

Emerging Methods Used in the Prevention and Repair of Carious Tissues

Brian H. Clarkson, PhD, Mary E. Rafter, MS

University of Michigan School of Dentistry
Cariology, Restorative Sciences, and Endodontics

Brian H. Clarkson, PhD
University of Michigan School of Dentistry
Cariology, Restorative Sciences, and Endodontics
1011 N. University
Ann Arbor, MI 48109-1078
Office (734) 763-1375
Fax (734) 936-1597
bricla@umich.edu

Key Words: Enamel, dentin, demineralization, remineralization, laser, fluoride release, BMP's, partitioned toothpaste

ABSTRACT

A systematic review was undertaken to investigate four emerging methodologies that might be used in the prevention of caries and/or repair of carious tissues. These included a partitioned dentifrice, laser technology, fluoride releasing dental materials, and for deep carious lesions, bone morphogenic protein (BMP) therapy. The search strategy was to review articles written in English, indexed in MEDLINE and EMBASE databases and published since 1976. Over 200 articles were read but because of the inclusion and exclusion criteria, only 33 were included in the evidence tables. The review of partitioned toothpaste, showed either a greater remineralizing effect, or a greater increase in the resistance to demineralization of both enamel and dentin with the exception of its lack of effectiveness on coronal caries in the only clinical trial. Five of the 6 *in vitro* studies on enamel and the one study on dentin reported that lased tissue was less soluble than non-lased. Six clinical and 4 *in situ* studies were reviewed in answering the question as to whether fluoride releasing restorative materials increase the remineralization or resistance to demineralization of human enamel and dentin. Eight of these reported positive findings. Six animal studies investigating BMP were reviewed and all showed ability of BMP to induce tubular dentin formation.

Although the laboratory, animal, and limited clinical trials report encouraging results, independent, randomized, controlled clinical trials need to be carried out before these emerging technologies can be recommended for use in general practice.

INTRODUCTION

Although there is evidence that caries has declined in children, it still affects some 50% of this population and approximately 95% of the adult population. Furthermore some 50-70% of a dentist's activity in the U.S. is devoted to the restoration of teeth which amounts to about 20-30 billion dollars in dental health care expenditures (1,2,3,4). In order to further combat the ravages of caries, new and alternative strategies, methods and materials must be used in its prevention and repair. Three of the techniques and technologies that were chosen for review, lasers, a partitioned dentifrice, and fluoride releasing materials, have already gained some acceptance by the dental profession and the general public. The other, the use of bone morphogenic proteins, has been suggested by the research community as a future treatment for deep carious lesions which may have resulted in pulp exposure. The evidence however, of the treatment efficacy of these emerging methods used in the prevention and repair of carious tissue, had not been subjected to a systematic review. Other modalities were considered, for example, gene therapy, protein initiated mineralization, self-assembling molecules and biofilm studies but insufficient data on their applicability to caries prevention and repair finally led to their exclusion from the review.

The questions addressed by this review were:

1. Does the partitioning of calcium from phosphate and fluoride in toothpastes increase the remineralization of demineralized enamel or dentin, or increase the resistance to demineralization of these tissues to a greater extent than a non-partitioned toothpaste?

This question was further broken down into 4 sub-questions by treating enamel, dentin, increasing remineralization, and increasing resistance to demineralization, as separate entities. A further division of these subgroups was conducted under the headings of human (clinical), animal and laboratory studies.

2. Is lased enamel and dentin more or less susceptible to demineralization compared to non-lased enamel and dentin?

In this question, only laboratory studies were found. Enamel and dentin were treated as separate questions.

3. Do fluoride releasing dental materials increase the remineralization of demineralized (cariou) human enamel or dentin, or increase the resistance to demineralization (caries) of these tissues?

Only human clinical trials and human *in situ* studies involving dental materials which had already gained some acceptance for use by the dental profession, were reviewed when answering this question. Experimental fluoride releasing devices were not included in the systematic review. Enamel and dentin studies were treated as different entities, as were remineralization and demineralization studies. Only studies reporting direct measures of changes in human enamel and dentin remineralization, and increased resistance to demineralization were included in answering this question. Articles using such indirect measures as fluoride uptake or plaque accumulation were excluded.

A final question was considered which was not as relevant to caries prevention but more closely linked to repairing dentinal caries.

4. Can bone morphogenic proteins, in particular BMP-7 (Op-1), be used to stimulate pulpal cells to produce new dentin (i.e., tubular dentin) in human, animal or *in vitro* studies?

