



Root Surface Biomodification: Current Status and a Literature Review on Available Agents for Periodontal Regeneration

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Authors' contributions

This work was carried out in collaboration between all authors. Author AHS designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors DG, RM, SPS and NB helped in managing the literature searches and analyses of the study performed. All authors read and approved the final manuscript.

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ABSTRACT

Background: A critical step in periodontal regenerative therapy is to alter the periodontitis affected root surface to make it a hospitable substrate, to support and encourage migration, attachment, proliferation and proper phenotypic expression of periodontal connective tissue progenitor cells. So the Concept of Biochemical modification or alteration of the root surface has emerged as a potential therapeutic approach to the reconstruction of the periodontal unit.

Aim: To review various agents used for root biomodification and update on the current status of root biomodification in periodontal regenerative therapy.

Materials and Methods: Google Scholar database is searched using keyword "Root Biomodification" and the studies with experimental design either In Vivo or In vitro were included in

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the search whereas Narrative reviews or Non – Systematic reviews were excluded. These studies were reviewed together to update the various agents used for root biomodification and their current status in Periodontal regenerative therapy.

Result: Only the representative studies of the agents used were included in this studies including 2 systematic review, 1 literature review and 1 world workshop report.

Conclusion: The present status suggests that root biomodification does not have any added advantage in periodontal regeneration. Large Size randomized clinical trials are necessary to give an definite conclusion.

Keywords: Root biomodifiers; periodontal regeneration; laser; root canal irrigants; literature review.

1. INTRODUCTION

One of the important goals in periodontal therapy is to facilitate formation of new connective tissue attachment on the denuded root surface. This type of regeneration is described by the term 'New attachment'. It can be described as embedment of new periodontal ligament fibers on to new cementum previously denuded by the periodontal disease. Research regarding periodontal therapy has made it clear that Standard treatment techniques do not result in periodontal regeneration. It has also become apparent that, if the goal of periodontal regeneration is to be realized, the problem of regeneration needs to be approached from a basic biological perspective. The periodontium consists of a cell and tissue complex organized into basic components of cementum, periodontal ligament and alveolar bone. The challenge of regeneration is to reconstitute this complex onto the root surface.

1.1 Root Surface Changes in Periodontal Disease

Periodontitis produces substantial changes on the root surface, and the root is commonly referred to as "Pathologically Exposed." The normal root is rich in collagen, with extrinsic and intrinsic fibers that form a renewable connection to the adjacent alveolar bone. Plaque- induced inflammation destroys these Sharpey's fibers allowing downgrowth of junctional and pocket epithelium. Thus, the root surface becomes exposed to the periodontal pocket and oral environment. With loss of collagen the root surface becomes 'Hypermineralized'. The bacterial plaque and calculus penetrate the cementum and or dentin of the root. The mineral content of cervical cementum was reported as 26% of Ca and Mg and 12.3% Phosphorus (as % dry weight). The reported Calcium value in healthy cementum was 25.7+/- 0.2% for age group 31-40 years which was increased to 27.5%

for diseased cementum in a comparable age group [1]. The elevated values in diseased cementum most likely reflect a remineralization of surface cementum by plaque once the junctional epithelium separates. The altered crystal structure and higher magnesium values suggest calcium deposition plaque accumulates fluorides which could account for the elevated levels on the exposed root surface. Thus, the exposed root surface, as a result of periodontitis will undergo substantial alterations and may no longer serve as an appropriate substrate for cell attachment and fiber development. These alterations include [2].

- Loss of collagen fiber insertion,
- Contamination of the root surface by bacteria and or endotoxins and
- Alterations in mineral density and composition.
- Also the pathologically exposed root surface may lack the necessary chemotactic stimuli for migration of cells capable of producing periodontal regeneration.

The apical migration of the junctional epithelium along the root surface over the connective tissue following surgical therapy appears to preclude regeneration by acting as a physical barrier between the gingival connective tissue and the root surfaces.

