Effect of remineralizing agents on white spot lesions after orthodontic treatment: A systematic review

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Introduction: White spot lesions are a common complication after orthodontic treatment. The aim of this systematic review was to investigate which remineralizing agents are effective for the treatment of white spot lesions after orthodontic treatment. **Methods:** According to predetermined criteria, 4 databases were searched for appropriate studies. References of the selected articles and relevant reviews were searched for any missed publications. **Results:** Seven randomized controlled trials were selected as eligible studies, and only qualitative analyses were performed because of the diversity of the interventions and outcome measures. Two studies showed significant effects of 2 different fluoride preparations: one with a small sample size and several methodologic deficiencies, and the other using only nonconventional detection methods (ie, DIAGNOdent pen, KaVo, Biberach, Germany) to assess white spot lesions. Two studies involved casein phosphopeptide-amorphous calcium phosphate, which seemed to be effective for the regression of white spot lesions. However, the statistical analysis in 1 study was based on the tooth surfaces instead of the patient, and the visual examination used in the other study to assess the white spots was not reliable. **Conclusions:** Based on the literature, there is a lack of reliable evidence to support the effectiveness of remineralizing agents for the treatment of postorthodontic white spot lesions. (Am J Orthod Dentofacial Orthop 2013;143:376-82)

White spot lesions (WSLs) are defined as a "subsurface enamel porosity from carious demineralization" that presents as "a milky white opacity when located on smooth surfaces."[1] Since fixed orthodontic appliances were introduced, WSLs have become a particular clinical problem that can be attributed to the difficulties in performing oral hygiene procedures on bonded dental arches and the prolonged plaque accumulation on tooth surfaces.[2] Despite many attempts at comprehensive prophylaxis, the prevalence of WSLs remains as high as 61% when debonding.[3] It is generally believed that these lesions will recover through natural remineralization with saliva once the orthodontic appliances have been removed and oral hygiene is restored.[4] However, the removal of stagnant plaque alone is not enough to achieve complete repair of WSLs, and some spots secondary to debonding can last from 5 to 12 years.[5,6] Natural remineralization through saliva involving mineral gain in the surface layer of WSLs has little improvement on the esthetics and structural properties of the deeper lesions.[7] Therefore, it is necessary to apply remineralizing agents to repair the deeper parts of WSLs for better esthetic results.

Although the treatment of postorthodontic WSLs differs from their prevention during orthodontic procedures, common interventions include fluoride and calcium phosphate-based remineralizing agents. Fluoride has been shown to arrest the development and progression of carious lesions during orthodontic treatment,[8] but concentrated fluoride is not recommended for treatment of WSLs on the labial surfaces of teeth, since hypermineralization maintains the whiteness of the lesions.[4,9] Casein phosphopeptide amorphous calcium phosphate is another agent that has garnered the most attention

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among the calcium phosphate-based technologies. It has been shown that casein phosphopeptides work by increasing the levels of calcium and phosphate ions in the subsurface lesions, and can be further enhanced by incorporating fluoride.[10,11] Hence, this remineralizing system has the potential to achieve subsurface remineralization and to esthetically repair WSLs.

Compared with the evidence on the prevention of WSLs during orthodontic treatment, less is known regarding their treatment with remineralizing agents after orthodontic therapy. Presently, several randomized controlled clinical trials have shown the effects of remineralizing agents on postorthodontic WSLs; however, there have been no systematic evaluations of these results. Therefore, the purposes of this systematic review were to assess the direct evidence regarding the effect of remineralizing agents on postorthodontic WSLs and to evaluate which remineralizing agents are effective for the treatment of WSLs after orthodontic treatment.

MATERIAL AND METHODS

The method for this review was according to Cochrane Oral Health Group's Handbook for Systematic Reviews of Interventions (http://ohg.cochrane.org).

The inclusion criteria were (1) randomized controlled clinical trials regarding the application of remineralizing agents for the treatment of postorthodontic WSLs; (2) studies in which participants completed the fixed orthodontic treatment and had at least 1 clinically visible lesion on the labial enamel surface upon removal of the fixed orthodontic appliances; (3) studies in which interventions included remineralizing agents for the treatment of postorthodontic WSLs (ie, any fluoride or casein phosphopeptide-based system); (4) studies in which the control group consisted of patients subjected to different agents or not subjected to an intervention (either a placebo or no intervention); and (5) studies in which the primary outcome was the change in the severity of the lesions between the experimental and control groups, and the severity was expressed macroscopically in terms of the area over the whiteness of the lesion or microscopically by the amount of mineral loss or lesion depth.

