REVIEW ARTICLE

Root Biomodification Agents: A Closer Look

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ABSTRACT

The ultimate goal of periodontal therapy has always been to achieve predictable regeneration of the periodontium at the diseased site. However the pathologic process of periodontitis results in a denuded and contaminated root surface with destruction of the attachment fibres. Conventional periodontal treatment procedures do not result in new connective tissue attachment or periodontal regeneration. The modification of this diseased root surface has thus been the means to achieve periodontal regeneration. Chemical root biomodification has been the most frequently attempted method to achieve this. A large variety of chemical root biomodification agents have been proposed from the conception of this mode of therapy. This review is a compilation of the various agents used for root biomodification, with a brief look at the historical background and a summary of literature on each of these agents.

Key words: Citric acid, Periodontal regeneration, Root biomodification, Root conditioning, Root surface, Tetracycline hydrochloride

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INTRODUCTION

Periodontitis results in damage to the root surfaces, including root surface contamination by bacteria and their endotoxins, reduced collagen fibre insertion, changes in surface mineral density and composition. Over the years, attempts have been concentrated on achieving periodontal regeneration. With the root surface serving as a base for this, the idea arose, to alter this root surface, in ways to promote regeneration.

Chemical modification of the root surface is probably the oldest and most frequently attempted method to do so. Decalcifying agents have been largely used, leading to chemical decalcification of the root surface, which makes the root surface conducive to connective tissue cell attachment and migration, thus promoting periodontal regeneration.[1]

The benefits of root biomodification in achieving periodontal regeneration, is thus, still a topic of debate. This article aims to provide an overview of all the various agents used to achieve root biomodification over the years.

BRIEF HISTORICAL PERSPECTIVE

In the 1800s, acid demineralization in periodontal therapy was introduced, to treat the root surface and make it compatible for regeneration.

In 1833, *Aromatic sulfuric acid* was used by Marshall. Also, use of acids was reported in the New York Dental Records in 1846, as an alternative for scaling and root planing. In the 1890s, Younger and Stewart described the use of acids on root surfaces, along with scaling and root planing.

In 1899, Stewart described the use of pure sulfuric or hydrochloric acid to decalcify the root surface, after elevation of the gingiva. Urist, 1965, popularized this method of acid demineralization to gain new attachment on the root surfaces, after his studies suggested that dentin, following acid demineralization,

possessed inductive properties. Register et al in 1973, performed the first controlled study on the use of acid on root surfaces.[2] Studies have since then focused on various other agents, and more predictable procedures that may provide periodontal regeneration. Polson and Caton, in 1982, stated that it is the exposed root surface, not lack of a periodontium, that inhibits the potential for a new connective tissue attachment.[3]

COMMONLY USED CHEMICAL ROOT CONDITIONING AGENTS

1. Zinc
2. Chondroitin Sulphate
3. Hydrochloric acid
4. Chlorhexidine
5. Citric acid
6. Lactic acid
7. Phosphoric acid
8. Bile Salts and Plasma fractions
9. EDTA
10. Enzymes
11. Laminin
12. Tetracycline hydrochloride
13. Cetyl pyridinium chloride and sodium - N- Lauryl sarcosine
14. Fibronectin
15. Formalin
16. Polyacrylic acid
17. Stannous fluoride
18. Sodium hypochlorite
19. Growth Factors
20. Enamel Matrix Derivative -"Emdogain"

ZINC

In 1971, Hatfield & Baumhammers[4] proposed the existence of a toxic factor (endotoxin) in the diseased root surfaces, which inhibits cell attachment, and thus periodontal regeneration. Extracting this substance would thus promote cell attachment. Phenol/water aids in this process, and may also be neutralized by zinc iontophoresis.[5] Kataoka M et al. in 1987[6] demonstrated that fibroblasts adhere equally well to healthy root surfaces, diseased root surfaces treated with 45% phenol, or diseased root surfaces treated by iontophoresis of zinc ions. However, diseased root surfaces are found to be hypermineralized, which may prevent collagen and fibrin linkage and thus act as a hindrance for new attachment. Thus the use of zinc received no further attention.

HYDROCHLORIC ACID and LACTIC ACID

Urist in 1973, suggested that certain proteins (bone morphogenetic proteins) had the property of inducing differentiation of cells, for regeneration of periodontal structures. However this property was appreciated only after acid demineralization took place on the root surface. Based on this, Register and Burdick conducted studies to determine the use of Citric, Hydrochloric, Lactic, Phosphoric, Trichloroacetic and Formic acid, and EDTA, in demineralization of root surfaces.[7] Histological analysis demonstrated that roots treated with acid, healed by connective tissue reattachment, along with accelerated cementogenesis as well as osteogenesis. Among them, Citric acid showed the most promising results and advocated further research.