1.2 Acid Demineralization: Historical Background

The concept of acid demineralization in periodontal therapy was first introduced in the 1800s as a substitute for scaling and calculus removal. The use of acids as an adjunct to scaling and calculus removal was reported in the New York Dental Records in 1846. As early as 1833, Marshall [3] presented a case of pocket eradication with "presumable clinical reattachment" after the use of Aromatic sulfuric

acid. In the 1890s, Younger and Stewart described the use of acids in conjunction with the mechanical removal of calculus and cementum. Their rationale for its use as an aid to reattachment was the microscopic evidence of hypermineralization of diseased roots with obliteration of lacunae of cellular cementum by calcific deposits [4].

The potential of acid demineralization of root surfaces as an adjunct to new attachment procedures gained popularity following studies by Urist [5] that suggested that dentin following acid demineralization possessed inductive properties.

Urist [6] demonstrated in a series of experiments that allogenic dentin matrix, following partial or total demineralization with 0.6N HCL possessed the ability to induce the formation of new bone or cementum on the implant surface. It was suggested that the dentin matrix contained a protein or a series of proteins (referred to as bone morphogenic protein) that possessed the ability to induce differentiation of cells. The inductive property, however, was only available following acid demineralization, suggesting that the inorganic component of dentin may obscure potential inductive proteins associated with the organic component. The results of the studies by Urist encouraged Register et al. in [7] to perform the first controlled study on the use of acid on root surfaces. They investigated whether new attachment, cementogenesis and osteogenesis could be induced adjacent to tooth roots demineralized *in vivo*.

2. MATERIALS AND METHODS

Google Scholar database was searched for articles using the keyword "Root Biomodification". Only the studies having an experimental design i.e *in vivo* Clinical trials, *in vitro* experimental studies or Animal Studies and Literature or Systematic reviews were included in the search whereas Narrative or Non-Systematic reviews were excluded from the search. After the respective data were collected, it was assessed and decided amongst the authors, not more than 4 studies per experimental design would be selected per agent used. This studies were individually selected by each author and after discussion final studies were included. (Kappa =0.69, p<0.01).The results of Literature review , Systematic review and World workshop Report were used to present the current status of root biomodification in periodontal therapy.

3. RESULTS

Out of the 767 articles assessed. 47 representative articles were selected. 43 articles (Table 1) studying different agents, with their respective authors, year and experimental design were mentioned in the review while the results of 2 systematic review, 1 literature review and 1 world workshop report were mentioned separately.

3.1 Various Acids

Register and Burdick [8] evaluated various acids for their potential to promote new connective tissue attachment. The acids tested were hydrochloric, lactic, citric, phosphoric, trichloroacetic and formic. Optimal cementogenesis and new connective tissue attachment occurred when roots were demineralized with citric acid pH 1.0 for 2-3 min. These findings have provided the basis for later studies using root surface demineralization in periodontal regeneration attempts in both *in vitro* and *in vivo* model systems.

3.2 Citric Acid

It was suggested for smear layer removal by Register in 1973 and has been studied extensively. It is essential to human metabolism and is found in many foods.

It has been used in the form of citrates as anticoagulants. Endogenous citric acid from the metabolic acid cycle has been associated with solubility of bone mineral during bone resorption. With *in vitro* systems, citric acid has consistently enhanced features thought to be relevant in the regeneration of periodontal tissues: Exposing collagen, inducing mesenchymal cell differentiation, extracting endotoxins and other toxic products, accelerating cementogenesis and widening dentinal tubules. It has been shown that citric acid demineralization enhances new attachment or reattachment and regeneration by one or more of the following mechanism (Table 2).

3.2.1 Technique of application [9]

Raise a mucoperiosteal flap. Thoroughly instrument the root surface removing calculus and underlying cementum. Apply cotton pledgets soaked in a highly saturated solution of citric acid (pH1) and leave on for 5 minutes on treated

surface. Care should be taken to “burnish” the root surface with acid using as much pressure on cotton pledget as applied during root planing. The pledget should be removed after every 1 minute. After 5 minutes period the area should

be thoroughly flushed with water. Care should be taken to prevent salivary contamination.

