



# Comparative Efficacy of MI Paste Plus and Fluoride Varnish Remineralizing Agents for Preventing White Spot Lesions in Patients on Fixed Orthodontic Treatment: A Clinical Trial

Sara Kaveh<sup>1</sup>, Amirali Karamifar<sup>1</sup>, Sina Kousha<sup>2,\*</sup>, Arash Azarbyjani<sup>1</sup>, Majid Mirmohammadkhani<sup>3</sup> and Yasaman Samani<sup>4</sup>

<sup>1</sup>Private Office, Tehran, Iran

<sup>2</sup>Postgraduate Student, Department of Pediatric Dentistry, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>3</sup>Department of Community Medicine, Research Center for Social Determinants of Health, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran

<sup>4</sup>Department of Restorative Dentistry, Semnan University of Medical Sciences, Semnan, Iran

\*Corresponding author: Postgraduate Student, Department of Pediatric Dentistry, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: sina.kousha@gmail.com

Received 2021 September 20; Revised 2021 December 14; Accepted 2021 December 25.

## Abstract

**Background:** White spot lesions (WSLs), as the initial form of dental caries, develop due to subsurface enamel demineralization. They have a relatively high prevalence in orthodontic patients. Several materials are used to prevent WSLs, and various studies have assessed their efficacy during orthodontic treatment.

**Objectives:** This study aimed to compare the efficacy of fluoride varnish and MI Paste Plus for preventing WSLs during orthodontic treatment.

**Methods:** This clinical trial evaluated 60 patients in three groups of control, fluoride varnish, and MI Paste Plus for six months. The presence/absence of WSLs was clinically evaluated at baseline and two, four, and six months after the intervention using the International Caries Detection and Assessment System. The patients' saliva pH was measured at baseline and six months after the intervention.

**Results:** The difference in the WSLs score was significant between the MI Paste Plus and control groups ( $P < 0.05$ ). However, despite the slightly lower frequency of WSLs in the varnish group, the difference between the varnish and control groups was not significant ( $P > 0.05$ ). The MI Paste Plus group results were superior to those in the varnish group but not significantly. The saliva pH did not change significantly after the intervention compared to the baseline.

**Conclusions:** MI Paste Plus caused a significant WSLs reduction in orthodontic patients but had no significant effect on the saliva pH.

**Keywords:** Dental Caries, Tooth Demineralization, Tooth Remineralization, Cariostatic Agents, Orthodontic Brackets

## 1. Background

Dental caries is defined as the local progressive destruction of tooth structure, characterized by demineralization of superficial enamel layers in acids caused by the fermentation of carbohydrates (1, 2). Orthodontic appliances increase the retention of dental plaque on the tooth surface. Following the placement of orthodontic appliances in the oral cavity, the oral microbial flora quickly shifts to acidogenic bacteria, resulting in the formation of white spot lesions (WSLs) around orthodontic brackets in about one-third of patients (3, 4). Moreover, dental caries are difficult to detect during orthodontic treatment because the teeth are covered with orthodontic brackets (5).

Education and training of orthodontic patients to adhere to oral hygiene measures and permanent behavioral change of patients for caries prevention are effective but hard to achieve (6). Fixed appliances impede access to tooth surfaces and increase the complexity of mechanical cleaning for patients. This highlights the importance of adjunctive measures to minimize the incidence of dental caries (7).

Fluoridated compounds are among the most effective caries prevention products, which are used for the prevention of WSLs. They are available in the form of mouthwash, gel, varnish, etc. (3). One advantage of fluoride varnish is that it is effective even in the presence of dental plaque and does not require tooth cleaning before its ap-

plication (8). However, limited effects of fluoride on pit and fissure caries and the risk of overexposure of patients to fluoride, as well as the general recommendations on limiting fluoride consumption, have decreased the popularity of fluoride compounds (9). Antibacterial agents, such as chlorhexidine, lack supporting evidence concerning their efficacy. Moreover, they often cause the discoloration of bracket bonding agents and adversely affect dental esthetics (10). Laser irradiation is another suggested modality that changes the structure of enamel crystals and can prevent enamel caries in fixed orthodontic patients. However, this modality requires further investigations and has some contradictions (6, 11).

The dependence of fluoride compounds on the salivary calcium and phosphate ions has focused the attention of researchers towards the production of calcium- and phosphate-based remineralizing agents (9). Tooth mousse, first produced by Reynolds et al. cited in Chambers et al., is among these products that contain casein phosphopeptide amorphous calcium phosphate (CPP-ACP) (10). As known, CPP prevents the adhesion of oral bacteria to saliva-coated hydroxyapatite. It selectively inhibits the adhesion of streptococci to tooth surfaces and can change the dental plaque microbial flora, resulting in less accumulation of cariogenic bacterial species such as oral *Actinomyces* (9).