The exclusion criterion was any study in which the participants underwent any nonremineralizing therapy (eg, bleaching, enamel microabrasion, or restoration) for WSLs after their orthodontic treatment.

For the identification of studies included in or considered for this review, the following databases were searched: PubMed (from 1966 to week 4 of July 2012), Ovid MEDLINE (from 1946 to week 4 of November 2011), Web of Science (from 1980 to week 4 of July 2012), and the Cochrane Library (to week 4 of July 2012). To locate additional studies, the references of the selected articles and relevant reviews were also checked. The search strategies included a combination of controlled vocabulary and free text terms (refer to the full strategy in Appendix 1). No limits were set on year, publication status, or language of the trials.

According to the predetermined inclusion and exclusion criteria, all titles and abstracts were examined by 1 reviewer (H.C.) to find relevant studies; the full texts of the relevant studies were scrutinized by 2 reviewers (H.C. and T.G.) independently to select eligible studies. Any disagreement was discussed, and the opinion of a third reviewer (Y.D.) was sought if necessary.

Data from all eligible studies were extracted by 2 reviewers (H.C. and T.G.) independently, in duplicate, using a specially designed data extraction form that was piloted in several articles and modified as required before use. Any disagreement was discussed, and a third reviewer (Y.D.) was consulted when necessary.

For each included study, descriptive and quantitative information was extracted, including citation author, year of publication, experimental treatment (number of subjects), control treatment (number of subjects), treatment duration, assessment method, results of baseline and follow-up visits, authors' conclusions, and all information needed for quality evaluation criteria. Authors were contacted for clarification or missing information.

Each study's methodologic quality was assessed by using the domain-based evaluation described in the Cochrane Handbook for Systematic Reviews of Interventions 5.0.2.[12] Using the guidelines in the Cochrane Handbook, 2 reviewers (H.C. and X.L.) independently assessed the quality of the identified studies. If their opinions differed, the articles were referred to the third reviewer (Z.J.) for independent review and recomparison of the results. The consensus approach was used for any disagreement.

The reviewers categorized the following 6 quality items as "yes" (low risk of bias), "unclear" (uncertain risk of bias), or "no" (high risk of bias): sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. The level of risk for each study was then classified as low (all quality items were met), medium (1 or 2 quality items were not met), or high (3 or more quality items were not met).

Statistical analysis

For studies with continuous outcomes that used patient units for statistical comparison, mean differences

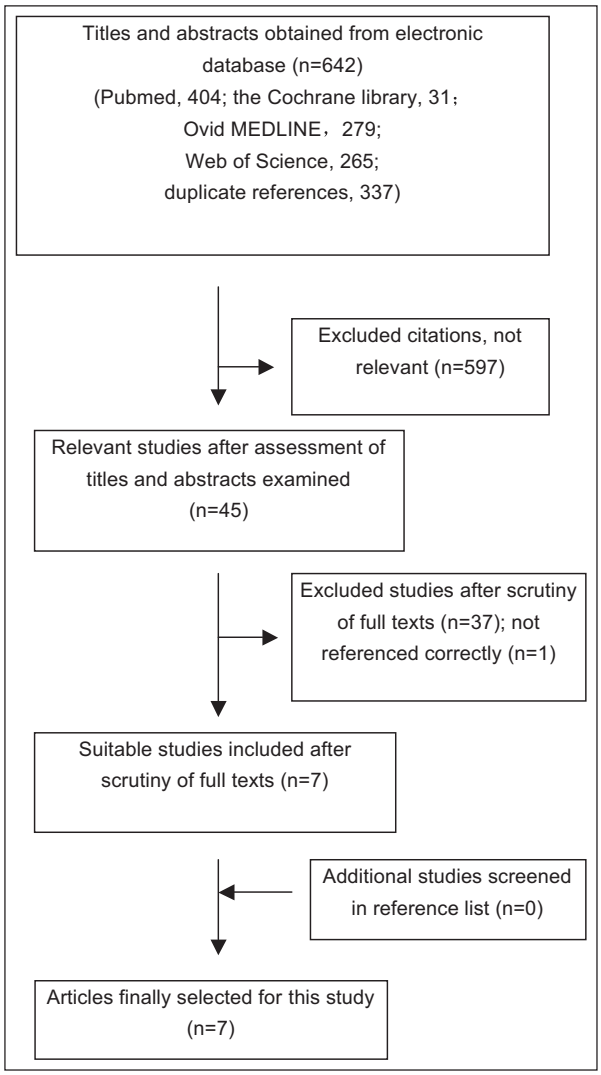

Fig. Flow diagram of the included studies.

