International Journal Dental and Medical Sciences Research
Volume 6, Issue 4, July-Aug 2024 pp 375-381 www.ijdmsrjournal.com ISSN: 2582-6018

Silver Diamine Fluoride---A Double Edgedsword

Dr Somen Roychowdhury[1], Dr Mekala Divya[2], Dr Nilanjana Saha[3].

1.Professor, HODdepartment of pedodontics and preventive dentistry, Dr R Ahmed dental college and hospital. State:West Bengal, India, 8910329823, email: sroych1996@gmail.com.

2. Post graduate trainee, department of pedodontics and preventive dentistry, Dr R Ahmed dental college and hospital. State: West Bengal, India, 6303988870 email: drdivyamekala24@gmail.com.

3. Associate professor, department of dentistry, Deben Mahato medical college and hospital, Purulia, state: west Bengal, India, 9051268743, email: sroych1996@gmail.com.

Submitted: 15-08-2024 Accepted: 25-08-2024

ABSTRACT: Metallic silver was used in past for disinfecting & preserving drinking water. In metallic state silver is inert. In aqueous media silver is ionised. In its ionic state silver enters bacterial cells by endocytosis and causes membrane inactivation. Silver diamine fluoride[Ag (NH3)2F] has two pronged effect in the shape of antimicrobial effect of silver while caries arrest by fluoride.SDF is effective in carious lesion in primary teeth following the standards set by WHO mellenium goals. SDF causes mineralization of peritubular dentin and increases dentin microhardness.Due to ease of manipulation,controlling pain and infection, non-invasive process etc SDF is termed as silver bullet.SDF inactivates metalloproteinases responsible for collagen breakdown in caries process.38% SDF solution is effective in inactivating MMP2,MMP8 & MMP9.

Key words: SDF;silver ion;endocytosis; dentin microhardness;metalloproteinases;MMP2; MMP8; MMP9.

I. INTRODUCTION

Silver has been used in human healthcare and medicine since long. But, it is not usedfor any nutritional benifit. The physiological level is(< 2.3 μg/l) of silver, higher in individualssubjected to silver for long periods [1,2]. Water was preserved and disinfected for drinking using metallic silver .Silver pots were used for storing and drinkingwater by Alexander the Great (335 BC) whenhe used to go on his many campaigns[3,4]. Silver was used to preserve and disinfect water aboard the Apollo spacecraft [5], the MIR space station [9] and the NASA space shuttle [6-8].In the 1800s silver was used as an antiseptic for post surgical infections, in dentistry,wound therapy and medical devices.

Later penicillin, sulfonamide and mafenide antibiotics replaced silver and its compounds in most parts of the world for 40 years after the Second World War [10-12]. The emergence of resistant strain organisms such as Pseudomonas aeruginosa and methicillin resistant Staphylococcus aureus (MRSA) to penicillin and sulfonamide drugs led to the need for new antibi-otics. Moyer et al., is credited for introducing the use of silver nitrate in the 1960s [13]. Following this, silver sulfadiazine (SSD)in 1968 [14], was introduced,as efficacious for local application. SSD(Figure 1) has a broad spectrum ofantimicrobial action.Pure metallic silver is inert and reacts with human tissue or kill microorganisms onlyafter ionisation . Metallic silver ionises into silver ions in aqueous media and is bioactive in the form of Ag+

ion. Recent developments have shown that the presence of higher halide concentration with fewer Ag+ ions results in the formation of anionic silver complexes (AgX2 -, where X = Cl-), which are soluble inaqueous media and are bio-active [15]. Maratech Holdings reports in vivo experimental evidence for the antiviral properties of Ag4O4 [16,17]. The mechanism of action of antimicrobial effects of oxidation states of silver needs further investigation.

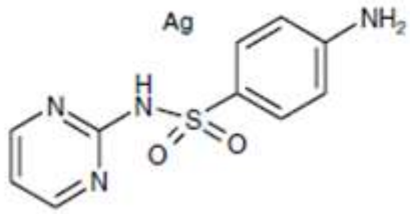

Figure 1 silver sulphadiazine.