Histological Studies on wound healing and attachment effects:

Table 1. Results

Author	Year	Type of study	Agent used
Register & Burdick	1975	Animal	Hydrochloric, Lactic, Citric, Phosphoric, Trichloroacetic and Formic acid
PD miller	1982	<i>In vivo</i> (clinical)	Citric acid
Cole et al.	1981		
Mark S.C, Mehta N.R	1986		
Register and Burdick,	1976	Animal	Citric acid
Ririe et al.	1980		
Nyman et al.	1981		
BL Dyer et al	1993		
Cole RT et al.	1980	<i>In vivo</i> (Histological)	Citric acid
Albair W.B. et al.	1982		
Stahl and Froum	1977		
Cogen et al.	1984		
Terranova et al.	1986	Animal	Tetracycline
Alger et al.	1990	<i>In vitro</i>	
Machtei et al.	1993	<i>In vivo</i>	
Isik AG	2000	<i>In Vitro</i>	
Caffesse RG et al.	1987	Animal	Fibronectin
Smith et al.	1987	Animal	
Wikesjo et al.	1988	Animal	
Raul G et al.	1991	<i>In vivo</i>	
Mayfield L et al.	1998	<i>In vivo</i>	EDTA
Blomlof et al.	2000	<i>Ex vivo</i>	
Terranova et al.	1986	Animal	Laminin
Bogle G et al.	1974	Animal	Chlorhexidine
Moss M, Kruger and Reynolds DC	1965	Animal	Chondroitin Sulfate
Wiland et al.	1990	animal	Polyacrylic acid
Lasho DJ et al.	1983	<i>In vitro</i>	Sodium Hypochlorite
Wirthlin MR and Hancock EB	1980	Tissue culture	Sodium Deoxy Cholate and Human Plasma Fraction Cohn IV
Morris and Singh	1988	<i>In vivo</i>	Formalin
Willey and Steinberg	1984	Animal	Enzymes: Hyaluronidase, Elastase and collagenase
Selvig et al.	1990	Animal	Stannous fluoride
UM Wikesjo et al.	1991	Animal	Stannous fluoride
Rubins RP et al.	2013	<i>In vivo</i>	Rh (PDGF) (Growth Factor)
Yamaguchi et al.	1997	<i>In vitro</i>	Er: YAG
R Fekrazad et al.	2015	<i>In vitro</i>	Er, Cr: YSGG
Morlock BJ et al.	1992	<i>In vitro</i>	
A Dilsiz et al.	2010	<i>In vivo</i>	ND:YAG
Misra V et al.	1999	<i>In vitro</i>	CO2 Laser
Pant V et al.	2004	<i>In vitro</i>	
R Crespi	2011	Human	
B. Houshmand et al.	2011	<i>In vitro</i>	MTAD
C. Tandon et al.	2014	<i>In vitro – In vivo</i>	
Shewale A and Gattani D	2015	<i>In – vitro</i>	Q- MIX

Table 2. Rationale for use of citric acid

-
- Antibacterial effect (Daly et al. 1982)
 - Root detoxification (Aleo et al. 1974)
 - Exposure of root collagen and opening of dentinal tubules (Polson et al. 1984)
 - Removal of smear layer (Polson et al. 1984)
 - Initial clot stabilization (Wikesjo et al. 1991)
 - Demineralization prior to cementogenesis (Register, 1975)
 - Enhanced fibroblast growth and stability (Boyko et al. 1980)
 - Prevention of epithelial migration along the denuded roots (Polson et al. 1983)
-

3.2.2 Animal histology: Positive effects

Register and Burdick [8] reported reattachment of collagen fibres to previously denuded root surfaces following treatment of root surface with citric acid. They suggested citric acid at pH1.0) was the acid of choice with an optimum application time of 2-3 minutes. Register referred to these collagenous infiltrations of the demineralized dentin as a "cemental pin." A molecular and mechanical reattachment was implied control dogs demonstrated rampant epithelial proliferation with attachment only at the apical one third of the wound.

Ririe et al. [10] studied healing of periodontal connective tissue after surgical wound and application of citric acid in dogs. Root surfaces were exposed surgically, root planned & etched with citric acid pH 1 for 3 minutes control teeth were not etched. Block sections were obtained at 7, 14, 21 and 42 days and examined and compared with the controls, the demineralized sites showed enhanced, connective tissue healing with rapid and consistent establishment, devoid of initial embedding of collagen fibers in newly formed cementum.

3.2.3 No effects

Nyman et al. [11] studied the potential for new attachment in the monkey model using citric acid. Experimental periodontitis was treated by flap and citric acid pH 1 for 3 minutes. Root planed alone (controls) and acid-treated teeth resulted in healing by long junctional epithelium. It was determined that citric acid application did not promote formation of new cementum and connective tissue.