CHLORHEXIDINE

In 1974, Bogle et al.[8] conducted a study to determine the use of chlorhexidine during surgery, on the amount of connective tissue and bone regeneration in dogs. Application of Chlorhexidine to the root surface during the study, did not result in connective tissue regeneration, but it resulted in an increase in bone height. Thus its use as a root biomodification agent was not advocated.

CITRIC ACID

It stands the most researched agent for root biomodification, with several animal and human studies in support. Citric acid was suggested for smear layer removal by Register in 1973.[2] It has been shown that citric acid demineralization enhances new attachment or reattachment and regeneration by one or more of the following mechanisms-

- Antibacterial Effect
- Root Detoxification

- Exposure of root collagen and opening of dentinal tubules
- Removal of smear layer
- Initial clot stabilization
- Demineralization prior to cementogenesis
- Enhanced fibroblast growth and stability
- Prevention of epithelial migration along the denuded roots
- Accelerated healing and new cementum formation after surgical detachment of the gingival tissues and demineralization of the root surface by means of citric acid.

Register and Burdick in 1976,[7] advocated the use of citric acid based on positive animal histologic studies. However Nyman et al. in 1981,[9] demonstrated no effects of citric acid use, in animal histologic studies.

Garrett et al. 1978,[10] demonstrated positive effects in human histologic studies. However, Stahl and Froum, 1977,[11] had claimed that it had no significant effect.

Cole et al., 1981[12] examined the effects of citric acid clinically, after replaced flap surgery, and found positive results. On the contrary, Mark and Mehta, 1986[13] stated that there is no added clinical advantage with the use of citric acid for root bio-modification.

PHOSPHORIC ACID

Lee et al. in 1973[14] initially showed the effects of phosphoric acid as a decalcifying agent when applied on dentin.

Passanezi et al. in 1979[15] first used phosphoric acid as an agent for root demineralization in their study, using the horizontal sliding flap to cover denuded roots. They credited the positive results of this study, to the root demineralization during the surgical procedure.

M. Heritier in 1983, microscopically examined the effects of phosphoric acid applied on human root dentin[16] with successful results. Clinically however, the use was insignificant.

BILE SALTS AND PLASMA FRACTIONS

Sodium Deoxy Cholate and Human Plasma Fraction Cohn IV - These agents can dissociate endotoxin into subunits and thus, might detoxify the diseased root surface. The human plasma fraction possibly contains fibronectin. Wirthlin and Hancock in 1980[17] conducted a tissue culture study, in which they applied 2% NAD and 5% Cohn's fraction IV to periodontally diseased root surfaces, after removal of local deposits. They found positive results, i.e. more fibroblast attachment to the treated surfaces than control sites. However, their results were statistically insignificant. Lasho et al.,1983[18] stated that Sodium hypochlorite alone, sodium deoxycholate followed by Cohn's fraction IV_1, and physiologic saline were relatively ineffective in surface debridement.

EDTA

EDTA was introduced in 1980 by Boyko et al.[1] It is a neutral pH chelating agent, thought to preserve the integrity of exposed collagen fibers, early cell colonization and periodontal wound healing and cause less periodontal damage. Blomlof et al.[19] proved efficient smear layer removal with use of EDTA as a root biomodification agent in vitro, but found that clinical results are not statistically significant.

ENZYMES

Willey and Steinberg in 1984[20] evaluated the effect of topical applications of hyaluronidase (H), pronase (P), elastase (E) and collagenase (C) to citric acid - demineralized root surfaces, to determine if a more effective demineralization took place with the use of these enzymes, along with citric acid.

Collagen exposure in all the test groups, particularly collagenase, appeared greater than that with only citric acid use. Thus, addition of enzyme agents, along with citric acid, histologically proved effective for root biomodification.

LAMININ

Fibronectin and laminin are said to be responsible for the directed movement of different cell types. Terranova et al. in 1986 demonstrated that laminin promotes epithelial cell adhesion and

growth to tetracycline and glycoprotein conditioned surfaces.[21]
Smith B. et al. in 1987[22] used citric acid and fibronectin-laminin application in beagle dogs. Ankylosis was seen in the test group. Thus it was thought that laminin may have a more significant role in the pathogenesis of disease than in treatment. It was thus concluded that the use of a combination of fibronectin and laminin in new attachment procedures does not seem to be justified.