between the experimental and control groups and 95% confidence intervals (CIs) were used to summarize the data.[13-17] For a study that used the tooth surface unit for statistical analysis, we could not calculate the mean differences and 95% CIs because the patient unit data could not be obtained.[18] The clinical methodologies of all studies were assessed by examining the types of interventions and outcomes. A meta-analysis was planned to combine the data of studies with sufficient similarities in their methodologies.

RESULTS

The electronic and hand searches retrieved 642 unique citations, which were entered into a flow chart (Fig 1) to illustrate the path for selecting the final trials. After evaluating titles and abstracts, we obtained 45 relevant studies (1 study[19] could not be located). After evaluating the full texts, we selected 7 studies as eligible[13-18,20]; 37 articles were excluded from the study. A list of the excluded articles and the reasons for exclusion is in Appendix II. After searching the references of the selected articles and relevant reviews, we identified no additional eligible studies. Finally, 7 studies, all in English, were used for the systematic review, and a description of each is given in Table I.

Among the 7 included studies, 3 randomized controlled trials evaluated the effects of 3 fluoride preparations: 50-ppm sodium fluoride mouth rinse, 5% sodium fluoride varnish, and 0.5% sodium fluoride chewing sticks. The remaining 4 studies compared the effects of remineralizing agents containing casein phosphopeptide amorphous calcium phosphate or casein phosphopeptide amorphous calcium fluoride phosphate; 2 studies had an inactive control, and 2 used a fluoride control. No significant similarities in methodologies could be found in these studies. Casein phosphopeptide amorphous calcium phosphate was included in 3 studies, with varying criteria for the visual examination.[13,18,20] Two studies used quantitative light-induced fluorescence, but with different interventions (one with casein phosphopeptide amorphous calcium phosphate alone, and the other with a combination of casein phosphopeptide amorphous calcium phosphate and fluoride).[13,14] Based on the circumstances, it was not feasible to create a pool of data to perform a meta-analysis. Thus, a qualitative analysis was undertaken.

All studies had methodologic problems after examination and contact with the authors (Table II). Whether the randomization had been blinded was not reported in 4 studies,[13,15,17,18] and the blinding procedure was unclear in 2 studies.[14,20] Whether the operator and the evaluator were separate persons was unclear in 2 studies.[17,18] Two studies[13,18] did not report the data based on patients, and 1 study[20] did not report a prespecified primary outcome measured by quantitative light-induced fluorescence. Statistical analyses of 2 studies were based on the number of teeth,[13,18] and the assessment methods of 2 studies were only through technology-based methods (DIAGNOdent pen [KaVo, Biberach, Germany] or quantitative light-induced fluorescence).[14,15]

The included studies were grouped into 3 comparisons according to the strategy of the interventions.

One study assessed the effect of 50 ppm of fluoride for the treatment of WSLs by using computerized image analysis to measure the lesion sizes.[16] In a 26-week follow-up, the value of the average difference in the percentage of reduction of lesion size was not significantly