BL Dyer et al. [12] used the beagle dog to study the effects of demineralization during guided tissue regeneration. Teeth in 12 quadrants were treated, 4 by citric acid, 4 by tetracycline, and 4 by membrane alone. Histometric analysis demonstrated that root conditioning by either agent did not enhance the amount of connective tissue and bone gained by membrane alone.

3.2.4 Human histology: Positive effects

Cole RT et al. [13] examined specimens histologically to determine if new attachment to periodontally-diseased root surfaces could be achieved by topical application of citric - acid. Teeth treated by flap procedures had citric acid applied for 5 minutes. Four months later block sections were recovered in all 10 specimens, results showed regeneration of soft tissue ranging from 1.2 to 2.6 mm coronal from the reference notch in 4 of the 10 specimens.

Albair W.B. et al. [14] studied the attachment of the connective tissue to periodontally diseased roots after citric acid demineralization in vivo. Eighteen periodontally involved teeth were treated surgically and vigorously root planed. The roots of 9 teeth were treated with citric acid and remaining 9 were served as untreated controls.6 of the 9 citric acid treated teeth demonstrated scanning electron and light microscopic evidence of connective tissue attachment. The control specimen weeks after surgery, showed no evidence of new connective tissue attachment

3.2.5 Human histology: No effect

Stahl and Froum [15] evaluated the effects of citric acid on pocket closure both clinically and histologically. Seven extracted teeth from 2 patients were examined. Root surfaces were treated with citric acid and measurements were repeated at 4, 8, 12 and 16 weeks. Block sections were performed at the 16-week visit. In 5 of 6 citric acid- treated teeth, no evidence was observed of accelerated cementogenesis or functional connective tissue attachment. They also noticed that the exposure citric acid had no apparent effect on supra alveolar collagen fibres, which were left intact on the root surfaces.

Cogen et al. [16] compared root planing alone, citric acid alone and a combination of root planing plus citric acid on fibroblast attachment to diseased roots. Human gingival fibroblasts adhered and grew on root planed surface and on the surfaces treated by citric acid additionally

citric acid treatment after root planing offered no additional fibroblastic attachment compared to root planing alone.

3.2.6 Clinical results

3.2.6.1 Positive effects

Cole et al. [17] examined the effects of citric acid in a pilot study after replaced flap surgery. A split mouth design was used in 12 patients with advanced periodontitis who were treated with citric acid pH 1 for 3 to 5 minutes on the experimental side. A probing attachment level gain of 2.1 mm for the acid-treated teeth resulted, compared to 1.5 mm for controls

3.2.6.2 No effects

Mark S.C Jr and Mehta N.R [18] concluded that there is no added clinical advantage of citric acid conditioning of the roots during treatment of periodontitis.

3.3 Tetracycline

They are broad-spectrum antibiotics which are effective in controlling periodontal pathogens. They are the derivatives of the polycyclic naphthalene carboxamide. Tetracycline hydrochloride, Doxycycline hydrochloride and Minocyclines have been used as root conditioning agents to demineralize the root surface as it binds strongly to the root surface and can be released in an active form over extended periods of time. Sub lethal concentrations of tetracycline reduces 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 and this can act as a calcium chelator resulting in demineralization. Tetracyclines possess several unique antibacterial characteristics that may contribute to their efficacy in periodontal therapy (Table 3).

It inhibits tissue collagenase production and bone resorption. In addition it is known that tetracycline is adsorbed to and subsequently desorbed from dentin. It also exposes the collagen matrix, and uncovers and widens the orifice of dentinal tubules. A matrix is thereby provided supporting migration and proliferation of cells related to periodontal wound healing. It has also been

found to be effective for removing smear layer. Another beneficial effect of tetracycline conditioning was that the drug was released in a biologically active concentration for 48 hours and upto 14 days after application. Various types of tetracyclines have been suggested, but tetracycline hydrochloride used for at least 30 seconds, has proven most effective in removing smear layer and opening dentinal tubules [19]. They are generally used as a 0.5% solution at a PH of 3.2 and is applied for 5 minutes [20]. The solution is prepared by adding 1 standard ml of sterile water to the contents of each capsule, then thoroughly mixing the two. The material is applied with lateral pressure using passive burnishing technique using a sterile cotton pledget [21].