TETRACYCLINE HYDROCHLORIDE

Tetracyclines bind strongly to the root surface and are released in an active form over extended periods of time. Sub lethal concentrations of tetracycline reduce adherence and co-aggregation properties of a number of disease associated bacteria including Porphyromonas gingivalis and Prevotella intermedia.
Tetracyclines have a low pH in concentrated solution, acting as a calcium chelator resulting in demineralization. It removes the smear layer, exposes the collagen matrix, and uncovers and widens the orifice of dentinal tubules. A matrix is formed, supporting migration and proliferation of cells. Terranova et al. in 1986[21] suggested that treatment of dentin surfaces with Tetracycline HCL increases binding of fibronectin. Tetracycline and subsequent application of fibronectin promotes the attachment and growth of gingival fibroblasts.
Alger et al. in 1990[23] stated that after periodontal surgery, application of Tetracycline and fibronectin group demonstrated some reattachment whereas the tetracycline treated group showed greater connective tissue attachment. However it was later found to be ineffective.

CETYL PYRIDINIUM CHLORIDE AND SODIUM - N- LAUROYL SARCOSINE

Blomlof et al. in 1987 compared 5 different methods for new attachment formation in monkeys: [24] plaque control only; surgery with ultrasonics or hand instrumentation; or chemical treatment by cetylpyridinium chloride and sodium-n-lauroyl sarcosine with or without citric acid. Both chemically- treated groups resulted in a significant new attachment formation, with the citric acid group showing a tendency for more new attachment. The supracrestal fiber bundle was 2 to 3 times thicker in the chemically-treated groups than the mechanically-scaled roots.

FIBRONECTIN

Fibronectin promotes cell adhesion to both collagen and scaled root surfaces and has a chemotactic effect on fibroblasts and mesenchymal cells. Periodontally the application of Fibronectin to partially demineralized roots has been shown significantly to -

- Enhance the effects of demineralization with regard to new attachment
- Enhance cell proliferation from periodontal ligament and supra crestal areas.

Smith et al. in 1987[22] reported on healing after periodontal flap surgery in dogs. There was a significant increase in new connective tissue attachment with fibronectin, but no advantage in increasing the concentration of fibronectin above the plasma level.
Caffesse et al. in 1991[25] determined the effects of guided tissue regeneration (GTR) with and without citric acid conditioning and autologous fibronectin application. Better results were seen with adjunctive citric acid plus autologous fibronectin, but were not statistically significant.
Tuter G. et al. in 2000[26] tested the effects of fibronectin (FN), vitronectin (VN) and a fibronectin analog, and concluded that these attachment factors cannot promote cell attachment to different cementum sites.

FORMALIN

Morris and Singh in 1988[27] reported clinical responses in patients treated by interproximal denudation and root surface conditioning with a formalin solution. Radiographic evaluations indicated bone growth in defects and clinical attachment gain. However, since there were no controls, they could not determine how much of the response was due to the surgical approach and

how much resulted from the formalin application. Thus, this did not have any clinical significance.

POLYACRYLIC ACID

In a comparative study on the healing of the periodontium using Polyacrylic acid for 20 seconds and citric acid for 3 minutes to condition root surfaces during periodontal therapy, Wiland et al. in 1990[28] observed that Polyacrylic acid treated teeth showed more apical migration. They also observed a greater connective tissue adhesion to root surfaces compared to citric acid treated root surfaces.

STANNOUS FLOURIDE

Selvig et al. in 1990[29] studied the use of stannous fluoride and tetracycline on repair after delayed replantation of root planed teeth in dogs. Root surface treatment with SnF followed by tetracycline, resulted in complete absence of inflammatory resorption and ankylosis as compared to the control group.

Wikesjo et al. in 1991[30] undertook a study in beagles to assess the effect of stannous fluoride as an adjunct to regenerative surgery. Those surfaces treated with stannous fluoride showed almost complete epithelialization of the defect and sometimes even epithelialization of the supporting alveolar bone.

SODIUM HYPOCHLORITE

Sodium hypochlorite acts as a bactericidal and cleaning agent. It degrades endotoxins by hydrolysis. However, it was found to be ineffective by Lasho et al.[18] Rezy Cheru et al. in 1992[31] in a study comparing citric acid, EDTA and sodium hypochlorite observed that surfaces treated with sodium hypochlorite were uneven with debris. When compared to the control group, however, these surfaces showed a better appearance by exposing dentinal tubules and less debris.

GROWTH FACTORS

Growth factors are polypeptide molecules released by cells in the inflamed areas that regulate events in wound healing. These factors include:

Fibroblast growth factors (FGFs), Platelet-derived growth factor (PDGF), Insulin like growth factors (IGFs), Transforming growth factors (TGFs), Epidermal growth factor (EGF).

