

Fluoride acts on the bacterial cell wall by affecting the synthesis of bacterial wall peptidoglycans by disrupting enzyme reactions responsible for the integrity of the cell wall. Fluoride inside the bacterial cell effects glycolysis by mainly inhibiting enolase and to a lesser extent on the phosphotransferase system necessary for cellular functioning. Fluoride is an inhibitor of glycolytic enzyme enolase and showed very effective action against *Streptococcus salivarius, Streptococcus sanguis and Streptococcus mutans*. Addition of phosphate provided an enhanced effect along with Mg. Oral streptococci have proton-translocating F ATPases in their cell membrane and this is inhibited by Fluoride and addition of chelate forms of Aluminum have shown to enhance the effect of fluoride and more research is needed to determine the effect. Also the effect on the ATPases can disrupt cations in the cell membrane and hydrogen ions in yeast cells. Lactoperoxidase and salivary peroxidases are inhibited in a pH dependent manner by fluoride and this effect is concentrated in plaque. Eukaryotic pyrophosphatases are another bacterial components that can be inhibited by fluoride where S mutans and *T Denticola* are relatively sensitive this form of action. Phosphoglucomutases are inhibited by fluoride in many organisms but later it was evaluated that S salivarius was resistant and rather the action of fluoride in producing intracellular deposits of idiophilic polysaccharide or

glycogen seemed to be the cause of the inhibitory effect rather than a direct inhibition of phosphoglucomutase in bacterial cell. Another perfect example would be Mutans streprococcus which is sensitive to Fluoride since there is a direct inhibitory effect of fluoride on the proton transporting ATP system but when lower concentrations of fluoride are encountered the bacterium mutates to form resistance to the action.

Other enzymes that are affected by fluoride are pyruvate kinase and phosphoglucomutase of S mutans but in particular one enzyme that can be inhibited especially in the oral flora would be the ureases from studies done on S salivarius where the reduction of ureolysis in bacterial cell may reduce production of ammonia that can neutralize glycolytically produced acids. Other effects include its effect on proton permeability in bacterial cell wall where peptidoglycans production is increased leading to cell lysis and the ability of Fluoride to combine with aluminium, and beryllium to form complexes that mimic phosphate to have a negative effect on various bacterial enzymes. In this there is increased proton accumulation by bacterial cells resulting in a reduction in bacterial growth that is favoured in the acidic environment[4-7.]

Advances in genetics has shed a whole new light into the uptake and resistance of bacterial to fluoride. Riboswitches that form parts of bacterial mRNA can disable the expression of certain genes that make or transport metabolites that the RNA has sensed and the current topic of research being that of *'crcB motif'* RNA and the one that is frequently associated with fluoride riboswitches being *crcB*, components that block these being the current topic of research for better efficacy of fluoride absorption when combined with antimicrobials by preventing the expression of fluoride toxicity expression genes preventing the inhibitory effect in the bacterial cell[7].

SILVER DIAMINE FLUORIDE (SDF)

It was first approved as a 38% solution for desensitization of teeth to cold with the common constitutents being Ammonia, Silver and Fluoride with variation among brands. The average content ranging between 4,753.6 to 53,728 ppm and the method of action being production of fluorhydroxyapatitie with silver being an antimicrobial agent and ammonia stabilizing the components. The effectiveness is because of its penetration capacity and the subsurface storage being more than 2 to 3 three times when compared to other topical forms[10]. The antimicrobial effect of SDF is quite partially known and various reports have been provided on its inhibitory effect. One effect seems to be an electrostatic mechanism where there is an attraction between the difference in the electric charges between the cell membrane of the microrganism and the silver nano particles. Other mechanisms include disruption of bacterial cell wall causing lysis by allowing lipopolysaccharide molecules and membrane proteins to be released from the microorganism[11,12] all this possible since the pharmacokinetics shows safe serum levels, evaluation of which was done by Vasquez E *et al* that showed a mean serum concentration of 206 nmol/L of silver and 1.86 nmol/L fluoride when 7.57 mg of SDF was applied and the maximum serum concentration reached over a period of 3 hours, showing little toxicity for human use[13].

