Review Article

JRAD Journal of Research and Advancement in Dentistry

J Res Adv Dent 2018;8:1:265-272.

Root Biomodification: A Controversial Modality

Niraj Motwani[1*] Mahak Gera[2] Khushboo Motwani[3]

[1]Reader, Department of Periodontology and Oral Implantology, Ahmedabad Dental College, Ahmedabad, Gujarat, India.
[2]Private Consultant, Department of Periodontology and Oral Implantology, Delhi, India.
[3]Private Consultant, Rajkot, Gujarat, India.

ABSTRACT

Background: Destruction of tooth supporting tissues occur in Periodontitis. Repair and regeneration of periodontium is a major goal in the treatment of periodontal disease. An important consideration in periodontal regeneration is the root surface which has been exposed to the oral environment because of Periodontitis. For regeneration to occur, the root surface must act as wound margins and should provide an appropriate bed for attachment of cells and development of fibres. The oldest and most frequently attempted type of regeneration is biomodification of root surfaces. Differing results from various clinical and histological studies have created controversial issues about the effectiveness of root biomodification. This review attempts to provide a basic idea about the present scenario of biomodification of root surfaces in clinical conditions along with an overview of related studies.

Keywords: Periodontitis, Root conditioning, Citric acid, EDTA, Tetracycline, Laser.

INTRODUCTION

An inflammatory condition induced because of plaque thereby involving and destroying the supporting alveolar bone and periodontal ligament is Periodontitis. It causes pathological alteration of the periodontium thereby leading to loss of attachment to the tooth, apical migration of the junctional epithelium along the root surface and loss of supporting alveolar bone.

The Root surface alterations are Cytotoxic changes thereby causing Endotoxins to penetrate deep into the dentin, Chemical changes leading to Increased mineral content and Structural changes which include areas of increased mineralization, presence of pathologic granules and areas of demineralization.

One of the major targets of periodontal treatment is formation of new connective tissue on to the root surface which is denuded by periodontal disease. This type of regeneration is reffered as New attachment which is defined as embedding of new periodontal ligament fibers on to the newly formed cementum which is previously denuded by periodontal disease. Thus, the challenge of regeneration is to reconstitute this whole complex onto the root surface.

Therefore the ultimate goal of the periodontal treatment seeks to preserve the teeth in relatively good health, thereby meeting the expectations of the patient. To achieve this, periodontal therapy mainly aims at suppressing the progression of such events thereby maintaining the long term prognosis of periodontium.[1]

RATIONALE

The rationale for developing a root surface which is biologically compatible has emerged as a consequence of structural and biochemical damage following exposure of root surface to the oral cavity because of periodontal disease.[2] These alterations on the root surface include reduction in insertion of collagen fiber, altered level of minerals their surface composition and contamination of root surface by bacteria and their endotoxins.[3-7]

Received: Feb. 10, 2018**: Accepted**: Mar. 6, 2018
***Correspondence Dr. Niraj Motwani.**
Department of Periodontology and Oral Implantology, Ahmedabad Dental College, Ahmedabad, Gujarat, India.
Email: nirajmotwani@yahoo.com

pISSN 2278-0076
eISSN 2321-9270

According to an experiment conducted by Polson and Caton in 1982, they concluded that Hence it was concluded that pathologically exposed root surface rather than a diseased periodontium precluded periodontal regeneration.[8]

Concept of Biochemical modification or root surface alteration, also referred to as Root Conditioning**,** has emerged as a potential therapeutic approach thereby leading to the reconstruction of periodontal complex.