PDGF: Lynch et al. in 1989[32] stated that topical application of a combination of PDGF and IGF-1 on the root surface of diseased teeth in dogs, exhibited periodontal regeneration with significant new cementum deposition and bone formation.

Transforming Growth Factors (TGF): Lynch et al.[33] showed that the topical application of TGF-β to epidermal wounds in pigs inhibited re-epithelialization and increased CT volume, collagen synthesis and angiogenesis. TGF-β alone and in combination with other factors showed significant increases in protein and collagen synthesis, enhanced growth of fibroblasts and capillaries.

However, the problems that may be faced include: the possibility of secondary endodontic involvement via dentinal tubules, no control over the depth of action, increased size of dentinal tubules with more penetration of micro-organisms leading to root caries, alteration of the morphology of collagen.

ENAMEL MATRIX DERIVATIVE – "EMDOGAIN"

Enamel matrix derivative is available commercially by the name of Emdogain. It acts to replicate the events that take place as a part of periodontal regeneration. It adsorbs to collagen, hydroxyapatite, and along denuded root surfaces and retains it's properties at the site for 2 to 4 weeks. This longer retention time period is necessary to allow the periodontal ligament cells to repopulate the area. EMD enhances proliferation of PDL cells, but not epithelial cells.

The effects of EMD on the viability of PDL cells were found to be dose dependent, with higher doses decreasing their viability. The effects of EMD include: increased attachment of PDL fibroblasts to diseased root surfaces; cell-cell adhesion, which plays a role in regeneration. Meta analyses have showed that EMD gives significantly better results, particularly when used

in treatment of periodontal defects.[34] However, meta analyses of various commonly used root biomodification agents, suggest that root biomodification provides no clinical benefit to the patient.[35,36]

CONCLUSION

A majority of the literature indicates towards significant results being seen only in-vitro, while clinical reports have remained negative. However, there seems to be no gross disadvantage of their use. Thus, in conclusion, it can be stated that, though providing no significant added benefit, the use of chemical root biomodification with the currently available agents, may be practised based on the choice and personal experience of the practitioner. Further research in the field of tissue engineering can lead to greater scope in the search of periodontal regeneration.

REFERENCES

1. Boyko, G. A., and A. H. Melcher. Cell attachment to demineralized root surfaces in vitro. Journal of periodontal research 1980;15:297-303.
2. Register AA. Bone and cementum induction by dentin, demineralized in situ. J Periodontol. 1973;44:49-54.
3. Polson AM, Caton J. Factors influencing periodontal repair and regeneration. J Periodontol. 1982;53:617-25.
4. Hatfield CG, Baumhammers A. Cytotoxic effects of periodontally involved surfaces of human teeth. Arch Oral Biol. 1971;16:465-8.
5. Aleo JJ, De Renzis FA, Farber PA, Varboncoeur AP. The presence and biologic activity of cementum-bound endotoxin. J Periodontol. 1974;45:672-5.
6. Kataoka M, Gado MH, Shimomura Y, Lake F, Sharawy M, Gangarosa LP Sr. The influence of zinc iontophoresis on in vitro adherence of fibroblasts to periodontally-diseased cementum. J Periodontal Res. 1987;22:296-9.
7. Register AA, Burdick FA. Accelerated reattachment with cementogenesis to dentin, demineralized in situ. II. Defect repair. J Periodontol. 1976;47:497-505.
8. Bogle G, Rathbun E, Oliver R, Hornbuckle C, Egelberg J. Effect of post-operative use of chlorhexidine on regeneration of bifurcation defects in dogs. J Periodontal Res. 1974;9:127-33.
9. Nyman S, Lindhe J, Karring T. Healing following surgical treatment and root demineralization in monkeys with periodontal disease. J Clin Periodontol. 1981;8:249-58.
10. Garrett JS, Crigger M, Egelberg J. Effects of citric acid on diseased root surfaces. J Periodontal Res. 1978;13:155-63
11. Stahl SS, Froum SJ. Human clinical and histologic repair responses following the use of citric acid in periodontal therapy. J Periodontol. 1977;48:261-6.
12. Cole R, Nilveus R, Ainamo J, Bogle G, Crigger M, Egelberg J. Pilot clinical studies on the effect of topical citric acid application on healing after replaced periodontal flap surgery. J Periodontal Res. 1981;16:117-22.
13. Marks SC Jr, Mehta NR. Lack of effect of citric acid treatment of root surfaces on the formation of new connective tissue attachment. J Clin Periodontol. 1986;13:109-16.
14. Lee HL Jr, Orlowski JA, Scheidt GC, Lee JR. Effects of acid etchants on dentin. J Dent Res. 1973;52:1228-33.
15. Passanezi E, Alves ME, Janson WA, Ruben MP. Periosteal activation and root demineralization associated with the horizontal sliding flap. J Periodontol. 1979;50:384-6.
16. Heritier M. Effects of phosphoric acid on root dentin surface. A scanning and transmission electron microscopic study. J Periodontal Res. 1984;19:168-76.
17. Wirthlin MR, Hancock EB. Biologic preparation of diseased root surfaces. J