Table 3. Rationale for use of Tetracycline hydrochloride (VP Terranova et al. 1986)

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- Increases fibronectin binding which stimulates fibroblast attachment and growth.
 - Smear layer removal, exposure of dentin tubules / collagen fibers.
 - Endothelial cell growth factor binding to dentin, stimulating periodontal ligament cell proliferation / migration.
 - Adsorbs to enamel and dentin. acts as antimicrobial local delivery system.
 - Collagenolytic enzyme inhibition preventing bone resorption.
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Terranova et al. [22] suggested that treatment of dentin surfaces with Tetracycline HCL increase binding of fibronectin. Tetracycline treatment of the tooth surface and subsequent application of fibronectin promotes the attachment and growth of gingival fibroblasts. These findings suggest that tetracycline and fibronectin may be used to treat periodontally involved tooth surfaces.

Alger et al. [23] carried out a study to determine how the treatment of human tooth roots with tetracycline Hcl and fibronectin during periodontal surgery influences the attachment of the gingiva to the root surface. Teeth were assigned to 3 groups. Group one received surgery with degranulation and root planing. Group 2 received surgery + tetracycline Hcl. Group 3 received surgery + tetracycline Hcl + fibronectin controls healed with long junctional epithelium. Tetracycline and fibronectin group demonstrated some reattachment whereas the tetracycline treated group showed greater connective tissue attachment.

Machtei et al. [24] evaluated the effect of tetracycline as a potential adjunctive treatment to expanded PTFE membranes in the treatments of class II furcation defects in mandibular molars. A 100 mg/ml solution of tetracycline HCl was applied for 5 minutes prior to placement of the membranes. There was a significantly greater reduction in pocket depths in tetracycline treated sites when compared to control sites after 3 and 6 months.

Isik et al. [25] compared different tetracycline HCl concentrations of 0, 10, 25, 50, 75, 100, 125 and 150 mg/ml for root conditioning and found that concentration between 50 mg/ml and 150 mg/ml showed a statistically significant opening of dentinal tubules at 1,3 and 5 minutes.

3.4 Fibronectin

It is a high molecular weight glycoprotein that is found in the extracellular tissue and is the main component that holds the clot together..It also performs several functions (Table 4) that fosters the reattachment of periodontal tissues to the root surface in the surgical treatment of periodontal disease.

Caffesse RG et al. [26] suggested that Periodontally the application of Fibronectin to partially demineralized roots has been shown significantly to enhance the effects of demineralization with regard to new attachment and enhance cell proliferation from periodontal ligament and supra crestal area.

Smith et al. [27] reported on effect of citric acid and fibronectin on healing after periodontal flap surgery on in dogs. fibronectin with increasing concentration was used (0.38, 0.75, 1.5 mg/ml of saline). There was a significant increase in new connective tissue attachment in all surgical sites where fibronectin had been added but there was no advantage in increasing concentration of fibronectin above the plasma level.

Wikesjo et al. [28] studied root surface demineralization with tetracycline HCl and topical fibronectin application in furcation defects of beagle dogs and observed that the tetracycline had the potential to induce connective tissue repair but application of fibronectin does not have any effect on connective tissue repair

Raul G et al. [29] evaluated 46 patients after treatment and reported significant gains in clinical attachment and probing depth reduction

when citric acid and fibronectin were used. 2 year follow up in 26 patients showed insignificant difference in probing depth reduction while improvement in clinical attachment was still maintained. No increased benefits are seen at concentration above serum levels. There have been encouraging results associated with citric acid conditioning and subsequent fibronectin application on root surfaces. Additional clinical investigations are indicated to determine the place of this treatment combination in periodontal therapy. Hence, the application of exogenous fibronectin to root surfaces would appear to be of limited benefit.