Table I. Summary of included studies

Authors	Participants, test/control	Follow-up	Test vs control	Assessment method	Start, test/control (SD)	End, test/control (SD)
Willmot[16]	15/11	Debond, 12 w, 26 w	50 ppm NaF rinse* vs control rinse*	Photographs		Difference of 0-26 w: ADPR 54.3% (12.3)/66.1% (15.5)
Du et al[15]	55/55	Debond, 3 m, 6 m	5% NaF varnish vs saline solution	DIAGNOdent	DR 17.66 (5.36)/16.19 (5.70)	DR 10.10 (4.86)/13.10 (5.19)
Baeshen et al[17]	19/18 Sites 152/140	Deband, 2 w, 4 w, 6 w	0.5% NaF Miswaks† vs control Miswaks†	DIAGNOdent, clinical scores	DR 13.2 (5.6)/11.5 (6.1) Clinical scores 2.4 (0.8)/2.0 (0.9)	DR 4.5 (2.9)/9.4 (5.3) Clinical scores 1.0 (0.8)/1.7 (1.0)
Andersson et al[18]	13/13 Sites 70/62	Debond, 1 m, 3 m, 6 m, 12 m	CPP-ACP (Topacal) vs fluoride rinse†	DIAGNOdent, clinical scores	DR 7.4 (10.2)/9.4 (9.5)	DR 4.4 (5.2)/6.4 (7.5) Difference of 0-12 m: PCS (score 0, 1): 64%/23%
Bröchner et al[13]	30/30	Deband, 4 w	CPP-ACP (tooth mousse) vs fluoride toothpaste	Clinical scores, QLF	PCS (score 1) 15.4%/14.9% ΔF 6.68 (0.58)/7.04 (1.65) A 0.12 (0.16)/0.19 (0.43)	PCS (score 1) 47.7%/52.7% ΔF4.45 (1.82)/4.51 (2.46) A 0.05 (0.09)/0.14 (0.31)
Bailey et al[20]	23/22 Sites 207/201	Deband 4 w, 8 w, 12 w	CPP-ACP (tooth mousse) † vs control cream†	Clinical scores		Difference of 0-12 w: PCS (score 0, 1): 8.6%/8.5% PWT (score 2, 3): 76.8%/58.6%
Beerens et al[14]	35/30	Debond, 6 w, 12 w	CPP-ACFP (MI-Paste) † vs control paste†	QLF	ΔF 8.45 (1.17)/9.10 (1.75) A 5.07 (5.69)/7.29 (7.91)	ΔF 7.52 (1.78)/7.96 (2.76) A 5.05 (6.98)/7.17 (7.76)

W, Week; *m*, month; *NaF*, sodium fluoride; *CPP-ACP*, casein phosphopepetide-amorphous calcium phosphate; *CPP-ACFP*, casein phosphopepetide-amorphous calcium fluoride phosphate; *ADPR*, average difference in the percentage of the reduction; *DR*, DIAGNOdent reading; *QLF*, quantitative light-induced fluorescence; *PCS*, proportion of clinical scores; *PWT*, proportion of WSLs transitions; *ΔF*, change in fluorescence; *A*, lesion area.
*Toothbrushing with fluoride-free toothpaste; †toothbrushing with fluoride toothpaste.

Table II. Risk of bias for every study

Author	Adequate sequence generation	Allocation concealment	Blinding of outcome assessors	Incomplete outcome data addressed	Selective outcome reporting	Free of other bias	Level of risk for bias
Willmot[16]	Yes	Yes	Yes	No	Yes	No	Medium
Du et al[15]	Yes	No	Yes	No	Yes	No	High
Baeshen et al[17]	Yes	No	Unclear	Yes	Yes	No	High
Andersson et al[18]	Yes	No	Unclear	No	No	No	High
Bröchner et al[13]	Yes	No	Yes	No	No	No	High
Bailey et al[20]	Yes	Unclear	Yes	Yes	No	No	High
Beerens et al[14]	Yes	Unclear	Yes	No	Yes	No	High

decreased in the test group compared with the control group (mean difference, −0.12; 95% CI, −0.25, 0.01). Another study tested the efficacy of fluoride varnish (5% sodium fluoride) assessed with laser fluorescence (DIAGNOdent), and indicated that the DIAGNOdent readings were significantly different between the fluoride-treated group and the control group (mean difference, −4.47; 95% CI, −6.59, −2.35).[15] The third study compared 0.5% sodium fluoride chewing sticks with nonfluoridated chewing sticks by using visual inspection (International Caries Detection and Assessment System II index criteria) and DIAGNOdent.[17] At the end of treatment, both the DIAGNOdent readings and the International Caries Detection and Assessment System II index were significantly decreased in the intervention group compared with the control group (mean difference, 6.60; 95% CI, 4.68, 8.52; mean difference, 1.10; 95% CI, 0.77, 1.43; respectively).

One study was performed by visual scoring (0-4) and laser fluorescence (DIAGNOdent).[18] After 12 months, the laser fluorescence readings were not significantly decreased in the casein phosphopeptide amorphous calcium phosphate group (mean, 4.4; SD, 5.2) compared with the fluoride group (mean, 6.4; SD, 7.5). The proportion of the visual scoring of 0 (no white spots) to 1 (slight white spot only visible after air drying) was significantly increased in the casein phosphopeptide amorphous calcium phosphate group compared with the fluoride group (64% vs 23%). Another study was carried out through visual inspection (Gorelick criteria) of digital photographs and quantitative light-induced fluorescence for 4 weeks.[13] At the end of treatment, there were no significant differences in fluorescence loss (mean difference, −0.02; 95% CI, −0.17, 0.13) and lesion areas (mean difference, 0.3; 95% CI, −0.75, 1.35) between the groups. The proportions of WSLs with a score of 1 were 47.7% in the intervention group and 52.7% in the control group; this was not a significant difference.