Mechanical instrumentation (scaling and root planing) leads to the formation of a smear layer, which affects cell reattachment of cells and serves as a reservoir for the growth of microbes.[9] Therefore, conditioning of the roots is done so as to remove the smear layer and improve its biocompatibility. After the smear-layer is removed, the dentinal collagen fibres are exposed and they are considered to be a chemo-attractant for periodontal fibroblasts.[10] The mechanism of action of these conditioning agents on the root surface is not very well elaborated, but it has been hypothesized that these demineralizing agents act by exposing the collagen fibers within the root matrix thereby leading to attachment and/or by decontaminating the root surface via complete removal of endotoxins and bacteria, and/or by elimination of the root debris thus allowing the attachment of regenerative cells to the root surface.[11] The rationale for this approach was that, for regeneration of connective tissue attachment to a periodontitis affected root surface to occur, migration and attachment of connective tissue cells to the root surface was essential.[12]

HISTORICAL BACKGROUND

The concept of root biomodification was first introduced in the 1800s for the treatment of periodontal disease as a substitute for scaling and calculus removal.[13] Also, acid treatment was used for the removal of hypermineralized cementum and to assist in pocket eradication.[14-17] Early histological studies in 1952 by Box suggested that the use of a citric acid-antiformin combination resulted in new attachment to the root surface, primarily by facilitating removal of epithelium.[18] Urist demonstrated in a series of experiments that following partial or total demineralization with 0.6 N HCl and its transplantation in vivo in various animal models, allogeneic dentin matrix led to the formation of new bone or cementum on the implant surface.[19-22] It was suggested that dentin matrix contained a series of proteins (bone morphogenetic protein) which had the capability so as to lead to differentiation of cells. Register investigated whether new attachment, cementogenesis and osteogenesis can occur adjacent to tooth roots which were demineralized in vivo.[23] The acids tested were phosphoric, hydrochloric, lactic, formic, citric and trichloroacetic acid. New connective tissue attachment and cementogenesis occurred when roots were demineralized with citric acid at a pH 1.0 for 2-3 min.

It has been shown that acid demineralization of the instrumented root surface with citric acid and phosphoric acid effectively removed the smear layer resulting from instrumentation of the root surface, exposed and enlarged the openings of dentinal tubules, exposed the collagen matrix of the root dentin and demineralized the intertubular dentin surface.[24,25]

METHODS OF ROOT CONDITIONING

Various methods of root conditioning include mechanical methods, chemical methods, growth factors and lasers.[26]

Mechanical methods : It includes Root planing which is a process by which residual embedded calculus and fragments of cementum are removed from the roots so as to produce a smooth, hard and a clean surface.[26]

Chemical methods : Various chemicals have been applied on root surfaces to remove the smear layer, thereby helping in healing and further improving clinical results.

Growth factors : They have been applied on root surface so as to enhance periodontal regeneration.

Lasers : They too have been used to remove smear layer from the root surface.

The root surface biomodification agents are broadly classified as :

1. Root conditioners : Citric acid, Tetracycline HCl, EDTA, Fibronectin, Laminin, Doxycycline, Minocycline, Chlorhexidine, Polyacrylic acid, ,

Formaline, , Hydrogen peroxide, Sodium deoxy cholate, Cohnns factor, Phosphoric acid, Bile salts and plasma fractions.
2. Enamel matrix proteins
3. Recombinant human growth factors
4. Platelet rich plasma
4. Hyaluronic Acid

6. Lasers

1. **CITRIC ACID:** Citric acid was used for smear layer removal by Register and has been studied widely.[27] It contains two or more groups within its molecule which combine with calcium thereby acting as a chelating agent. It can also participate in surface exchange; with citric ions in the hydroxyapatite crystals. It acts on dentinal hydroxyapatite by releasing hydrogen ions which demineralizes the crystalline structure.[28] The depth of demineralization of dentin with citric acid for 2-4 minutes is 3-12 μm.