Besides, MI Paste Plus is a recently introduced product suggested for treating incipient caries, which is composed of CPP-ACP and 900 ppm fluoride. Simultaneous application of CPP-ACP and fluoride can exert a synergistic effect. This product has shown promising results for caries control (9, 12, 13).

As mentioned earlier, dental caries is a public health dilemma, affecting a considerable number of fixed orthodontic patients. Several methods have been suggested to prevent and control caries in orthodontic patients; however, each method has its advantages and shortcomings. More recent studies have focused on CPP-ACP use, but controversial results have been reported regarding its caries prevention efficacy (14-16). A large number of studies on this topic have been conducted in vitro. Clinical studies have mainly focused on its application after orthodontic treatment completion (3, 17-21), while the incidence of caries drops significantly after bracket debonding (5).

Considering the high risk of caries during orthodontic treatment, the application of remineralizing agents seems to be a conservative approach.

## 2. Objectives

This study aimed to compare the efficacy of MI Paste Plus and fluoride varnish remineralizing agents to prevent WSLs in fixed orthodontic patients.

## 3. Methods

The inclusion criteria were healthy males and females aged 12 to 35 years, no systemic disease, no syndromic anomalies, and no allergy to milk protein or benzoate preservatives. The exclusion criteria included patients whose orthodontic treatment would be completed in less than six months, patients with physical or mental disabilities, alcoholics and substance abusers, and unwillingness to participate in the study.

After obtaining ethical approval from the university's ethics committee, necessary arrangements were made with an orthodontist to refer patients on fixed orthodontic treatment to the university. He was requested to randomly refer young adult patients visiting during four working days to the dental school for participation in the study.

### 3.1. First Visit

All patients were visited in four sessions within four working weeks. The patients were first briefed about the study, and written informed consent was obtained from them. Next, data including age, education level, and systemic health status were recorded in predesigned datasheets. Clinical examination was performed using a dental mirror and an explorer. The DMFT and plaque index of patients were calculated and recorded. Patients requiring dental treatments were referred to the respective departments.

### 3.2. Grouping of Patients

After data collection, 60 patients were randomly divided into the following four groups to standardize the groups in terms of patient adherence to oral hygiene measures according to their plaque index:

- (A) Plaque index < 50%: 9 patients
- (B)  $50\% \leq$  plaque index < 70%: 12 patients
- (C)  $70\% \leq$  plaque index < 80%: 24 patients
- (D)  $80\% \leq$  plaque index  $\leq$  100%: 15 patients

The patients in each of the aforementioned groups were then randomly divided into three subgroups. Table 1 presents the properties of the materials used in this study.

### 3.3. Second Visit

In the second visit, the patients' saliva pH was measured using a pH kit (Merck, Germany). This was done by placing the pH-meter strip in the saliva and comparing the obtained color with the standard chart on the kit's label (Figure 1).

Next, the patients' teeth were clinically examined using a dental mirror, an explorer, and air spray under the dental unit light. The presence and severity of WSLs were

**Table 1.** Material Comparison

Substance	Ingredient	Mechanism of Action
Fluoride varnish	Fluoride	Blockage of bacterial enzymes; Inhibition of demineralization; Progression of remineralization
MI Paste Plus	Casein phosphopeptides-amorphous calcium phosphate; Fluoride; Xylitol	Stabilization of calcium and phosphate on the enamel surface; Synergic effect of fluoride and CPP-ACP

**Figure 1.** The pH kit

evaluated and recorded using the International Caries Detection and Assessment System. The date of intervention initiation was also recorded for each patient (Table 2).