In its metallic form, silver is inert and exhibits no biocidal action. But metallic silver ionizes in aqueous media or tissue fluids to release Ag or other biologically active ions. The ionised silverpossess a strong affinity for sulphydryl groups and protein residues on cell membranes. Silver at a very low concentration (1 ppm)possess antimicrobial property and is important for the widely known oligodynamic effect coined by von Naegeli in 1895.

Mode of antimicrobial action of silver in sensitive organisms are complex and not welldefined(fig. 2). Attachment of silver to cell membranes and endocytosis is an obligatory first step; silver attaches to negatively charged receptors, notably disulphide, amino, imidazole, carbonyl and phosphate residues on cell membranes resulting in intracellular absorption by endocytic vacuoles and phagocytosis. Intracellular absorption of silver paralyses membrane-related enzymes like phosphomannose isomerase which in turnmodifies the bacterial cell envelope and its efficacy of controling the inward diffusion of nutrients (e.g. phosphates, succinates) and interferes with outward passage of essential electrolytes and metabolites.

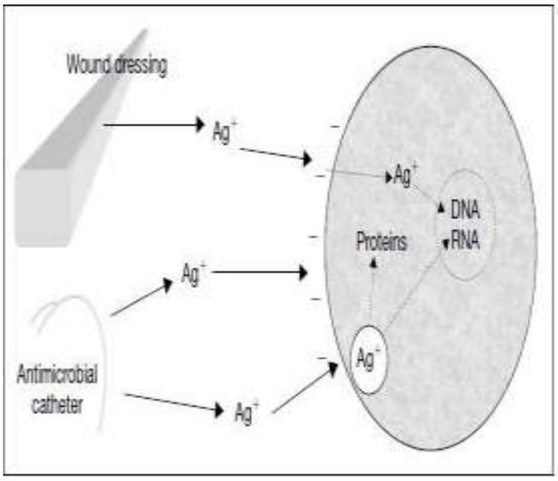

Figure 2 showing Ag+ (silver ion), invading bacterial cell membrane by endocytosis.

Membrane damage has been identified by pitting and increased permeability as a prelude to lethality. Principal intracellular effect of silver ion is possiblythe ability to paralyse key intracellular enzyme systems.The trace metals and electrolytes are inactivatedcausing defective respiratory pathways and RNA and DNA replication [18].

AgNO3 is used medically in eye drops to prevent infections in newborns, and in dentistry it is often used in stomatological treatments for mouth ulcers[19,20]. In 1969, silver diamine fluoride [F(NH3)2Ag] (SDF) solution was synthesized for dental treatments[21-23]. Since then, it has been used in Japan as Saforide R Solution for application to carious lesions due to its capacity as an antimicrobial agent and to stabilize caries processes, particularly in primary teeth, thanks to which it has an important role in pediatricdentistry[24,25]. SDF is a colorless solution which is used at 38-40%, pH 8-10. On contacting the caries surface it produces calcium fluoride (CaF2) and silver phosphate (Ag3PO4)[25]. The F:Ag ion ratio is 44,800:255,000 ppm[24,26,27].

II. CARIES PREVENTION IN PRIMARY TEETH

SDF has been observed as biocompatible and competent caries controlling compound as per the standards laid down by the WHO Millennium Goals and the US Institute[28].Arresting progression of carious lesion and occurrence of new lesions in primary teeth by SDF has been shown in clinical trials[29,30] and root caries in permanent teeth[31]. SDF is also capable of enhancing microhardness[32-34] and maturation of dentine shown in many laboratory studies.[33,35,36].