Table 4. Rationale for use of fibronectin

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- The initial stage after demineralization and prior to new attachment is fibrin formation and linkage (Poison & Proye 1983).
 - Promotes mesenchymal cell adhesion, Chemotaxis and growth (Okochi et al. 2008)
 - Fibronectin stimulates the coronal growth of cells from the periodontal ligament that is responsible for new attachment
 - Favors the growth and attachment of fibroblasts over epithelial cells to the root surface (Terranova et al. 1982)
 - Speeds the linkage process by being chemoattractive for fibroblasts and stabilizing the clot between the exposed root surface collagen and new fibers within the tissue.
-

3.5 EDTA (Ethylenediamine Tetracetic Acid)

Studies have shown that a chelating agent such as EDTA working at a neutral pH appears preferable with respect to preserving the integrity of exposed collagen fibers, early cell colonization and periodontal wound healing. It is suggested that neutrally buffered EDTA will reduce the probability that the soft tissues of the periodontium will be damaged. It has been shown that pH that is not close to neutral, inhibit periodontal ligament fibroblasts. Thus, it is suggested that neutrally buffered EDTA will reduce the probability that the soft tissues of the periodontium will be damaged. Various concentrations of EDTA has been used in studies ranging from 12%-24%, neutral pH for 30 s to 3 min aiming at removing smear layer and widening dentin tubules without damaging biological structures [30]. However, initial fibrin clot adhesion is limited with its use [31].

Mayfield L et al. [32] conducted a study to compare the treatment outcome following root surface conditioning using an EDTA gel preparation in conjunction with surgical therapy with that following conventional flap surgery in periodontal intraosseous defects and observed that after 6-months a significant probing attachment level gain of 1.8+/-1.5 mm and 1.0+/-1.7 mm in the EDTA and control groups respectively and A probing bone gain of 1.0+/-1.3 mm in the EDTA group was measured with a non-significant gain of 0.4+/-1.2 mm in the control group.

Blomlof et al. [33] conducted a study in order to examine the smear layer formation following different root planing modalities. 24 periodontitis affected human teeth were mechanically root planed. 12 teeth were etched with EDTA preparation for 2 minutes. The surfaces were examined by SEM. The results showed that root planing resulted in a smear layer covering the root surface irrespective of treatment modality. The smear layer could be efficiently removed with EDTA gel preparation. During the process, the collagen fibers were exposed in varying degree.

3.6 Laminin

It is a glycoprotein of high molecular weight. It is capable of adhering to various substrates. Fibronectin and laminin have been implicated in the directed movement of different cell types. Studies have demonstrated that Laminin promotes gingival epithelial Chemotaxis and in addition, movement of gingival fibroblasts from confluent cultures to dentin has been observed.

Terranova et al. [22] have demonstrated that laminin promotes epithelial cell adhesion and growth to tetracycline and glycoprotein conditioned surfaces

3.7 Chlorhexidine

Bogle G, Rathburn E, Oliver R, and Egelberg J. [34] studied the effect of post operative use of chlorhexidine on regeneration of bifurcation defects in dogs. Chlorhexidine applied to the root surface during surgical treatment of bifurcation defects in dogs resulted in an increase in bone height but not in the level of connective tissue attachment.

3.8 Chondroitin Sulfate

Moss M, Kruger and Reynolds DC [35] observed that the use of chondroitin sulfate in extraction

sites accelerated the repair but did not affect the ultimate quantity or quality of bone produced.

3.9 Polyacrylic Acid

Wiland et al. [36] 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 surface during periodontal therapy, observed that Polyacrylic acid treated teeth have shown more apical migration. They also observed a greater connective tissue adhesion to root surfaces compared to citric acid treated root surfaces.

3.10 Sodium Hypochlorite

Sodium hypochlorite acts as a bactericidal and cleaning agent. It degrades endotoxins by hydrolysis.

Lasho DJ et al. [37] 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, the surface, showed a better appearance by exposing dentinal tubules and less debris. Sodium hypochlorite solution was prepared from chlorinated lime (22 gms), Anhydrous Sodium Carbonate (8.5 g) and water up to 100 ml.

3.11 Sodium Deoxy Cholate and Human Plasma Fraction Cohn IV

These agents can dissociate endotoxin into subunits and might thereby detoxify the diseased root surface. The human plasma fraction possibly contains fibronectin.

Wirthlin MR and Hancock EB [38] in a tissue culture study applied 2% NAD and 5% Cohn's fraction IV to periodontally diseased root surfaces from which plaque and calculus had been removed. This resulted in significantly more fibroblast attachment to the surfaces than treatment with phosphate buffered physiologic saline.