One study used the International Caries Detection and Assessment System II index criteria to compare the effect of casein phosphopeptide amorphous calcium phosphate cream with a placebo cream for 12 weeks.[20] The results showed that, compared with baseline scores, the proportion of the visual scoring of 0 or 1 did not increase to a greater extent in the casein phosphopeptide amorphous calcium phosphate group compared with the control group (8.6% vs 8.5%). With regard to the lesions with visual scores of 2 (white spot visible when wet) and 3 (loss of enamel surface integrity), the significant regression of the proportion of WSLs with a score of 2 or 3 to 0 after 12 weeks was detected in the casein phosphopeptide amorphous calcium phosphate group compared with the placebo group (76.8% vs 58.6%). Another study used quantitative light-induced fluorescence to compare casein phosphopeptide amorphous calcium fluoride phosphate paste with a control paste for a 3-month intervention period.[14] No statistically significant differences between the groups were observed with regard to the sizes of the lesion areas (mean difference, 0.10; 95% CI, −3.72, 3.92) or the fluorescence loss (mean difference, 0.21; 95% CI, −0.88, 1.30).

DISCUSSION

A limited number of eligible studies were identified in this review. None of them was adjudged to be at low risk of bias, with most having a high risk of bias either due to inadequacies in several quality items or arising from other biases, chiefly problems associated with assessment methods or inadequate designs. Other shortcomings included small sample sizes, unclear selection criteria, unreliable statistical analyses that failed to account for clustering effects, and use of unproven assessment methods without relating them to more accepted techniques (eg, visual inspection). Future study designs should include appropriate randomization, blinding of treatment groups, masking of outcome assessments, rigid eligibility criteria, and appropriate analyses to reduce bias. As a result of both methodologic deficiency and the diverse interventions and outcome measures, quantitative synthesis was not possible. Of all 7 included studies, 3 failed to find significant effects of low fluoride and casein phosphopeptide amorphous calcium phosphate or casein phosphopeptide amorphous calcium fluoride phosphate for reversing WSLs.[13,14,16] However, although the absence of effects might have been due to the ineffectiveness of these agents, insufficient sample sizes to detect significant differences could also have been a factor.

Visible WSLs can evoke concern from patients[21]; therefore, visual assessment by clinical or photographic examination is the most relevant approach for the assessment of WSLs. With clinical index systems, visual assessment can be used to quantify the severity of WSLs, although it is not sufficiently sensitive to detect small changes in WSLs.[22,23] With clinical photography, consensus can be reached between raters, permitting quantification of the lesions.[21] However, reproducible assessment of photographs is contingent on consistent lighting to reduce reflections, which can mask or mimic WSLs. Quantitative light-induced fluorescence and DIAGNOdent are sensitive techniques that can also be used to quantitatively assess WSLs. With quantitative light-induced fluorescence, the images of enamel with incipient lesions are captured, and the fluorescence loss and lesion area can be quantified.[24] Quantitative light-induced fluorescence has the advantage of a closer correlation with changes in enamel structure and mineral content.[25,26] The DIAGNODent readings should be interpreted with caution because statistically significant differences might not necessarily have clinical significance. DIAGNOdent readings can also be affected by stains, calculus, and plaque[27] and are based on bacterial metabolites,[28] which are not directly related to the problems perceived by patients or doctors. Combined use of both technology-based methods and visual assessment could be the best approach in future studies.

Importantly, for the assessment of demineralized lesions, only 1 included study referred to preorthodontic images to exclude white spots of nonorthodontic origin.[16] Developmental white spots can preexist in orthodontic patients and be misdiagnosed as demineralization.[29,30] However, developmental opacities can be differentiated from WSLs by higher luminescence and more circular boundaries than postorthodontic

lesions.[31] Authors of future studies should refer to the pretreatment photographic slides to exclude any preexisting white lesions.