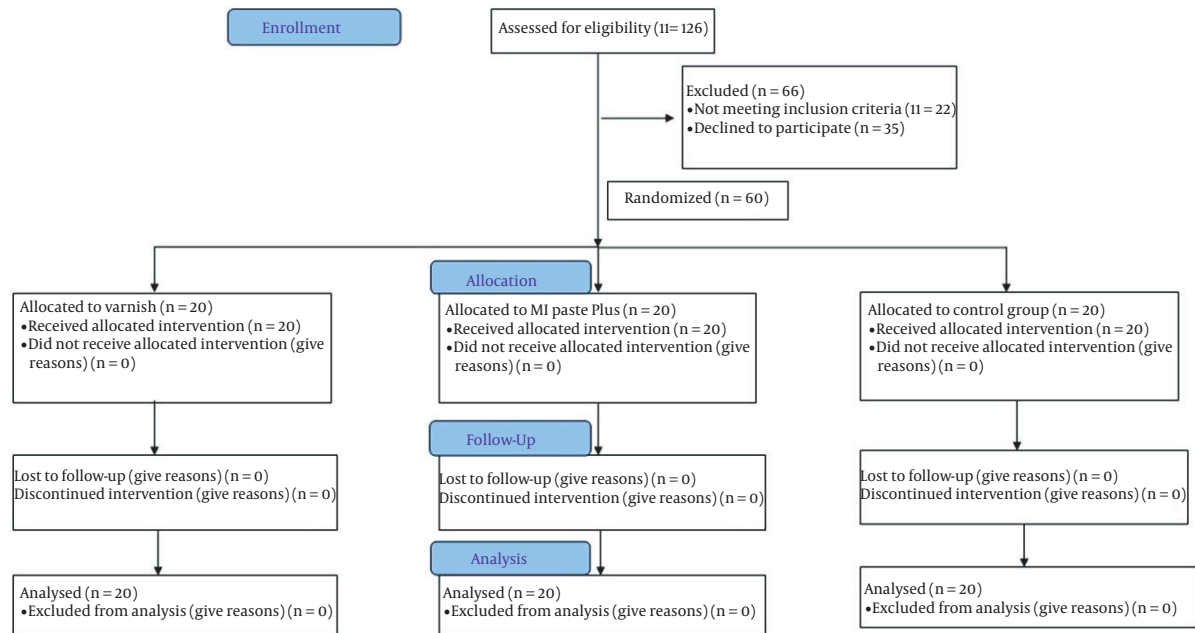
**Table 2.** International Caries Detection and Assessment System Index

Code	Description
0	Intact
1	The first observable change in tooth enamel (it can be seen just after prolonged drying by air, or it is confined to the pit or fissure area)
2	An observable and distinct change in enamel
3	Local breakdown of enamel (without visible clinical symptoms of crown involvement)
4	The dark shadow of dentine which is localized below
5	Evident cavity with a visible dentine
6	An extensive evident cavity with visible dentine

Next, according to the group allocation of patients, the MI Paste Plus group received verbal instructions on the correct use of this product (frequency, amount, and time of use) according to the manufacturer's instructions. The patients were instructed to use a pea-sized amount of the paste every night after toothbrushing (once a day) (Figure 2).

In the fluoride varnish group, fluoride varnish was applied to the teeth. The patients were requested to spit out their saliva five minutes after use and refrain from eating and drinking for three hours. They were also asked to refrain from toothbrushing for 24 hours. Measurement of the saliva pH and grading of WSLs were the only procedures performed in the control group.

In this session, all patients were scheduled for a follow-up session (first follow-up) two months later. In the third (first follow-up) and fourth (second follow-up) visits sched-



**Figure 2.** The enrollment, random allocation, follow-up, and analysis of study participants flowchart

uled two months after the first follow-up, the International Caries Detection and Assessment System Score was determined. In the fluoride varnish group, fluoride varnish was applied. In the MI Paste group, patients were questioned about the amount and method of paste use, and their questions were answered.

### 3.4. Fifth Visit (Third Follow-up)

About two months after the fourth visit, each patient was contacted and reminded about the subsequent follow-up. In the third follow-up, the saliva pH was measured (compared with the baseline value). All procedures performed in previous follow-ups were also repeated in this session. Also, all patients underwent a thorough clinical examination of their teeth for dental caries. They were referred to respective specialists in case of requiring restorative treatments.

The mean and standard deviation of quantitative variables were reported and analyzed using one-way ANOVA. Repeated measures ANOVA was applied to compare the groups regarding the respective indices. The Bonferroni adjustment was applied for pairwise comparisons of the groups.

## 4. Results

The DMFT scores at the onset of fixed orthodontic treatment are shown in [Table 3](#). As shown, there was no significant difference in baseline data between the study groups ( $P = 0.442$ ).

**Table 3.** Comparison of DMFT Scores in Three Groups Before Intervention

Group	Mean $\pm$ SD	P-Value
Control	3.95 $\pm$ 3.3	0.442
Varnish	2.75 $\pm$ 2.7	
MI Paste	3.45 $\pm$ 2.7	

[Table 4](#) presents the results of ANOVA regarding the effect of assessment time and intervention type on WSLs. As shown, there was a significant difference among the groups in the score of WSLs ( $P = 0.021$ ), which was due to the difference between the control and MI Paste Plus groups ( $P < 0.05$ ).

[Table 5](#) shows the mean saliva pH in the three groups after six months and the WSLs score after two, four, and six months.