III. ACT FOR DISADVANTAGED COMMUNITY

Untreated dental caries is a global pandemic[37]. Dental caries remains untreated due to financial constraint,inadequate availability of oral care & expensive restorative treatment; this in turn is affecting average health, social life, and learning abilities of children of low income states [38]. Arresting Caries Treatment (ACT) has been adoptedfor combating unattended carious lesions in under privileged children [39]. Silver diamine fluoride (SDF), Ag(NH3)2F, has been in use to halt cariesas long as before 1969 [40,41]. 38% SDF (44,800 ppm F) applied once a year to carious deciduous anterior teeth of Chinese preschool children have been found to be significantly more successful in stopping progression of caries and preventing new caries than single applications of sodium fluoride varnish (22,600 ppm F) [42]. 38% SDF applicationbiyearly proved effective in stopping lesion progression andnew lesion in teeth of adolescent age groups of Cuban children over a three-year period [43].

Importance of silver diamine fluoride centers around its 5 presumed effects (Bedi and Sardo-Infirri, 1999)44: 1.control of pain and infection, 2.ease and simplicity of use (paint on), 3. affordability of material (pennies per application), 4.minimal requirement for personnel time and training (one minute, once per year), and the fact that 5.it is non-invasive. In this sense, SDF has the inherentspecific efficacy to be a "silver-fluoride bullet," simultaneously halting the cariogenic process and preventing caries.

International Journal Dental and Medical Sciences Research
Volume 6, Issue 4, July-Aug 2024 pp 375-381 www.ijdmsrjournal.com ISSN: 2582-6018

➢The caries preventive effects of SDFare emphasized in terms of the World Health Organization (WHO) Millennium Development 1.Goals for Health (Wagstaff and Claeson, 2004),45 and in particular the ➢2. oral health goals (Hobdell et al., 2003)46. These aims can be reachedby satisfying provision of a basic oral health package, consisting of: 1.emergency care, ➢2. prevention, and ➢. Costeffective interventions, in that order (Frencken et al., 2008)47

Silver diamine fluoride(SDF)was used in clinical trials to halt dentin caries and the results were prospective[48-50] in Children, specially fearful children of tender age, unable to cooperate for long and not very simple restorative procedures. There are various methods proposed to arrest dental caries in children, such as xylitol gum chewing and the use of fluoridated agents.

IV. ADVANTAGES OF SDF

As silver diamine fluoride is cost-effective and simple procedure it is given much importance in child dental patients. Reduced pain and infection,ease of manipulation,minimum cost,non-invasive technique and less time and training are the benefits of caries control with SDF. According to a systematic review the objective of millennium by WHO and United States Institute of Medicine's standard of 21 st century are satisfied by SDF [51].

V. REVIEW OF LITERATURE

According to studies infected dentin and affected dentin are distinct layers of carious dentin differ chemically as well as structurally. [52,53]. The superficialinfected layer harbouring bacteria whilethe inner affected dentine layer is softened by plaque acid but relatively less infected. Due to higher content of mineral salts this affected layer can be re-mineralised in favourable conditions [54].

Intertubular dentin hypercalcification and tubular occlusion results following treatment with SDF (Fig. 3). Microscopically sealing of tubules following SDF application results in reduced permeability(Fig. 4).Dentin under the SDF treated lesion appears normal while pulp shows inflammatory infiltrate and tertiary dentin formation (Fig. 5). Mei et al[55] showed silver phosphate formation and precipitation with SDF in patients with increased caries. Reduction in mineral loss from carious lesion occurs due to formation of protective layer of calcium fluoride,silver phosphate and silver with less soluble protein [55,56].