The recommended technique for the application of citric acid by Register and Burdick is Raise a mucoperiosteal flap, Instrument the root surface by removing calculus & underlining cementum, Apply cotton pledgets soaked in a saturated solution of citric acid 20-30% concentration ph 1 for 2-3 min, Remove pledgets. Irrigate the root surface profusely with saline, Replace the flap & suture it.[29]

Register reported when citric acid was applied on the root surfaces (pH 1.0) for 2-3 minutes using a rubbing pressur, it led to the collagen fibers reattachment to the previously denuded root.[30] It resulted in a complete removal of smear layer thereby exposing smoother root dentin surface with wider dentinal tubule openings (flared or funnel shaped) up to 8.88 μm.[31,32] A few histological studies were conducted so as to determine regeneration when citric acid was applied on to the root surfaces. The pH of citric acid was between 1-3, and the duration of application was 2-5 minutes. The results demonstrated regeneration of connective tissue (1.2-2.1 mm) following acid treatment. A contrasting study was done on monkey models to determine that application of citric acid did not promote formation of new cementum and connective tissue. It was seen when citric acid with a pH of 1was applied to the root surface for 3 minutes after SRP, it led to the demineralization of the root surface, opening of the dentinal tubules and exposure of collagen fibres. When SRP alone was done, smear layer was left along with scattered islands of cementum and no collagen fibres or exposed dentinal tubules.[33]

Animal studies have shown Root resorption and ankylosis following citric acid demineralization. Because of its Acidic Ph it has an unfavorable healing response.[11]

2. TETRACYCLINE HYDROCHLORIDE: It is a Broad spectrum antimicrobial. Tetracycline has a low pH (1-2) in concentrated solution, acts as a calcium chelator. It Removes smear layer, leads to Demineralization of dentin, Exposes collagen matrix --- Uncovers and widens dentinal tubules, Increases the binding of matrix proteins to dentin, increased attachment to fibronectin hence stimulates fibroblast attachment & growth. It has a property of Substantivity & Antimicrobial activity --- 14 days. It Inhibits neutrophil collagenase & bone resorption.

It also has an indirect relation to regeneration. When low pH tetracycline is applied, it increases fibronectin and other extracellular matrix glycoprotein binding to the root surface, thereby increasing the attachment and growth of fibroblast on the root surface. At the same time it downregulates the growth and proliferation of epithelial cells. Tetracycline hydrochloride leads to sustained release from root surface for 48 hours and up to 14 days, which provides its antibacterial properties during healing period.[34] It was seen that when10 or 100 mg/ml of tetracycline were used, they were sufficiently concentrated so as to lead to the removal of smear layer thereby exposing dentinal tubules.[35] The application time suggested is 2-3 minutes because if etching was done for more than 3 minutes, it had shown to impair periodontal healing.[36,37]

3. **ETHYLENE-DIAMINE-TETRA-ACETICACID (EDTA):** It is Chelating agent, forms a solution that chelates divalent cations such as Ca ions, Softens root surface, Removes smear layer, leads to Partial demineralization upto 20 to 30 microns in 5 min (conc. 8%). It works at a neutral pH thereby preserving the integrity of collagen fibres, early cell colonization & fibrous wound healing. Studies have shown that when EDTA in the concentration of 18% was used on root surface, it improves attachment and migration of fibroblasts on the root

surface thereby facilitating development of an oriented fiber attachment system between the demineralized surfaces.[38,39] A contrasting study was done where when 24% of EDTA (pH 7.07.2) was used for 23 minutes on the root surfaces, it showed absolutely no difference in clinical attachment level, probing depth and probing bone levels between EDTA treatment and control root surfaces.[40,41]

4. FIBRONECTIN: A glycoprotein found on the surface of the cells, plasma, extracellular matrix and in the basement membrane. It Promotes at ntachment of cell to one another, to extra-cellular matrix and collagen, a Chemo-attractant for fibroblasts and PDL cells and Enhances cell proliferation from PDL into supracrestal region. The optimum concentration has been shown to be 0.38mg/ml saline. Smith et al determined healing after periodontal flap surgery in dogs and reported the effect of citric acid and fibronectin on dogs. Results showed significant increase in new connective tissue attachment in all surgical sites where fibronectin had been applied.[42]