As no human studies have been reported, and *in vitro* studies did not show tubular dentin formation, only animal studies were reviewed.

METHODS

The reviewers were not blinded to the identity of the authors or the source of the publication because there is no evidence that such blinding has any effect on the outcome of the review. Nor is blinding of reviewers required by the Agency for Health Care Policy and Research or recommended by experts in the field of systematic review (5).

The search strategy was to use articles published in peer-reviewed journals, written in English, and indexed in the MEDLINE and EMBASE databases. Literature review articles of the various topics were also reviewed by the investigators. None of these were systematic reviews and none contained original data. These literature reviews were therefore used to search for peer reviewed articles which may have been missed or inappropriately indexed in the MEDLINE and EMBASE searches. Only articles published since 1976 were considered. The databases were searched using appropriate key words for each question. Use was also made of the caries hedge, set up for reviewers involved in the systematic review for the Consensus Development Conference (CDC) entitled "Dental Caries Diagnosis and Management Throughout Life". References given in the reviewed articles were also searched for other relevant reports. The two investigators independently read all the abstracts from the MEDLINE, EMBASE, and

hand searches. Relevant reports were then tagged. Discrepancies between the investigators as to whether articles should be tagged or untagged were resolved by consensus after a further reading of the disputed abstracts. The articles of the tagged abstracts were then photocopied and shared equally between the two investigators, except for articles on the bone morphogenic protein, which were read only by one investigator (BHC). All articles were then abstracted and entered into the evidence tables under certain headings which varied with each question. Purely descriptive studies on BMP activity were included, but other descriptive studies where statistical analysis was deemed appropriate but not carried out, were excluded. Several other articles were excluded because:

- conclusions had been drawn on inappropriate statistics
- investigations had no control groups.

The scoring system for the articles was an all or none system based on the evidence table headings. For each heading where the information was available in the article a score of 1 was given. If this information was missing, it was given a score of 0. Abbreviated evidence tables are presented in this article, for complete tables and scores, see NIDCR's website <http://www.nider.nih.gov> All articles were scored independently and disagreements were resolved by consensus.

RESULTS

A total of over 200 abstracts were read in the four topic areas. In the final analysis only 33 were included in the evidence tables. Of these only 2 scored the maximum number of points available. The two major headings which were most

consistently without data were “Calibration and Reliability of Examiners” and “Blinding of Examiners” (see Evidence Tables <http://www.nider.nih.gov>). In only 1 of the included studies was a power calculation given to justify the number of samples (specimens, animals, humans) to be included in the investigations.

A decision was made by the investigators to include descriptive studies for question 4. All these studies were histological investigations and no direct numbers were generated in 3 of the 6 studies. In the laser studies (Question 2) descriptive investigations were not included, as the solubility measurements used to assess the effects of laser treatment on the tissue could have been statistically compared. The investigators in this study however, chose to draw their conclusions from the percentage difference in solubility between the experimental and control groups.

In question 1 (Table 1), dealing with partitioned toothpastes, only 12 of 35 abstracts dealt with a toothpaste that had the calcium separated from the other active ingredients, phosphate and fluoride, until these ions were delivered to the tooth surface. Of these, 7 were *in vitro* investigations, 3 were animal studies and 2 were clinical trials. On reading the full article, one *in vitro* study and one clinical study were excluded because insufficient data was reported to make a review meaningful.

All but two of the included studies relating to this question had one author’s name in common, but the research was carried out at several different institutions. Seven of the included animal and *in vitro* studies dealt with remineralization of enamel and there were no studies reporting on remineralization of dentin. The remaining 2 animal studies tested the partitioned toothpaste’s ability to increase the resistance of enamel to demineralization. There were no studies addressing dentin resistance to demineralization.

The only clinical trial tested the partitioned toothpaste's ability to inhibit both coronal and root caries. All these studies reported positive findings with the exception of the clinical trial, where the partitioned toothpaste reduced root caries but not coronal caries. Thus, in all but the class I clinical trial investigating coronal caries, the partitioned toothpaste showed either greater remineralizing effect, or a greater increase in the resistance to demineralization of either enamel or dentin when compared to a control toothpaste which was not partitioned.

Question 2 (Table 2) focused on the susceptibility to demineralization of lased versus non-lased enamel or dentin. Of the 84 abstracts initially read, 14 *in vitro* studies were finally evaluated. Seven of these were excluded because of no or inappropriate statistics. Of the 7 remaining, 5 concluded that lased enamel was less soluble than non-lased, and the article relating to lased dentin reached the same conclusion.