Periodontol. 1980;51:291-7.
18. Lasho, David J., Timothy J. O'Leary, and Abdel H. Kafrawy. A scanning electron microscope study of the effects of various agents on instrumented periodontally involved root surfaces. J periodontol. 1983;54: 210-220.
19. Blomlof JP, Blomlof LB, Lindskog SF. Smear layer formed by different root planing modalities and its removal by an ethylenediaminetetraacetic acid gel preparation. Int J Periodontics Restorative Dent. 1997;17:242-9.
20. Willey R, Steinberg AD. Scanning electron microscopic studies of root dentin surfaces treated with citric acid, elastase, hyaluronidase, pronase and collagenase. J Periodontol. 1984;55:592-6.
21. Terranova VP, Franzetti LC, Hic S, DiFlorio RM, Lyall RM, Wikesjo UM et al. A biochemical approach to periodontal regeneration: tetracycline treatment of dentin promotes fibroblast adhesion and growth. J Periodontal Res. 1986;21:330-7
22. Smith B, Caffesse R, Nasjleti C, Kon S, Castelli W. Effects of citric acid and fibronectin and laminin application in treating periodontitis. J Clin Periodontol. 1987;14:396-402.
23. Alger FA, Solt CW, Vuddhakanok S, Miles K. The histologic evaluation of new attachment in periodontally diseased human roots treated with tetracycline-hydrochloride and fibronectin. J Periodontol. 1990;61:447-55.
24. Blomlof L, Lindskog S, Appelgren R, Jonsson B, Weintraub A, Hammarstrom L. New attachment in monkeys with experimental periodontitis with and without removal of the cementum. J Clin Periodontol. 1987;14:136-43.
25. Caffesse RG, Nasjleti CE, Anderson GB, Lopatin DE, Smith BA, Morrison EC. Periodontal healing following guided tissue regeneration with citric acid and fibronectin application. J Periodontol. 1991;62:21-9.
26. Tuter G, Yalim M, Gurhan I, Baloş K. The effects of attachment factors on initial attachment of human periodontal ligament fibroblasts on different root surfaces: a light and scanning electron microscopic study. J Oral Sci. 2000;42:33-8.
27. Morris ML, Singh IJ. Clinical observations on bone regeneration in intrabony pockets following periodontal treatment. Int J Periodontics Restorative Dent. 1988;8:56-71.
28. Wiland, Bruce B. The effect of polyacrylic acid on the root surface. Diss. Indiana University School of Dentistry, 1990.
29. Selvig KA, Bjorvatn K, Claffey N. Effect of stannous fluoride and tetracycline on repair after delayed replantation of root-planed teeth in dogs. Acta Odontol Scand. 1990;48:107-12.
30. Wikesjo UM, Claffey N, Nilveus R, Egelberg J. Periodontal repair in dogs: effect of root surface treatment with stannous fluoride or citric acid on root resorption. J Periodontol. 1991;62:180-4.
31. Rezy Cheru, M. D. S. The Effect Of Citric Acid As An Adjunct to Conventional Root Preparation in Periodontal Therapy - A Clinical Study.
32. Lynch SE, Williams RC, Polson AM, Howell TH, Reddy MS, Zappa UE, Antoniades HN. A combination of platelet-derived and insulin-like growth factors enhances periodontal regeneration. J Clin Periodontol. 1989;16:545-8.
33. Lynch SE, Colvin RB, Antoniades HN. Growth factors in wound healing. Single and synergistic effects on partial thickness porcine skin wounds. J Clin Invest. 1989;84:640-6.
34. Giannobile WV, Somerman MJ. Grow-th and amelogenin-like factors in

periodontal wound healing. A systematic review. Ann Periodontol. 2003;8:193-204.
35. Mariotti, A. Efficacy of chemical root surface modifiers in the treatment of periodontal disease. A systematic review. Annals of periodontology. 2003;8:205-226.
36. Singhal N, Barman I. Podoplanin: A Novel Diagnostic And Prognostic Marker In Oral Tumors. A Brief Review Int J Cont Med Res. 2014;1(2):56-60