3.12 Formalin

Morris and Singh [39] reported clinical responses in 44 cases treated by interproximal denudation and root surface conditioning with a formalin solution. Radiographic evaluations indicated bone growth in 45 of 65 defects and clinical attachment gain of 2.7 mm. Since there were no

controls, they did not determine how much of the response was due to the surgical approach and how much resulted from the formalin application

3.13 Enzymes

Willey and Steinberg [40] evaluated the effect of topical applications of Hyaluronidase, Elastase and collagenase to citric acid - demineralized root surface.

All of the enzyme treatments appeared to expose more collagen than demineralization one. Collagenase application appeared to clear all ground substance from the collagen fibrils. The other enzymes appeared to clear partially the intercollagenous ground substance.

3.14 Stannous Fluoride

Selvig et al. [41] 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.

UM Wikesjo et al. [42] 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. The mechanism, whereby stannous fluoride has this untoward effect on the connective tissue dentine wound interface is not yet clear.

3.15 Growth Factors

They are polypeptide molecules released by cells in the inflamed area that regulate events in wound healing.

Rubins RP et al. [43] in a prospective consecutive case series, used recombinant human platelet-derived growth factor BB (rhPDGF-BB) with CTGs for the treatment of Miller Class I or II gingival recession defects and observed improved outcomes in terms keratinized tissue gains and percent root coverage at 6 months post surgery when compared to historic norms and concluded that the addition of rhPDGF-BB appeared to improve early wound healing as well.

3.16 Root Conditioning by Lasers

Recently, lasers have been recommended as an alternative or adjunctive therapy in the control and treatment of periodontally diseased root surface. Lasers are capable of sterilizing the diseased root surface and thus ultimately promoting cell reattachment.

Hess and Myers [44] said that the removal of root surface contaminants with these techniques allows for the, elimination of inflammation and possible attachment to adjacent hard tissue.

3.16.1 Commercially available laser systems

The number of commercially available laser systems is limited to some infrared laser namely, ER: YAG (Erbium: Yttrium, aluminum and garnet) lasers, ND: YAG (Neodymium: Yttrium; aluminum and garnet) and Carbon dioxide

3.16.2 ER: YAG laser

Hibst et al. [45] gave a first description of effects of Er: YAG laser on dental hard tissues. It is a very promising laser system because the emission wavelength of 2.9 μm coincides with the absorption peak of water resulting in good absorption in all biological tissues including enamel and dentin.

Er: YAG laser is also absorbed by hydroxyapatite. Therefore, the Er: YAG laser would ablate hard tissues containing some water more effectively and causes less thermal damage to the adjacent tissues.

Yamaguchi et al. [46] have demonstrated the ability of Er: YAG laser to remove lipopolysaccharides from root surfaces, facilitate removal of smear layer after root planing, remove calculus and cementum and leave a surface similar to an acid etched appearance.

Vamsi Lavu et al. [47] conducted a literature review on using Er: YAG laser for root biomodification concluded that Erbium lasers shows benefited outcomes when used as a root modifier owing to its anti-bacterial action, predictable calculus removal and minimal root substance removal favouring cell attachment.

3.16.2.1 Er, Cr:YSGG laser

R. Fekrazad et al. [48] conducted an *in-vitro* Study to evaluate Fibroblast Attachment in Root Conditioning with Er, Cr:YSGG Laser Versus

EDTA and found Er, Cr:YSGG laser conditioning can promote enhance fibroblast attachment on dentinal root surfaces more than EDTA

3.16.2.2 ND: YAG laser

It was developed by Geusic in 1964 and it has been proposed as an instrument with great potential for effective root preparation. Use of Nd: YG lasers as an adjunct to hand instruments and ultrasonics may have a role in both surgical and non-surgical periodontal therapy [49].

However, there are certain limitations with use of ND: YAG for the treatment of dental hard tissues. They cause thermal side effects such as cracking or charring at the target site and also pulpal damage unlike Er: YAG laser.

Application of the Nd: YAG laser to root surfaces results in [50].

- Alterations in root surface protein to mineral ratio,
- Affects the ability of fibroblasts to attach
- Alters the nature of the smear layer following conventional scaling and root planing.

A dilsiz et al. [51] have also reported negative outcomes of Nd:YAG laser in a clinical study on 17 patients for the Treatment of Gingival Recession with Subepithelial Connective Tissue Grafts.