Question 3 (Table 3) asked whether fluoride releasing restorative materials increase the remineralization or the resistance to demineralization of human enamel and dentin. One hundred and twenty abstracts were tagged and read. Of the 8 clinical trials 2 were excluded because there were no control groups. Of the remaining 6, 1 was designated a class 11-1 study, 4 were class 11-2 studies, and 1 was a class 11-3 study. Of the 6 *in situ* studies which were also reviewed, two were excluded, one because it used bovine tissue and one for incomplete data. All but one of the clinical and *in situ* studies were short-term, < 16.3 months. The other lasted 3 years. A variety of methods were used for measuring remineralization and resistance to demineralization of both enamel and dentin. The study participants or specimens were also subjected to several different

caries challenges. Eight of the 10 studies did not report on examiner calibration and reliability.

Of the 6 clinical trials, 5 dealt with enhancing the resistance of enamel to demineralization and 1 with dentin remineralization. No clinical trials were included in this systematic review on enamel remineralization or increasing the resistance of dentin to demineralization, as either no studies had been conducted or those that had, did not meet the review criteria. Of the 5 clinical trials investigating the effects of fluoride releasing materials on enhancing enamel's resistance to demineralization, 4 recorded increased resistance and 1 showed no difference between the experimental and control groups. The single study relating to increased remineralization of dentinal lesions by these materials, demonstrated no difference between the experimental and control groups. The only study which had investigated remineralization of enamel in conjunction with increasing enamel resistance to demineralization failed to state the remineralization results. Of the 4 *in situ* studies, 2 investigations dealt with increasing the resistance to enamel demineralization, one study looked at both increasing the resistance to enamel demineralization and enhancing enamel remineralization, and one looked at dentin remineralization. This indicated that the fluoride-releasing materials increased dentin remineralization. No *in situ* studies investigating enhanced resistance of dentin to demineralization had been performed. All 3 studies investigating changes in enamel resistance to demineralization recorded increased resistance.

To answer question 4 (Table 4), eighty-three abstracts relating to bone and pulpal cell stimulation by growth factors were read. However, only 6 articles relating to BMP's ability to stimulate dentin formation, as defined by the formation of tubular dentin were

located. All six articles finally reviewed were animal studies, and irrespective of the species, all showed that BMP stimulated new dentin formation. The reparative dentin formed included both tubular and non-tubular (osteo) dentin. One study, which tested transdentin diffusion of BMP, showed that BMP activity did, in fact, cross dentin. Two of these studies used a crude BMP extract and 4 used purified or recombinant BMP-7 (Op-1).

CONCLUSIONS

Question 1: In spite of the fact that several of the studies undertaken using the partitioned toothpastes had one author in common, and that only a few studies had been conducted, there is sufficient evidence from the animal and *in vitro* investigations to suggest that this technology has promise in the prevention of enamel caries. However, in humans, the only class I clinical trial in a high risk population failed to show a difference in enamel caries reduction between experimental and control groups. However, in the same study the partitioned toothpaste prevented root caries to a greater extent than a conventional toothpaste. Independent, randomized, controlled, clinical trials need to be conducted before the usefulness of this therapy can be generalized to all population groups. Laboratory, animal and further human studies, need to be conducted to ascertain its usefulness in dentin caries prevention.

Question 2: *In vitro* testing of the solubility of lased enamel has documented that it is less susceptible to demineralization than non-lased enamel. The results for dentin are similar but only 2 studies met the criteria to be included in this review. Further *in vitro* investigations to determine if lased dentin is indeed less soluble, should be undertaken.

The reviewed studies used several different laser types, application times, wavelengths, power, demineralization models, and target distances (i.e., distance from laser head to tissue) making it impossible to recommend a standard procedure. Thus, investigations should be performed which result in a standard protocol for application in clinical trials. These should be carried out before this procedure can be recommended for caries prevention in dental practice.

Questions 3: The small number of studies investigating the effectiveness of fluoride releasing dental materials that used direct measures of caries prevention, and the short duration of these studies, make it impossible to draw any conclusions concerning the long-term benefits for their use in caries preventive programs. Therefore randomized, controlled clinical trials need to be conducted over a period of at least 2 years, to answer the four sub-questions reviewed in this paper, that is, whether fluoride releasing dental materials increase the remineralization of carious enamel and dentin; and whether these materials increase the resistance of enamel and dentin to caries.