5. LAMININ : A glycoprotein of high molecular weight that Promotes gingival epithelial chemotaxis, movement of gingival fibroblasts from confluent cultures to dentin. Laminin also promotes growth and adhesion of epithelial cells to tetracycline and glycoprotein conditioned surfaces. The affinity of laminin and fibronectin is different for mineralized surface. A mineralized surface attract laminin which favours epithelial proliferation whereas a demineralized surface leads to the attraction of fibronectin and favour fibroblastic proliferation.[43]

6. DOXYCYCLINE : When it is topically applied on root surfaces in vitro it shows high substantivity and total exposure of dentin. Topical application of doxycycline (100 mg/ml) shows inhibition zones with microorganisms at all time intervals.

7. ENAMEL MATRIX DERIVATIVE : Amelogenins are secreted by Hertwigs epithelial root sheath during tooth development and induce acellular cementum formation. It is a Viscous gel obtained by mixing 1 ml of a vehicle solution with the powder and apply with the syringe into the site.

8. GROWTH FACTORS : These are natural biologic mediators, polypeptide molecules released by the cells in inflamed area. Various growth factors which contribute to periodontal regeneration include the platelet derived growth factor (PDGF), epidermal growth factor (EGF), insulin like growth factor (IGF), fibroblast growth factor (FGF), transforming growth factor (TGF), bone morphogenetic protein (BMP). These growth factors lead to the proliferation and attachment of fibroblasts from the periodontal ligament thereby favouring bone formation. An investigation was done so as to determine the effect of human platelet derived growth factor- BB on attachment of periodontal ligament cells on root surfaces. The results demonstrated that the combination of citric acid with platelet derived growth factor-BB showed better results on proliferation and attachment of periodontal cells than EDTA and tetracycline hydrochloride.[44] Hence it has an important role in the healing and regeneration of periodontal tissues.[45]

9. BONE MORPHOGENETIC PROTEINS : They form a unique family within the transforming growth factor beta (TGF-β) superfamily of proteins which play an important role in bone formation. BMPs are involved in morphogenesis and organogenesis. It has the ability to convert connective tissue cells into osteoprogenitor cells and is the only morphogen of all growth factors. BMP-2, 3 and 7 have been identified in cementoblasts, periodontal ligament and alveolar bone.

10. SODIUM DEOXYCHOLATE WITH COHN'S FRACTION IV : These agents dissociate endotoxin into subunits & detoxify the diseased root surfaces thereby increasing connective tissue attachment.

11. LASERS: Lasers have been studied for their effect on root surface as well as for their effects on the behaviour on periodontal ligament cells.[46-48] One of the studies concluded that when CO_2 and Er:YAG laser were used together at the determined power settings, they can treat dentin hypersensitivity significantly. However, the Er:YAG laser leads to less thermal damage on tubular occlusion thereby acting as a useful conditioning tool under such conditions.[49]

12. MTAD : It was originally developed as a final irrigant for endodontics for the removal of intracanal smear layer created during endodontic preparation. MTAD is a mixture of doxycycline (a

tetracycline isomer), citric acid and polysorbate 80 (a detergent).

13. HYALURONIC ACID (HA) : HA is an integral constituent of periodontal ligament matrix and helps in cell adhesion, differentiation and migration with the help of cell-surface receptors such as CD44 and HA binding proteins.[50] Gengigel® (Ricerfarma, Milano, Italy) in a concentration of 0.2% contains high molecular weight molecules of HA (gel form) so as to treat plaque-induced gingivitis when used as an adjunct to SRP[51]. Hyaluronan also leads to the production of proinflammatory cytokines by various cells thereby leading to inflammatory response and consequently helps in stimulating hyaluronan synthesis by endothelial cells.[52]

LIMITATIONS OF CHEMICAL SUBSTANCES :