3.16.2.3 Carbon-di-oxide laser

Patel et al. (1964) were the first to develop CO₂ laser. CO₂ lasers are capable of ablating calcified tissues effectively. However, they have the same limitations of thermal side effects such as cracking or charring at target site and pulpal damage like the Nd: YAG laser. Based on the various characteristics of lasers such as ablation, vaporization and sterilization, researchers have suggested their use for scaling, root planing and root conditioning.

Misra V, et al. [52]. In an in vitro study evaluates the effect of CO₂ laser on the periodontally involved root surface observed that Laser irradiation of 1 second at 3W completely removed the smear layer with minimal change in the diameter of the dentinal tubules.

Pant V, et al. [53] In an in vitro study observed the attachment behavior of human periodontal ligament fibroblasts on periodontally involved

root surface after conditioning with CO₂ laser and compare its efficacy with chemical conditioning agents, namely tetracycline hydrochloride, citric acid, hydrogen peroxide (H₂O₂) and EDTA, using scanning electron microscopy and found that CO₂ laser irradiation for 1.0 s promote comparatively better attachment of periodontal ligament fibroblast on dentinal root surfaces than the conventional chemical conditioning agents used in the study.

R Crespi et al. [54] in a randomized clinical trial comparing modified widman flap surgery with that of coronally advanced flap surgery with Co2 laser root conditioning for a follow up period of 15 years found that CAF + Co2 resulted in statistically significant result in terms pocket reduction at sites ≥7 mm and clinical attachment level at 5 to 6 mm.

3.17 Root Canal Irrigants as Root Biomodifier

The use of intracanal irrigant on periodontally affected root surface was first suggested by B.Houshmand et al. [55] using MTAD (root canal irrigant) as a root conditioner. He suggested that a statistically significant difference were seen in smear layer removal from periodontally affected root surface when compared with saline. C. Tandon et al. [56] concluded that MTAD as a root biomodifier have a significant role in periodontal wound healing and future new attachment both *in vitro* and *in vivo*.

Shewale A, Gattani D [57], in an In vitro study studied the potential of Q mix[®] a root canal irrigant containing Chlorhexidine and EDTA as a root biomodifier and concluded that Q mix was efficient in removing smear layer from periodontally affected root surface.

4. CURRENT STATUS

Angelo Mariotti² in a systematic review on efficacy chemical root surface biomodifiers in the treatment of periodontal disease concluded that chemical modifiers like EDTA, citric acid or tetracycline provides no benefit clinical significance to regeneration in patients with chronic periodontitis.

AAP Regeneration Workshop on Periodontal Soft Tissue Root Coverage Procedures [58] concluded that the use of root modifiers or other surface biomodification procedures did not provide superior gains in clinical outcomes, either

short or long term, than those expected for procedures performed without such agents.

Karam PSBH, et al. [59] conducted a systematic review on root surface modifiers and subepithelial connective tissue graft for treatment of gingival recessions and concluded that Based on the present clinical data, the use of root surface modifiers to improve clinical outcomes in gingival recessions treated with SCTG is not justified.

5. CONCLUSION

It is well established that the periodontally diseased root surface does not favour regeneration of the periodontium due to its surface characteristics. Demineralization has been shown to alter the diseased root surface, creating a more acceptable surface that can influence events in wound healing. The *in vivo* and *in vitro* studies clearly indicate a greater potential for cell and fiber attachment to demineralized root surfaces. Other factors such as spatial relationships and wound stabilization may also play a role in the extent and predictability of periodontal wound healing following root surface demineralization. Appropriate root surface conditioning may, therefore, regulate the adsorption of plasma proteins, enhance adhesion of the blood clot and stimulate deposition of collagen against the root surface. An understanding of the early events in wound healing, therefore, appears critical to the selection of appropriate agents and their potential to promote regeneration.

The recent use of Lasers on root surface does show promising results *in vitro* but more human randomized clinical trials are needed to prove its potential. Root canal irrigants are newly emerging agents tested for its therapeutic efficacy on root surface and still more studies are required. However, the present status suggests that root biomodification does not have any added advantage in periodontal regeneration. Large Size randomized clinical trials are necessary to give a definite conclusion.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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