Question 4: All the animal studies reviewed reported that crude BMP extracts, purified and recombinant BMP-7 were able to regenerate dentin (tubular and atubular) when placed on vital pulps. One study also showed that the active signaling molecule can cross dentin and stimulate a pulpal response. One anecdotal report of a clinical trial using BMP-7 suggested that the results of the study were equivocal. The animal studies however, suggest a very positive performance of this therapy. Further investigations should be undertaken controlling for the drug carrier and studying the effect of inflammation on the BMP-7 activity. On completion of these animal studies, human clinical trials should be conducted.

It was disappointing to note that only two of the studies in this review obtained the maximum score based on the usual data (see Evidence Table headings <http://www.nider.nih.gov>) required to be included in published articles. Certainly headings, e.g., calibration and blinding of examiners, may not be as pertinent to some *in vitro* studies, but these scores indicate a lack of attention to detail in describing the experimental design in the articles, and on the thoroughness of the review the articles received prior to publication.

REFERENCES

1. American Dental Association. 1991 survey of dental practice. General characteristics of dentist. Chicago.
2. Elderton RJ, Davies JA. Restorative dental treatment in the General Dental Service in Scotland, *British Dent J* 1984;157(6): 196-200.
3. Maryniuk GS, Kaplan SH. Longevity of restorations: survey results of dentists' estimates and attitudes, *J Am Dent Assoc* 1986;112(1): 39-45.
4. Mjor IA. Placement and replacement of restorations, *Operative Dentistry* 1981;6: 49-54.
5. Meade MO, Richardson WS. Selecting and appraising studies for a systematic review. In: Mulrow C, Cook D, eds. *Systematic reviews: synthesis of best evidence for health care decisions*. Philadelphia: American College of Physicians, 1998.
6. Papas A, Russell D, Singh M, Stack K, Kent R, Triol C, Winston A. Double blind clinical trial of a remineralizing dentifrice in the prevention of caries in a radiation therapy population, *Gerodontology*. 1999 Jul; 16(1): 2-10.
7. Grant LP, Thompson A, Tanzer JM. Caries inhibition in rats by a remineralizing toothpaste. *J Clin Dent* 1999;10: 30-33.
8. Thompson A, Grant LP, Tanzer JM. Model for assessment of carious lesion remineralization, and remineralization by a novel toothpaste, *J Clin Dent* 1999;10: 34-39.

9. Mundorff-Shrestha SA, Proskin HM, Winston AE, Triol CW, Cornell G, Sharpe T. Cariostatic effect of a two-part fluoride dentifrice in rats. *J Clin Dent* 1999;10: 26-29.
10. Hicks MJ, Flaitz CM. Enamel caries formation and lesion progression with a fluoride dentifrice and a calcium-phosphate containing fluoride dentifrice: A polarized light microscopic study. *J Dent Child* 2000 Jan-Feb; 67(1): 21-8.
11. Kardos S, Shi B, Sipos T. The in vitro demineralization potential of a sodium fluoride, calcium and phosphate ion-containing dentifrice under various experimental conditions. *J Clin Dent* 1999;10: 22-25.
12. Schemehorn BR, Wood GD, Winston AE. Laboratory enamel solubility reduction and fluoride uptake from enamelon dentifrice. *J Clin Dent* 1999;10: 9-12.
13. Wolinsky LE, Gnagne-Agnero NDY, Chamkasem P, Jason S, Triol CW, Winston AE. An in vitro assessment and a pilot clinical study of electrical resistance of demineralized enamel. *J Clin Dent* 1999;10: 40-43.
14. Munoz CA, Feller R, Haglund A, Triol CW, Winston AE. Strengthening of tooth enamel by a remineralizing toothpaste after exposure to an acidic soft drink. *J Clin Dent* 1999;10: 17-21.
15. Schemehorn BR, Orban JC, Wood GD, Fischer GM, Winston AE. Remineralization by fluoride enhanced with calcium and phosphate ingredients. *J Clin Dent* 1999;10: 13-16.