- May give rise to secondary endodontic involvement via dentinal tubules
- Depth of action is not controlled
- Increased size of dentinal tubules -- more penetration of micro-organism
- Root caries
- Chemicals may infavourably alter the morphology of collagen

CURRENT STATUS OF ROOT BIOMODIFICATION AGENTS IN REGENERATION :

Out of 63 studies (1966-2014), only 20 reported evidence of regeneration for citric acid, EDTA, tetracycline, fibronectin, Growth factors, sodium deoxycholate, lasers and human plasma fraction COHN IV hardly showed any role in regeneration. The application of root biomodification agents such as citric acid, enzyme lysozyme, EDTA, tetracycline hydrochloride, fibronectin, lasers, laminin, EDTA, sodium deoxycholate, growth factors provide no or minimal clinical benefit in regard to gain in clinical attachment levels or reduction in probing pocket depths. Thus, the role of these demineralising agents in regard to regeneration is still unpredictable and questionable.[53]

CONCLUSION

Current information strongly indicates a role for root surface demineralisation to enhance wound healing. Periodontal diseased root surface doesn't favour regeneration of periodontium due to its surface characteristics. Demineralisation has been shown to alter the diseased root surface thereby creating a better surface that can promote wound healing. Evidence does not support the use of citric acid, EDTA, tetracycline to reduce probing depth or to enhance clinical attachment levels.[54] They may have a role in detoxification and removal of smear layer but this too has been proved only in *in-vitro* and animal studies.[26] Therefore further evidence needs to be collected so as to support and prove the concept of root surface demineralization.

REFERENCES

1. Alpiste Illueca FM, Buitrago Vera P, Feunmayor Fernandez V, Gil Loscos FJ. Periodontal regeneration in clinical practice. Med Oral Patol Oral Cir Bucal 2006;11:382-92.

2. Selvig KA. Biological changes at the tooth-saliva interface in periodontal disease. J Dent Res 1969;48:846-55.

3. Selvig KA, Hals E. Periodontally diseased cementum studied by correlated microradiography, electron probe analysis and electron microscopy. J Periodont Res 1977;12:419-29.

4. Selvig KA, Zander HA. Chemical analysis and microradiography of cementum and dentin from periodontally diseased human teeth. J Periodontol 1962;33:303-10.

5. Adriaens PA, Edwards CA, DeBoever JA, Loesche WJ. Ultrastructural observations on bacterial invasion in cementum and radicular dentin of periodontally diseased human teeth. J Periodontol 1988;59:493-503.

6. Aleo JJ, DeRenzis FA, Farber PA, Varboncoeur AP. The presence of biologic activity of cementum-bound endotoxin. J Periodontol 1974;45:672-5.

7. Hatfield CG, Baumhammers A. Cytotoxic effects of periodontally involved surfaces of human teeth. Arch Oral Biol 1971;16:465-8.

8. Polson AM, Caton J. Factors influencing periodontal repair and regeneration. J Periodontol 1982:53:617-25.

9. Mariotti A. Efficacy of chemical root surface modifiers in the treatment of periodontal disease. A systematic review. Ann Periodontol 2003;8:205-26.

10. Boyko GA, Brunett DM, Melcher AH. Cell attachment to demineralized root surfaces in vitro. J Periodontal Res 1980;15:297-03.

11. Blomlof JP, Blomlof LB, Lindskog SF. Smear removal and collagen exposure after non-surgical root planing followed by etching with an EDTA gel preparation. J Periodontol 1996;67:841-5.

12. Polson AM, Frederick GT, Ladenheim S, Hanes PJ. The production of a root surface smear layer by instrumentation and its removal by citric acid. J Periodontol1984;55:443-6.

13. Register AA. Bone and cementum induction by dentin, demineralized in situ. J Periodontol 1973;44:49-54.

14. Stewart HT. Partial removal of cementum and decalcifi- cation of tooth in treatment of pyorrhea alveolaris. Dent Cosmos 1895;41:617-26.