Yu *et al* evaluated the effect of Silver Nitrate on the growth of S *mutans* biofilm on dentin surface and the results revealed a significant effect of Silver Nitrate with or without fluoride. The evaluation of the effect of silver as an antibacterial agent showed that the ions have an intra and extracellular action, disrupting bacterial proteins and enzymes by binding with the thiol groups and inactivating them. Other methods could be the binding effect of silver with nuclear acids leading to a disruption in DNA replication. Combining Silver Nitrate with Sodium Fluoride varnish and functionalized Tricalcium Phosphate had significant remineralization effects[14] Karched M *et al* compared the efficacy of SDF with SDF and Potassium Iodide (KI) and Chlorhexidine (CHX). *Streptococcus mutans* grown on mitis salivarius-bacitracin agar and were individually treated with SDF SDF + KI, CHX and sterile saline. *S mutans* showed an increased inhibitory rate with SDF than others with CHX following the effectiveness. [15] Jabin Z *et al* evaluated the effective concentration level of SDF and the results showed that 38% SDF was more effective in arresting carious lesions than other forms of interventions and even lower concentrations did not show much of statistical significance in the effectiveness even when compared to other topical cariostatic agents, resin an glass ionomer cements[16]. The more recent advancement in Silver based formulations are Nano-Silver based particles that have shown effectiveness as high as 81% in arresting carious lesions[17].

CPP-ACP BASED VARNISHES

Varnishes containing case in phosphopeptide-amorphous calcium phosphate (CPP-ACP) have also been a recent trend in Topical Fluoride therapy. In addition to fluoride they have an additional remineralization capacity by incorporating Calcium and increased acid resistance than other forms of fluoride though the action is quite debate. There is interaction with the saliva to form CaF_2 on the enamel that is stabilized by proteins in the plaque pellicle at a neutral pH. When the pH becomes acidic, CaF_2 beings to dissolve and release the fluoride ions, neutralizing the acidic action this is a prolonged natured compared to other types of Fluorides applied topically and thus there is also a prolonged time for antibacterial action of the fluoride ions[18].

DISCUSSION

The oral biotome is a complex environment where there is a functional evolution where both the microbiome and host had a functional integration. The benefits include formation of resistance to infection, digestion and metabolism to the host. Nitric oxide released during the metabolism of nitric oxide during nitrate reduction is said to have a regulating effect on blood pressure. It's only when there is an imbalance caused by improper nutrition or other systemic factors does the composition of the oral biotome have a disruption with the initial effect being an increase in the pH, persistence of which leads to demineralization. The origin,

progress or inhibition of dental caries are determined by the equilibrium status between protective factors, most of them being components of saliva (Ca^{2+}, phosphates, fluoride, protective proteins of the pellicle, saliva antibacterial components and external factors), and pathological factors (cariogenic bacteria, a dysfunction of the salivary glands, frequent consumption of carbohydrates). A preponderance of pathological factors results in the processes of demineralization and dental caries. The formation of the layer of microorganisms is a dynamic process. Adhesion, growth, removal and re-attachment constitute a continuous process and thus dental plaque microbiome undergoes a constant reorganization. This naturally-constructed biofilm consortia of bacteria may reach a thickness of 300–500 cells on the surface of the teeth. The surface of mature biofilm may release individual cells, which can then form a biofilm on other sites, teeth, tooth surfaces, gingival sulcus or transform into the planktonic form forming a source of formation for other sites[5].

More than half a century fluoride has become a symbol of preventive dentistry leading to a significant impact on dental caries. Though prevention plays a major role, the success lies in understanding the need to enhance the protective role and decrease the lacunae that can occur to increase the risk of dental caries. Though initially thought to remineralize the teeth the antibacterial effect by affecting the cellular functioning of the bacteria is now determined to be a major role in prevention. The judicious use and method of action must be studied and the knowledge of the antibacterial action must be made available to general practitioners.

CONCLUSION

The term “microbiome” is coined by Joshua Lederberg, a Nobel Prize laureate, to describe the ecological community of symbiotic, commensal and pathogenic microorganisms and these form the community of microbial residents. The oral microflora is a key to the maintenance of systemic health and though there may be a synergistic the control of the same is the first priority to maintain the state of health.