Although the remineralizing capacity of fluoride on enamel is accepted, the evidence is insufficient to support the effectiveness of fluoride for the remineralization of postorthodontic WSLs.[32] Factors that might have confounded this potential relationship include inappropriate fluoride concentration and poor compliance.[33] However, variations in fluoride concentration were not found to be important in 1 clinical study.[16] Compliance with daily fluoride rinsing among orthodontic patients has been shown to be as low as 13%.[34] Nevertheless, 1 randomized controlled trial found that fluoride varnish is effective in reversing WSLs after debonding as assessed with DIAGNOdent.[15] However, unclear inclusion criteria regarding WSLs and use of an overly sensitive assessment method most likely influenced the reliability of the results. Additionally, the statistically significant differences detected by DIAGNOdent might not necessarily have clinical significance. In another randomized controlled trial, the authors used the International Caries Detection and Assessment System II index and DIAGNOdent, and studied the remineralizing effect of fluoridated chewing sticks on WSLs.[17] Although the therapeutic effect of fluoridated chewing sticks was simultaneously demonstrated by using 2 assessment methods, this trial had a small sample size, inadequate inclusion criteria, inadequate randomization, and unclear blinding of the evaluator, rendering the evidence weak. Therefore, additional larger trials of this fluoridated preparation are required to provide a more definitive assessment.

Both in-vitro[10,35] and in-situ studies[36,37] have demonstrated that casein phosphopeptide amorphous calcium phosphate can promote the remineralization of subsurface enamel lesions; however, current clinical evidence is insufficient to prove a clinical benefit of casein phosphopeptide amorphous calcium phosphate in noninvasive management of postorthodontic WSLs. Two randomized controlled clinical trials[13,18] compared casein phosphopeptide amorphous calcium phosphate against fluoride, one of which over a 4-week period did not show a significant benefit of casein phosphopeptide amorphous calcium phosphate[13]; however, the experimental period was short, and compliance was unclear. Another study, using visual inspection, found statistically significant differences between the interventions, although the statistical unit was the tooth surface rather than the patient; the authors failed to adjust for clustering effects.[18]

It has been suggested that the combination of casein phosphopeptide amorphous calcium phosphate and fluoride can increase the incorporation of fluoride in subsurface enamel and might promote remineralization.[11] One study investigated the effect of casein phosphopeptide amorphous calcium phosphate in combination with fluoride toothpaste and found that the more active WSLs in the casein phosphopeptide amorphous calcium phosphate group regressed to inactive WSLs.[20] However, visual assessment of the activity of WSLs is challenging, and even inactive lesions can result in esthetic impairment.[38] A further 3-month study using sensitive technology (quantitative light-induced fluorescence) failed to detect any remineralizing effects of casein phosphopeptide amorphous calcium fluoride phosphate.[14] Consequently, further research to verify the efficacy of this combined therapy would be beneficial.

CONCLUSIONS

This systematic review indicated a lack of reliable evidence to support the effectiveness of remineralizing agents for the treatment of postorthodontic WSLs. Additional high-quality studies with strict eligibility criteria, a combination of specific and sensitive detection methods, and reliable statistical analyses are required.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found in the online version at http://dx.doi.org/10.1016/j.ajodo.2012.10.013.

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Appendix I. PubMed search strategy (from 1966 to week 4 of July 2012)

Number	*Search history*	*Articles (n)*
1	Caries	43,204
2	"Dental Caries"[Mesh]	34,491
3	demineral*	7,771
4	"Tooth Demineralization"[Mesh]	35,449
5	White spot?	43,166
6	#1 or #2 or #3 or #4 or #5	50,698
7	Orthodontics	49,001
8	"Orthodontics"[Mesh]	40,782
9	#7 or #8	49,001
10	remineral*	2,221
11	"Tooth Remineralization"[Mesh]	1,197
12	Fluori*	73,455
13	"Fluorides"[Mesh]	29,016
14	calcium phosphate	9,909
15	#10 or #11 or #12 or #13 or #14	85,434
16	#6 and #9 and #15	404

*Truncation of a text word.