15. Younger WJ. Some of the latest phases in implantation and other operations. Dent Cosmos 1893;35:102-108.

16. Box KF. Concerning the role of antiformin-citric acid in pocket treatment. J Ont Dent Assoc 1952;29:437-439.

17. Marshall JS. A remarkable case of pyorrhea alveolaris, with reproduction of bone, occurring in practice of Dr. Allport. JAMA 1883;1:641-43.

18. Urist MR, lwata H. Preservation and biodegradation of the morphogenesis property of bone matrix. J Theor Biol 1973;38:155-68.

19. Urist MR, Nogami H. Morphogenetic substratum for differentiation of cartilage in tissue culture. Nature 1970;225:1051-52.

20. Urist MR, Mikolski A. Lietze A. Solubilized and insolubilized bone morphogenetic protein. Proc Natl Acad Sci USA 1979;76:1828-32.

21. Urist MR, Silverman BF, Buring K, Dubuc FL, Rosenberg JM. The bone induction principal. CIin Orthop Rel Res 1967;53:243-83.

22. Polson AM, Frederick GT, Ladenheim S, Hanes PJ. The production of a root surface smear layer by instrumentation and its removal by citric acid. J Periodontol 1984;55:443-46.

23. Heritier M. Effects of phosphoric acid on root dentin surface. A scanning and transmission electron microscopic study. J Periodont Res 1984;19:167-76.

24. Garberoglio R, Brannstrom M. Scanning electron microscopic investigation of human dentinal tubules. Arch Oral Biol 1976;21:355-62.

25. Garrett JS, Crigger M, Egelberg J. Effects of citric acid on diseased root surfaces. J Periodont Res 1978;13:155-63.

26. Suchetha A, Darshan BM, Prasad R, Bharwani Ashit G. Root Biomodification- A Boon or Bane? Indian J Stomatol 2011;2:251-5.

27. Register AA. Bone and cementum induction by dentin, demineralized in situ. J Periodontol 1973;44:49-54.

28. Oles RD, Ibbot CG, Laverthy WH. Effects of citric acid treatment on pedicle flap coverage of localized recession. J Periodontol 1985;56:259-61.

29. Register AA, Burdick FA. Accelerated reattachment with cementogenesis to dentin, demineralized in situ. I. Optimum range. J Periodontol 1975;46:646-55.

30. Register AA. Induced reattachment in periodontal endodontic lesion by root demineralization in situ. Oral Surg Oral Med Oral Pathol 1978;45:774-83.

31. Hanes PJ, O'brien NJ, Garnik JJ. A morphological comparison of radicular dentin following root planing and treatment with citric acid or tetracycline HCl. J Clin Periodontal 1991;18:660-8.

32. Haghighati F, Arefi V. A comparative study on root surface demineralization using citric acid

and tetracycline in vitro: a scanning electron microscopy study. Acta Medica Iranica 2002;40:247-55.

33. Chaves E1, Cox CF, Morrison E, Caffesse R. The Effect of Citric Acid Application on Periodontally Involved Root Surfaces. II. An In Vitro Scanning Electron Microscopic Study. Int J Period ant Rust Dent 1993;13:189-96.

34. Madison JG, Hokett SD. The effects of different tetracyclines on the root surface of instrumented, periodontally involved human teeth: A comparative scanning electron microscope study. J Periodontol 1997;68:739-45.

35. Wikesjo UM, Baker PJ, Christersson LA, Genco RJ, Lyall RM, et al. A biochemical approach to periodontal regeneration: Tetracycline treatment conditions dentin surfaces. J Periodont Res 1986;21:322-9.

36. Penmatsa T, Varma S, Mythili, Rao KP, Kishore T, Bindu H. Effect of various concentrations of tetracycline hydrochloride demineralization on root dentin surface: A scanning electron microscopic study. J Pharm Bioallied Sci 2013;5:48-53.