FINANCIAL SUPPORT AND SPONSORSHIP:

Nil

CONFLICTS OF INTEREST:

There are no conflicts of interest.

REFERENCES

1. Struzycka I. The oral microbiome in dental caries. Polish journal of microbiology. 2014;63(2):127-35.

2.Adler P. [Effect of protective, although atoxic fluoride content in drinking water on secondary dentition with special reference to cutting of molars]. Acta medica Academiae Scientiarum Hungaricae. 1951;2(2):349-60..

3.Lesher RJ, Bender GR, Marquis RE. Bacteriolytic action of fluoride ions. Antimicrobial agents and chemotherapy. 1977 Sep;12(3):339-45

4.Marquis RE. Antimicrobial actions of fluoride for oral bacteria. Canadian journal of microbiology. 1995 Nov;41(11):955-64.

5.Kilian M. The oral microbiome - friend or foe? European journal of oral sciences. 2018 Oct;126 Suppl 1:5-12.

6.Cephas KD, Kim J, Mathai RA, Barry KA, Dowd SE, Meline BS, et al. Comparative Analysis of Salivary Bacterial Microbiome Diversity in Edentulous Infants and Their Mothers or Primary Care Givers Using Pyrosequencing.

7.Breaker RR. New insight on the response of bacteria to fluoride. Caries research. 2012;46(1):78-81.

8.Sutton SV, Bender GR, Marquis RE. Fluoride inhibition of proton-translocating ATPases of oral bacteria. Infection and immunity. 1987 Nov;55(11):2597-603.

9.Marquis RE, Clock SA, Mota-Meira M. Fluoride and organic weak acids as modulators of microbial physiology. FEMS Microbiology Reviews. 2003;26(5):493-510.

10.Burgess JO, Vaghela PM. Silver Diamine Fluoride: A Successful Anticarious Solution with Limits. Advances in dental research. 2018 Feb;29(1):131-4.

11.Ahmed F, Prashanth ST, Sindhu K, Nayak A, Chaturvedi S. Antimicrobial efficacy of nanosilver and chitosan against Streptococcus mutans, as an ingredient of toothpaste formulation: An in vitro study. Journal of the Indian Society of Pedodontics and Preventive Dentistry. 2019 Jan-Mar;37(1):46-54.

12.Fancher ME, Fournier S, Townsend J, Lallier TE. Cytotoxic effects of silver diamine fluoride. American journal of dentistry. 2019 Jun;32(3):152-6.

13.Vasquez E, Zegarra G, Chirinos E, Castillo JL, Taves DR, Watson GE, et al. Short term serum pharmacokinetics of diammine silver fluoride after oral application. BMC oral health. 2012 Dec 31;12:60.

14.Yu OY, Zhao IS, Mei ML, Lo EC, Chu CH. Effect of Silver Nitrate and Sodium Fluoride with Tri-Calcium Phosphate on Streptococcus mutans and Demineralised Dentine. International journal of molecular sciences. 2018 Apr 25;19(5). PubMed PMID: 29693627.

15.Karched M, Ali D, Ngo H. In vivo antimicrobial activity of silver diammine fluoride on carious lesions in dentin. Journal of oral science. 2019 Mar 28;61(1):19-24

16.Jabin Z, Vishnupriya V, Agarwal N, Nasim I, Jain M, Sharma A. Effect of 38% silver diamine fluoride on control of dental caries in primary dentition: A Systematic review. Journal of family medicine and primary care. 2020 Mar;9(3):1302-7.

17.Santos VE, Jr., Vasconcelos Filho A, Targino AG, Flores MA, Galembeck A, Caldas AF, Jr., et al. A new "silver-bullet" to treat caries in children--nano silver fluoride: a

randomised clinical trial. Journal of dentistry. 2014 Aug;42(8):945-51.

18. Jafari K, Hekmatfar S, Fereydunzadeh M. In vitro Comparison of Antimicrobial Activity of Conventional Fluoride Varnishes Containing Xylitol and Casein Phosphopeptide-Amorphous Calcium Phosphate. Journal of International Society of Preventive & Community Dentistry. 2018 Jul-Aug;8(4):309-13..