Appendix II. Articles excluded in this review

Article	*Reason for exclusion*
1. Aljehani A, Yousif MA, Angmar-Mansson B, Shi XQ. Longitudinal quantification of incipient carious lesions in postorthodontic patients using a fluorescence method. Eur J Oral Sci 2006;114:430-4.	Not RCT
2. Mensinkai PK, Ccahuana-Vasquez RA, Chedjieu I, Amaechi BT, Mackey AC, Walker TJ, et al. In situ remineralization of white-spot enamel lesions by 500 and 1,100 ppm F dentifrices. Clin Oral Investig 2012;16:1007-14.	Inclusion criteria for population not met
3. Wu G, Liu X, Hou Y. Analysis of the effect of CPP-ACP tooth mousse on enamel remineralization by circularly polarized images. Angle Orthod 2010;80:933-8.	In-vitro study
4. Uysal T, Amasyali M, Ozcan S, Koyuturk AE, Akyol M, Sagdic D. In vivo effects of amorphous calcium phosphate-containing orthodontic composite on enamel demineralization around orthodontic brackets. Aust Dent J 2010;55:285-91.	Inclusion criteria for population not met
5. Shungin D, Olsson AI, Persson M. Orthodontic treatment-related white spot lesions: a 14-year prospective quantitative follow-up, including bonding material assessment. Am J Orthod Dentofacial Orthop 2010;138:136.e1-8; discussion, 136-7.	Not RCT
6. Marchisio O, Esposito MR, Genovesi A. Salivary pH level and bacterial plaque evaluation in orthodontic patients treated with Recaldent products. Int J Dent Hyg 2010;8:232-6.	Inclusion criteria for population not met
7. He WD, Liu YZ, Xu YY, Chen D. Study on application of CPP-ACP on tooth mineralization during orthodontic treatment with fixed appliance. Shanghai Kou Qiang Yi Xue 2010;19:140-3.	Inclusion criteria for population not met
8. Guzman-Armstrong S, Chalmers J, Warren JJ. White spot lesions: prevention and treatment. Am J Orthod Dentofacial Orthop 2010;138:690-6.	Not RCT
9. Bansal K, Gauba K, Tewari A, Chawla HS, Sahni A. In vivo remineralization of artificial enamel carious lesions using a mineral-enriched mouthrinse and a fluoride dentifrice: a polarized light microscopic comparative evaluation. J Indian Soc Pedod Prev Dent 2010;28:264-70.	Inclusion criteria for population not met
10. Zhou CH, Sun XH, Zhu XC. Quantification of remineralized effect of casein phosphopeptiode-amorphous calcium phosphate on post-orthodontic white spot lesion. Shanghai Kou Qiang Yi Xue 2009;18: 449-54.	Not RCT
11. Trairatvorakul C, Techalertpaisarn P, Siwawut S, Ingprapankorn A. Effect of glass ionomer cement and fluoride varnish on the remineralization of artificial proximal caries in situ. J Clin Pediatr Dent 2009;34:131-4.	Inclusion criteria for population not met
12. Suri L, Huang G, English JD Jr, Owen S, Nah HD, Riolo ML, et al. Topical fluoride treatment. Am J Orthod Dentofacial Orthop 2009;135:561-3.	Not RCT
13. Langhorst SE, O'Donnell JN, Skrtic D. In vitro remineralization of enamel by polymeric amorphous calcium phosphate composite: quantitative microradiographic study. Dent Mater 2009;25:884-91.	In-vitro study
14. Fu H, Liang R, Xiao Y, Zhang XJ. Efficacy of tooth mousse in reducing enamel demineralization and promoting remineralization. Hua Xi Kou Qiang Yi Xue Za Zhi 2008;26:301-5.	Not RCT
15. Van der Veen MH, Attin R, Schwestka-Polly R, Wiechmann D. Caries outcomes after orthodontic treatment with fixed appliances: do lingual brackets make a difference? Eur J Oral Sci 2010;118:298-303.	Inclusion criteria for intervention not met
16. Kleber CJ, Milleman JL, Davidson KR, Putt MS, Triol CW, Winston AE. Treatment of orthodontic white spot lesions with a remineralizing dentifrice applied by toothbrushing or mouth trays. J Clin Dent 1999;10 (1 Spec No):44-9.	Focus not on the efficacy of the remineralizing agent, but on the efficacy of the applied methods for remineralizing fluoride dentifrice
17. Al-Khateeb S, Forsberg CM, de Josselin de Jong E, Angmar-Mansson B. A longitudinal laser fluorescence study of white spot lesions in orthodontic patients. Am J Orthod Dentofacial Orthop 1998;113:595-602.	Not RCT
18. Linton JL. Quantitative measurements of remineralization of incipient caries. Am J Orthod Dentofacial Orthop 1996;110:590-7.	Inclusion criteria for population not met