16. Goodman BD, Kaufman HW. Effects of an argon laser on the crystalline properties and rate of dissolution in acid of tooth enamel in the presence of sodium fluoride. *J Dent Res* 1977;56(10): 1201-1207.
17. Nelson DGA, Shariati M, Glana R, Shields CP, Featherstone JDB. Effect of pulsed low energy infrared laser irradiation on artificial caries-like lesion formation. *Caries Res* 1986;20: 289-299.
18. Hicks MJ, Flaitz CM, Westerman GH, Berg JH, Blankenau RL, Powell GL. Caries-like lesion initiation and progression in sound enamel following argon laser irradiation: An in vitro study. *J Dent Child* 1993;May-June: 201-206.
19. Tagomori S. Ultrastructural change of enamel exposed to a normal pulsed Nd-YAG laser. *Caries Res* 1995;29: 513-520.
20. Featherstone JDB, Barrett-Vespone NA, Fried D, Kantorowitz Z, Seka W. CO₂ laser inhibition of artificial caries-like lesion progression in dental enamel. *J Dent Res* 1998;77(6): 1397-1403.
21. Kantorowitz ZVI, Featherstone JDB, Fried D. Caries prevention by CO₂ laser treatment: Dependency on the number of pulses used. *J Am Dent Assoc* 1998;129: 585-590.
22. Kimura Y, Wilder-smith P, Arrastia-Jitosho AMA, Liaw L-HL, Matsumoto K, Berns MW. Effects of nanosecond pulsed Nd:YAG laser irradiation on dentin resistance to artificial caries-like lesions. *Lasers Surg Med* 1997;20: 15-21.
23. Wenderoth CJ, Weinstein M, Borislow AJ. Effectiveness of a fluoride-releasing sealant in reducing decalcification during orthodontic treatment. *Am J Orthod Dentofacial Orthop* 1999;116: 629-634.

24. Kreulen CM, deSoet JJ, Weerheijm KL, van Amerongen WE. In vivo cariostatic effect of resin modified glass ionomer cement and amalgam on dentine. *Caries Res* 1997;31: 384-389.
25. Twetman S, McWilliam JS, Halgren A, Oliveby A. Cariostatic effect of glass ionomer retained orthodontic appliances. *Swed Dent J* 1997;21: 169-175.
26. Banks PA, Burn A, O'Brien K. A clinical evaluation of the effectiveness of including fluoride into an orthodontic bonding adhesive. *Eur J Ortho* 1997;19: 391-395.
27. Øgaard B, Rezk-Lega F, Ruben J, Arends J. Cariostatic effect and fluoride release from a visible light-curing adhesive for bonding of orthodontic brackets. *Am J Orthod Dentofac Orthop* 1992;101: 303-307.
28. Rezk-Lega F, Øgaard B, Arends J. An in vivo study on the merits of two glass ionomers for the cementation of orthodontic bands. *Am J Orthod Dentofac Orthop* 1991; 99: 162-167.
29. Dijkman EHM, Arends J. Secondary caries in situ around fluoride-releasing light-curing composites: A quantitative model investigation on four materials with a fluoride content between 0 and 26 vol%. *Caries Res* 1992;26: 351-357.
30. Donly KJ, Segura A, Wefel JS, Hogan MM. Evaluating the effects of fluoride-releasing dental materials on adjacent interproximal caries. *J Am Dent Assoc* 1999;130: 817-825.
31. Benelli EM, Serra MC, Rodrigues AL Jr, Cury JA. In situ anticariogenic potential of glass ionomer cement. *Caries Res* 1993;27: 280-284.

32. De Los Santos R, Lin Y-T, Corpron RE, Beltran ED, Strachan DS, Landry PA. In situ remineralization of root surface lesions using a fluoride chewing gum or fluoride-releasing device. *Caries Res* 1994;28: 441-446.
33. Nakashima M. Dentin induction by implants of autolyzed antigen-extracted allogeneic dentin on amputated pulps of dogs. *Endod Dent Traumatol* 1989;5: 279-286.
34. Nakashima M. The induction of reparative dentine in the amputated dental pulp of the dog by bone morphogenetic protein. *Archs oral Biol* 1990;35(7): 493-497.
35. Lianjia Y, Yuhao G, White FH. Bovine bone morphogenetic protein-induced dentinogenesis. *Clin Orthopaed Related Res* 1993;295: 305-312.
36. Rutherford RB, Wahle J, Tucker M, Rueger D, Charette M. Induction of reparative dentine formation in monkeys by recombinant human osteogenic protein-1. *Archs oral Biol* 1993;38(7): 571-576.
37. Rutherford RB, Spångberg L, Tucker M, Rueger D, Charette M. The time-course of the induction of reparative dentine formation in monkeys by recombinant human osteogenic protein-1. *Archs oral Biol* 1994;39(10): 833-838.
38. Rutherford B, Spångberg L, Tucker M, Charette M. Transdental stimulation of reparative dentine formation by osteogenic protein-1 in monkeys. *Archs oral Biol* 1995;40(7): 681-683.