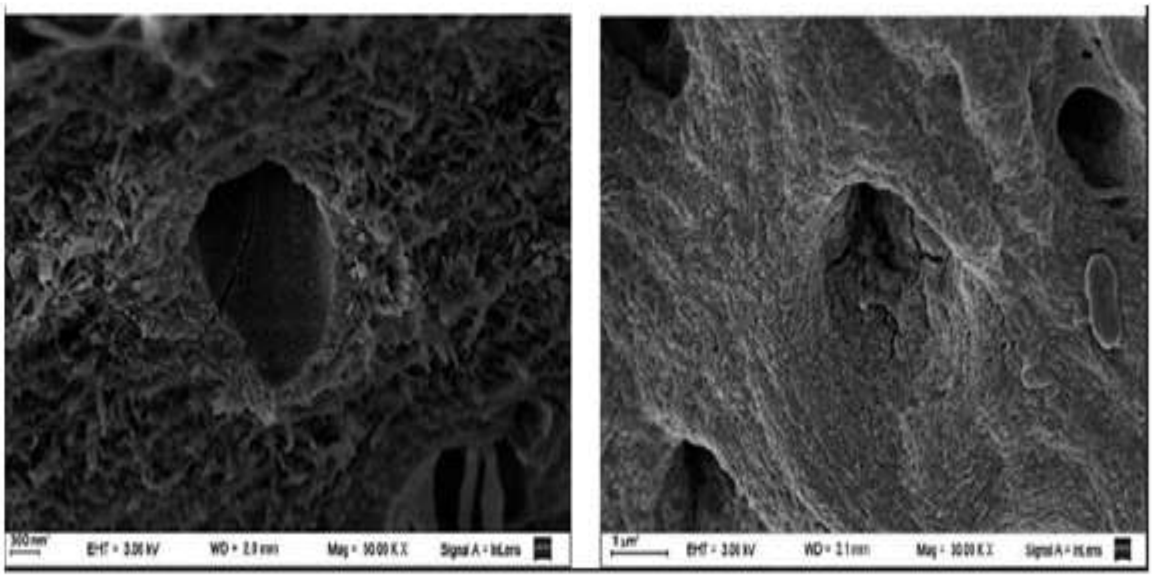

Figure 3: showing dentin structures before SDF application (left), and partially occluded tubules and hyper mineralized inter-tubular dentin following SDF application in SEM photograph (right)

International Journal Dental and Medical Sciences Research
Volume 6, Issue 4, July-Aug 2024 pp 375-381 www.ijdmsrjournal.com ISSN: 2582-6018

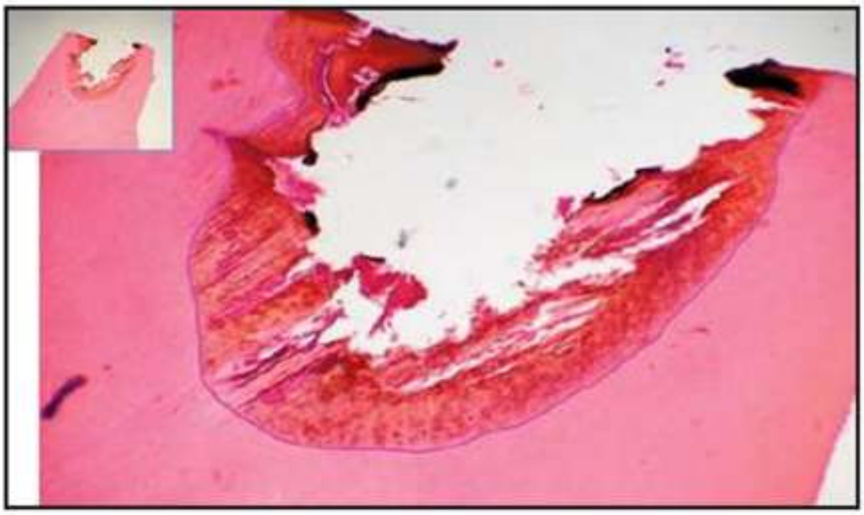

Figure 4: microscopical image of dental tissue following demineralization and staining, image showing deposits if silver in carious dentin, line of demarcation limits SDF – 100X enlargement.