37. Blomlf J, Jansson K, Blomlf L, Lindskog S. Long time etching at low pH jeopardizes periodontal healing. J Clin Periodontol 1995;22:459-63.

38. Pitaru S, Melcher AH. Organization of an oriented fibre system in vitro by human gingival fibroblasts attached to dental tissue: relationship between cells and mineralized and demineralized tissue. J Periodontol Res 1987;22:6-13.

39. Pitaru S, Melcher AH. Orientation of gingival fibroblasts and newly synthesized Collagen fibers in vitro. Resemblance to transseptal and dentogingival fibers. J Periodontal Res 1983;18:483-500.

40. Blomlof L, Jonsson B, Blomlof J, Lindskog S. A Clinical study of root surface conditioning with an EDTA gel. II. Surgical periodontal treatment. Int J Periodontics Restorative Dent 2000;20:567-73.

41. Mayfield L, Soderholm G, Norderyd O, Attstrom R. Root conditioning using EDT A gel as an adjunct to surgical therapy for the treatment of intraosseous periodontal defect. J Clin Periodontol 1998;25:707-14.

42. Smith BA, Smith JS, Caffesse RG, Nasjleti CE, Lopatin DE, Kowalski CJ. Effect of citric acid and various concentrations of fibronectin on healing following periodontal flap in dogs. J Periodontol 1987;58:667-73

43. Terranova V, Martin S. Molecular factors determining gingival tissue interactions with tooth structure. J Periodontal Res 1982;17:530-3.

44. Becerik S, Sonmez S, Sen BH, Deliloglu-Gurhan I, Evrenosoglu E. Effect of human platelet derived growth factor-BB on attachment of periodontal ligament cells on root surfaces. Saudi Med J 2009;30:60-6.

45. Gamal AY, Mailhot JM. The effect of local delivery of PDGF-BB on attachment of human periodontal ligament fibroblasts to periodontitis affected root surfaces – in vitro. J Clin Periodontol 2000;27:347-53.

46. Crespi R, Barone A, Covani U, Ciaglia RN, Romanos GE. Effects of CO_2 laser treatment on fibroblast attachment to root surfaces: a scanning electron microscopy analysis. J. Periodontol 2002;73:1308-12.

47. Pant V, Dixit J, Agrawal AK, Seth PK, Pant AB. Behavior of human periodontal ligament cells on CO2 laser irradiated dentinal root surfaces: an in vitro study. J Periodontal Res 2004;39:373-9.

48. Feist IS, De Micheli G, Carneiro SR, Eduardo CP, Miyagi S, et al. Adhesion and growth of cultured human gingival fibroblasts on periodontally involved root surfaces treated by Er:YAG laser. J Periodontol 2003;74:1368-75.

49. Belal MH, Yassin A. A comparative evaluation of Co2 and erbium doped yttrium aluminium garnet laser therapy in the management of dentin hypersensitivity & assessment of mineral content. J Periodontal Implant Sci 2014;44:227-34.

50. Oksala O, Salo T, Tammi R, Häkkinen L, Jalkanen M et al. Expression of proteoglycans and hyaluronan during wound healing. J Histochem Cytochem 1995;43:125-35.

51. Jentsch H, Pomowski R, Kundt G, Gocke R. Treatment of gingivitis with hyaluronan. J Clin Periodontol 2003;30:159-64.

52. Larjava H, Heino J, Kahari VM, Krusius T, Vuorio E. Characterization of one phenotype of human periodontal granulation-tissue fibroblasts. J Dent Res 1989;68:20-5.

53. Sharma K, Chaubey K, Sharma S, Trehan M. Current Status Of Root Biomodification Agents In Regeneration. J Dent Scie 2015;1:1-2.

54. Bhushan K, Chauhan G, Prakash S. Root Biomodification in Periodontics -The Changing Concepts. J Dent Oral Care Med 2016;2:105.