Appendix II. Continued

Article	*Reason for exclusion*
19. Donly KJ, Istre S, Istre T. In vitro enamel remineralization at orthodontic band margins cemented with glass ionomer cement. Am J Orthod Dentofacial Orthop 1995;107:461-4.	In-vitro study
20. Ogaard B, Ten Bosch JJ. Regression of white spot enamel lesions. A new optical method for quantitative longitudinal evaluation in vivo. Am J Orthod Dentofacial Orthop 1994;106:238-42.	Not RCT
21. El-Mangoury NH, Moussa MM, Mostafa YA, Girgis AS. In-vivo remineralization after air-rotor stripping. J Clin Orthod 1991;25:75-8.	Inclusion criteria for population not met
22. Ogaard B. Prevalence of white spot lesions in 19-year-olds: a study on untreated and orthodontically treated persons 5 years after treatment. Am J Orthod Dentofacial Orthop 1989;96:423-7.	Inclusion criteria for intervention not met
23. Ogaard B, Rolla G, Arends J, ten Cate JM. Orthodontic appliances and enamel demineralization. Part 2. Prevention and treatment of lesions. Am J Orthod Dentofacial Orthop 1988;94:123-8.	Not RCT
24. Bergstrand F, Twetman S. Evidence for the efficacy of various methods of treating white-spot lesions after debonding of fixed orthodontic appliances. J Clin Orthod 2003;37:19-21.	Not RCT
25. Aljehani A, Yousif MA, Angmar-Månsson B, Shi XQ. Longitudinal quantification of incipient carious lesions in postorthodontic patients using a fluorescence method. Eur J Oral Sci 2006;114:430-4.	Not RCT
26. Knösel M, Attin R, Becker K, Attin T. External bleaching effect on the color and luminosity of inactive white-spot lesions after fixed orthodontic appliances. Angle Orthod 2007;77:646-52.	Inclusion criteria for intervention not met
27. Aljehani A, Yousif MA, Angmar-Mansson B, Shi XQ. Longitudinal quantification of incipient carious lesions in postorthodontic patients using a fluorescence method. Eur J Oral Sci 2006;114:430-4.	Not RCT
28. Al-Khateeb S, Forsberg CM, de Jong ED, Angmar-Mansson B. A longitudinal laser fluorescence study of white spot lesions in orthodontic patients. Am J Orthod Dentofacial Orthop 1998;113:595-602.	Not RCT
29. Kleber CJ, Milleman JL, Davidson KR, Putt MS, Triol CW, Winston AE. Effect of remineralizing dentifrice on orthodontic white spots after 3 months. J Dent Res 1998;77(Spec Iss B):843.	Not RCT
30. Knosel M, Attin R, Becker K, Attin T. External bleaching effect on the color and luminosity of inactive white-spot lesions after fixed orthodontic appliances. Angle Orthod 2007;77:646-52.	Inclusion criteria for intervention not met
31. Van der Veen MH, Mattousch T, Boersma JG. Longitudinal development of caries lesions after orthodontic treatment evaluated by quantitative light-induced fluorescence. Am J Orthod Dentofacial Orthop 2007;131:223-8.	Not RCT
32. Hammad SM, El Banna M, El Zayat I, Mohsen MA. Effect of resin infiltration on white spot lesions after debonding orthodontic brackets. Am J Dent 2012;25:3-8.	Inclusion criteria for intervention not met
33. Mahony D. Treatment of "white spot lesions" after removal of fixed orthodontic appliances. Int J Orthod Milwaukee 2012;23:59-60.	Not RCT
34. Akin M, Basciftci FA. Can white spot lesions be treated effectively? Angle Orthod 2012;82:770-5.	Not RCT
35. Pliska BT, Warner GA, Tantbirojn D, Larson BE. Treatment of white spot lesions with ACP paste and microabrasion. Angle Orthod 2012;82:765-9.	Not RCT
36. Splieth CH, Treuner A, Gedrange T, Berndt C. Caries-preventive and remineralizing effect of fluoride gel in orthodontic patients after 2 years. Clin Oral Investig 2012;16:1395-9.	Not RCT
37. Robertson MA, Kau CH, English JD, Lee RP, Powers J, Nguyen JT. MI Paste Plus to prevent demineralization in orthodontic patients: a prospective randomized controlled trial. Am J Orthod Dentofacial Orthop 2011;140:660-8.	Inclusion criteria for population not met

RCT, Randomized controlled trial.