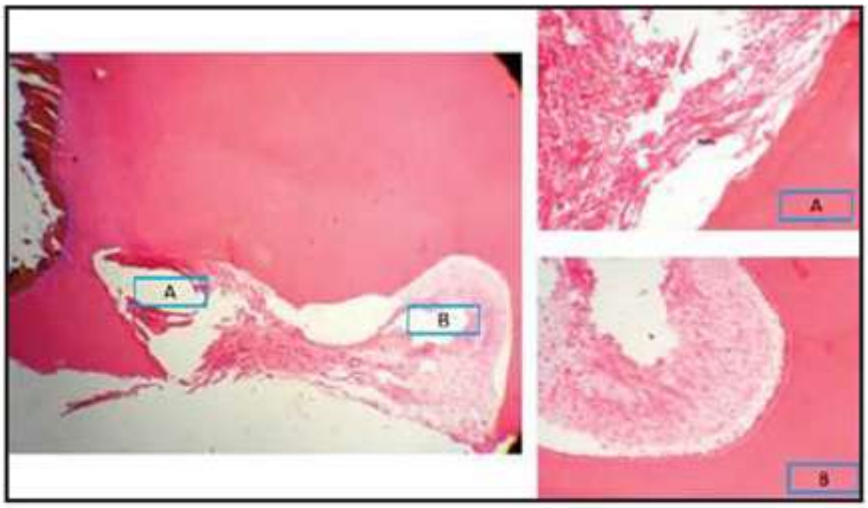

Figure 5: image showing histopathological tissue, following SDF application after demineralization and staining, affected pulp tissue in A(on left), on right higher resolution showing pulp inflammatory cells and fibroblasts,B is pulp with unaffected dentin, Pulpal circulation seen in higher resolution

38%SDF causes decrease in mineral loss from carious lesion as well as collagen destruction and thus stops lesion progression,Mei et al[55]. Besides, high concentration of silver and fluoride prevent growth of cariogenic bacteria in carious plaque---thus SDF acts as double-edged weapon against dental caries. SDF blocks metalloproteinases and prevents disintegration of collagen in caries, and thus protects against dentin disintegration. In vitro study by Mei et al[55]shows that SDF primarilyinteracts with hydroxyapatite of dentin andthe reaction product calcium fluoride prevents against caries. As microhardness dependson mineral content of dentin,changes due to SDF application may thus also be determined by microhardness.

VI. POSSIBLE MECHANISM OF ACTION OF SDF IN CARIES INHIBITION

Caries progression is a factor of decalcification of hydroxyapatite and destruction of collagen matrix. collagenases,microbial enzymescause destruction of organic matrix.Critical role of metalloproteinases in dentin disintegration has been found in different contemporary studies[57].Matrix metalloproteinase’s ormatrixinsare calcium - dependent zinc containing endopeptidases[58]. Characteristically MMP is made up of predomain, prodomain, hinge, catalytic domain and hemopexin domain.An eighty aminoacid compound predomain is attached to prodomain.MMPs are inactive zymogens,have cysteine lock present in prodomain prevents their intracellular activation[59].MMPs can be activated by proteinases[57],chemical agents and,in caries state by acidic pH of the environment.Prodomain is connected with the catalytic domain by a hinge and the catalytic domain holds an active Zn-cystine binding site. The activation of MMP occurs by breaking Zn cysteine interaction[58].One fibronectin domain present in MMP-2(gelatinaseA)and MMP 9(gelatinaseB), has a strong affinity forgelatin.The catalytic domain is connected to the hemopexin domain.The hemopexin domain of MMP-2 and MMP-9 activates the tissue inhibitor enzymes formetalloproteinases[59]. Disintegration of extracellular collagen matrix is mediated by MMPs in presence of zinc ion(Zn2+) which acts as a cofactor[57]. In health MMPs are present in dentin matrix[60,61]or in saliva[62].Action of MMPs is stimulated in low pH environment namely lactate release by causative bacteria[57].MMP 8(neutrophil collagenase)is capable of degrading triple helical fibrillar collagens into distinctive ¾ and ¼ fragments.MMP-2 and MMP-9 are gelatinase,which cause breakdown of typeIV collagen.Collagenolysis is an integral part of dentin caries during which stimulation of MMP-2,MMP-8 and MMP-9 has been shown to have a crucial role [57].So inactivation of MMPs is an important mechanism of caries arrest.

VII. CONCLUSION:

38% SDF has highest efficacy in inactivating effect on MMP2,MMP8 and MMP9.Comparative to silver nitrate(AgNO3) and sodium fluoride(NaF) SDF possess greater inhibition on MMPs. Thus success of 38% of SDF in causing caries arrest is attributed to its inhibition on MMPs in clinical trials.

REFERENCES:

[1]. WAN AT, CONYERS RA, COOMBS CJ, MASTERTON JP: Determination of silver in blood, urine, and tissues of volunteers and burn patients. Clin. Chem. (1991) 37(10):1683-1687.
[2]. LANSDOWN AB: Physiological and toxicological changes in the skin resulting from the action and interaction of metal ions. Crit. Rev. Toxicol. (1995) 25(5):397-462.
[3]. WHITE RJ: An historical overview on the use of silver in modern wound management. Br. J. Nurs. (2002) 15(10):3-8.
[4]. RUSSELL AD, PATH FR, HUGO WB: Antimicrobial activity and action of silver. Prog. Med. Chem. (1994) 31:351-370.
[5]. ALBRIGHT CF, NACHUM R, LECHTMAN MD: Electrolytic silver ion generator for water sterilization in Apollo spacecraft water systems. Apollo applications program. NASA Contract Rep. (1967).
[6]. http://www.sti.nasa.gov/tto/Spinoff2004/er_1.html Water treatment systems make a big splash.
[7]. http://www.carefreeclearwater.com/ewp.html Electronic water purifier.
[8]. http://www.water-technology.net/contractors/disinfection/cavion/ CAVion Water Systems.
[9]. CONRAND AH, TRAMP CR, LONG CJ, WELLS DC, PAULSEN AQ, CONRAND GW: Ag+ alters cell growth, neurite extension, cardiomyocyte beating, and fertilized egg constriction. Aviat. Space Environ. Med. (1999) 70(11):1096-1105.
[10]. LANSDOWN AB: Silver I: its antibacterial properties and mechanism of action. J. Wound Care (2002) 2(4):125-130.
[11]. KLASEN HJ: Historical review of the use of silver in the treatment of burns. I. Early uses. Burns (2000) 26(2):117-130.
[12]. KLASEN HJ: A historical review of the use of silver in the treatment of burns. II. Renewed interest for silver. Burns (2000) 26:131-138.
[13]. MOYER CA, BRENTANO L, GRAVENS DL, MARGRAF HW, MONAFO WW: Treatment of large human burns with 0.5% silver nitrate solution. Arch. Surg. (1965) 90:812-867.
[14]. FOX CL: Silver sulphadiazine: a new topical therapy for pseudomonas in burns. Arch. Surg. (1968) 96:184-188.
[15]. GUPTA A, MAYNES M, SILVER S: The effect of halides on plasmid silver resistance in Escherichia coli. Appl. Environ. Microbiol.(1998) 64(12):5042-5045.
[16]. MARATECH HOLDING LLC: WO0149301 (2001).
[17]. MARATECH HOLDING LLC: WO0149302 (2001).cherichia coli. Appl. Environ. Microbiol. (1998) 64(12):5042-5045.

[18]. Lansdown ABG: A review of the use of silver in wound dressings: facts and fallacies. Br J Nurs 2004;13(suppl):S6–S13.
[19]. Rosenblatt A, Stamford TC, Niederman R. Silver Diamine Fluoride: A Caries “SilverFluoride Bullet”. J Dent Res 2009; 88:11625.
[20]. Mei ML, Ito L, Cao Y, Li Q, Chu CH, Lo EC. The inhibitory effects of silver diamine fluoride on cysteine cathepsins. J Dent 2014; 42:329335.
[21]. Yamaga R, Nishino M, Yoshida S, Yokomizo I. Diammine silver fluoride and its clinical application. J Osaka Univ Dent Sch 1972; 12:120.
[22]. Fung M, Wong M, Lo EC, Chu CH. Arresting Early Childhood Caries with Silver Diamine FluorideA Literature Review. Oral Hyg Health 2013; 1:117. doi: 10.4172/23320702.1000117
[23]. VinodB M, Koppolu M, Nuvulla S, Thangala V, RedderuK R. Antimicrobial efficiency of silver diamine fluoride as an endodontic medicament An ex vivo study. Contemp Clin Dent 2012; 3:262264.
[24]. Chu CH, Lo EC, Lin HC. Effectiveness of silver diamine fluoride and sodium fluoride varnish in arresting dentin caries in Chinese preschool children. J Dent Res 2002; 81:767770.
[25]. Llodra JC, Rodriguez A, Ferrer B, Menardia V, Ramos T, Morato M. Efficiency of silver diamine fluoride for caries reduction in primary teeth and first permanent molars of school children: 36month clinical trial. J Dent Res 2005; 84:721724.
[26]. Vasquez E, Zegarra G, Chirinos E, Castillo J, et al. Short term serum pharmacokinetics of diammine silver fluoride after oral application. BMC Oral Health 2012; 12:60.
[27]. Mei ML, Li Q, Chun CH, Lo EC, Samaranayake LP. Antibacterial effects of silver diamine fluoride on multispecies cariogenic biofilm on caries. Ann Clin MicrobiolAntimicrob 2013; 12:17.
[28]. Rosenblatt A, Stamford TC, Niederman R. Silver diamine fluoride: a caries ‘‘silver-fluoride bullet’’. Journal of Dental Research 2009;88:116–25.
[29]. Llodra JC, Rodriguez A, Ferrer B, Menardia V, Ramos T, Morato M. Efficacy of silver diamine fluoride for caries reduction in primary teeth and first permanent molars of schoolchildren: 36-month clinical trial. Journal of Dental Research 2005;84:721–4.
[30]. Chu CH, Lo EC, Lin HC. Effectiveness of silver diamine fluoride and sodium fluoride varnish in arresting dentin caries in Chinese pre-school children. Journal of Dental Research 2002;81:767–70.
[31]. Tan HP, Lo EC, Dyson JE, Luo Y, Corbet EF. A randomized trial on root caries prevention in elders. Journal of Dental Research 2010;89:1086–90.
[32]. Liu BY, Lo EC, Li CM. Effect of silver and fluoride ions on enamel demineralization: a quantitative study using micro-computed tomography. Australian Dental Journal 2012;57:65– 70.
[33]. Chu CH, Mei L, Seneviratne CJ, Lo EC. Effects of silver diamine fluoride on dentine carious lesions induced by Streptococcus mutans and Actinomyces naeslundii biofilms. International Journal of Paediatric Dentistry 2012;22:2–10.
[34]. Chu CH, Lo EC. Microhardness of dentine in primary teeth after topical fluoride applications. Journal of Dentistry 2008;36:387–91.
[35]. Lou YL, Botelho MG, Darvell BW. Reaction of silver diamine [corrected] fluoride with hydroxyapatite and protein. Journal of Dentistry 2011;39:612–8.
[36]. Mei ML, Li QL, Chu CH, Lo EC, Samaranayake LP. Antibacterial effects of silver diamine fluoride on multi-species cariogenic biofilm on caries. Annals of Clinical Microbiology and Antimicrobials 20
[37]. Edelstein BL (2006). The dental caries pandemic and disparities problem. BMC Oral Health 6(Suppl 1):2.
[38]. Baelum V, van Palenstein Helderman W, Hugoson A, Yee R, Fejerskov O (2007). A global perspective on changes in the burden of caries and periodontitis: implications for dentistry. J Oral Rehabil34:872-906.
[39]. Bedi R, Sardo-Infirri J (1999). The root cause–a proposal for action. London, UK: FDI World Dental Press Ltd.
[40]. Nishino M, Yoshida S (1969). Clinical effects of diamine silver fluoride on caries and on pulp of deciduous teeth [in Japanese]. Jpn J Pedodont7:55-59.
[41]. Nishino M, Yoshida S, Sobue S, Kato J, Nishida M (1969). Effect of topically applied ammoniacal silver fluoride on

dental caries in children. J Osaka Univ Dent Sch 9:149-155.

[42]. Lo EC, Chu CH, Lin HC (2001). A community-based caries control program for pre-school children using topical fluorides: 18-month results. J Dent Res 80:2071-2074.

[43]. Llodra JC, Rodriguez A, Ferrer B, Menardia V, Ramos T, Morato M (2005). Efficacy of silver diamine fluoride for caries reduction in primary teeth and first permanent molars of schoolchildren: 36-month clinical trial. J Dent Res 84:721-724.

[44]. Bedi R, Sardo-Infirri J (1999). Oral health care in disadvantaged communities. London: FDI World Dental Press.

[45]. Wagstaff A, Claeson M (2004). The millennium development goals for health. Rising to the challenges. Washington, DC: The World Bank.

[46]. Hobdell M, Petersen PE, Clarkson J, Johnson N (2003). Global goals for oral health 2020. Int Dent J 53:285-288.

[47]. .Frencken JE, Holmgren CJ, Helderman WHvP (2008). Basic package of oral care. The Netherlands: WHO Collaborating Centre, College of Dental Science, University of Nijmegen.

[48]. Chu CH, Lo EC, Lin HC. Effectiveness of silver diamine fluoride and sodium fluoride varnish in arresting dentin caries in Chinese pre-school children. Journal of Dental Research 2002;81:767–70.

[49]. Lo EC, Chu CH, Lin HC. A community-based caries control program for pre-school children using topical fluorides: 18-month results. Journal of Dental Research 2001;80: 2071–4.

[50]. Yee R, Holmgren C, Mulder J, Lama D, Walker D, van Palenstein Helderman W. Efficacy of silver diamine fluoride for Arresting Caries Treatment. Journal of Dental Research 2009;88:644–7.pg-4 bottom

[51]. Rosenblatt A, Stamford TC, Niederman R (2009) Silver diamine fluoride: a caries “silver-fluoride bullet”. J Dent Res 88: 116-125

[52]. Daculsi G, LeGeros RZ, Jean A, Kerebel B (1987) Possible physico-chemical processes in human dentin caries. J Dent Res 66: 1356-1359.

[53]. Fusayama T (1979) Two layers of carious dentin; diagnosis and treatment. Oper Dent 4: 63-70.

[54]. ten Cate JM (2001) Remineralization of caries lesions extending into dentin. J Dent Res 80: 1407-1411.

[55]. Mei ML, Li Q, Chun CH, Lo EC, Samaranayake LP. Antibacterial effects of silver diamine fluoride on multispecies cariogenic biofilm on caries. Ann Clin MicrobiolAntimicrob 2013; 12:17.

[56]. Chu CH, Lo EC. Promoting caries arrest in children with silver diamine fluoride: a review. Oral Health Prev Dent 2008; 6:315321.REST OF PG 5

[57]. Chaussain-Miller C, Fioretti F, Goldberg M, Menashi S. The role of matrix metalloproteinases (MMPs) in human caries. Journal of Dental Research 2006;85:22–32.

[58]. Souza AP, Gerlach RF, Line SR. Inhibition of human gelatinases by metals released from dental amalgam. Biomaterials 2001;22:2025–30.

[59]. Leonard JD, Lin F, Milla ME. Chaperone-like properties of the prodomain of TNFa-converting enzyme (TACE) and the functional role of its cysteine switch. Biochemical Journal 2005;387:797–805.

[60]. Martin-De Las Heras S, Valenzuela A, Overall CM. The matrix metalloproteinase gelatinase A in human dentine. Archives of Oral Biology 2000;45:757–65.

[61]. Pashley DH, Tay FR, Yiu C, Hashimoto M, Breschi L, Carvalho RM. Collagen degradation by host-derived enzymes during aging. Journal of Dental Research 2004;83:216–21.

[62]. Lo EC, Chu CH, Lin HC. A community-based caries control program for pre-school children using topical fluorides: 18-month results. Journal of Dental Research 2001;80: 2071–4. PG 9