Pairwise comparisons of the groups with Bonferroni adjustment revealed a significant difference between the control and MI Paste Plus groups (mean diff. =  $1.23 \pm 0.4$ ,  $P = 0.033$ ). The differences between the control and varnish ( $P$

**Table 4.** Comparison of WSLs Score in Three Groups by Repeated Measures ANOVA

Source of Variations	Sum of Squares	Degree of Freedom	Mean of Squares	F	P-Value
Time	4.434	1	4.434	1.300	0.259
Time × WSLs (before intervention)	78.940	1	78.940	23.141	< 0.001
Time × group	28.477	2	14.238	4.174	0.020
WSLs (before intervention)	687.707	1	687.707	107.974	< 0.001
Intervention group	53.106	2	26.553	4.169	0.021

**Table 5.** Mean Saliva pH in Three Groups After Six Months and WSLs Score After Two, Four, and Six Months

Index	Mean ± SD	P-Value
<b>Saliva pH at six months</b>		0.814
Control	6.45 ± 0.6	
Varnish	6.45 ± 0.5	
MI Paste	6.45 ± 0.5	
<b>WSLs score at two months</b>		0.472
Control	2.75 ± 3.2	
Varnish	1.65 ± 1.8	
MI Paste	2.25 ± 3.1	
<b>WSLs score at four months</b>		0.017
Control	3 ± 3.1	
Varnish	1.15 ± 1.3	
MI Paste	1.3 ± 1.6	
<b>WSLs score at six months</b>		0.034
Control	3.15 ± 2.9	
Varnish	1.6 ± 1.6	

= 0.078) and MI Paste Plus and varnish ( $P > 0.999$ ) groups were not significant. The change in the mean WSLs score was not significant over time in the control group ( $P = 0.378$ ). As shown in [Figure 1](#), the trend of change in the WSLs score was almost horizontal in the control group while descending in other groups. However, the trend of WSLs score reduction was steeper in the MI Paste Plus group than in the varnish group.

## 5. Discussion

White spot lesions (WSLs) are the initial phase of caries development, characterized by demineralization of sub-surface enamel without cavitation. White spot lesions can progress and create a cavitated lesion. These lesions develop in a high percentage of orthodontic patients (6, 20). Several materials are used to treat WSLs, such as fluoridated toothpaste, fluoridated mouthwashes, fluoride varnish, and CPP-ACP. Each of these products has a different

mechanism of action in preventing WSLs, and each has its advantages and disadvantages. Studies conducted on the efficacy of these products have shown controversial results and mainly concentrated on the post-orthodontic phase (14-16). Thus, the present study compared the efficacy of fluoride varnish and MI Paste Plus to prevent WSLs in orthodontic patients.

The mean score of WSLs in the control group decreased by 0.2 units during six months, which was not statistically significant. In a study by Robertson et al. (22), the control group showed a 91% increase in WSLs, highlighting the significance of patients' oral hygiene instruction at the study onset. Other studies evaluated WSLs after orthodontic treatment or in-vitro; thus, their results cannot be compared with ours.

In this study, the mean score of WSLs in the MI Paste Plus group after two months of intervention showed a significant reduction by 2.9 units; this reduction was 3.85 units after four months. The WSLs score reduction was expected considering the cariostatic properties of fluoride and CPP-ACP. However, the difference between the baseline value and the value at six months was insignificant. A possible reason for the decreased efficacy of the materials may be the reduced motivation of patients during the long course of the study.

In pairwise comparisons of the groups, the difference between the control and MI Paste Plus groups was significant such that the MI Paste Plus group experienced a greater reduction (1.23) in the mean score of WSLs during six months compared with the control group. Similar results were reported by Robertson et al. (22) and Abdoli (23). However, Ballard et al. (24), Huang et al. (12), and Beerens et al. (25) found no significant difference between the intervention and control groups in this respect. Nevertheless, the duration of these studies was less than three months, which may explain the differences in the results. In the present study, MI Paste Plus was used according to the manufacturer's instructions. However, its application method was variable in previous studies, which could have affected the results.

The superior results of MI Paste Plus compared with

the control group can be due to its mechanism of action. As known, MI Paste Plus is composed of fluoride and CPP-ACP. Fluoride decreases enamel demineralization and enhances enamel remineralization. It also inhibits metabolic enzymes in cariogenic bacteria (3, 6, 26). On the other hand, CPP-ACP causes the accumulation of calcium and phosphate on the enamel surface and results in enamel remineralization. Besides, CPP prevents the attachment of oral bacteria to saliva-coated hydroxyapatite on the enamel surface. It selectively inhibits the attachment of streptococci and changes the microbial flora of dental plaque, resulting in less colonization of cariogenic species such as oral Actinomyces. Elevated levels of calcium and fluoride ions in the tooth surface and within the dental plaque inhibit acid production, while phosphate ions contribute to buffering plaque pH changes. As a result, the combined application of CPP-ACP and fluoride exerts synergistic effects (26).

Pairwise comparisons of the groups revealed that the mean WSLs score reduction within six months in the varnish group was 1.05 units higher than that in the control group, although this difference was insignificant. The mean score of WSLs decreased by 0.85 units in the varnish group at six months, but this reduction was not significant either. Huang et al. (12) and Singh et al. (16) reported similar results and showed that the varnish group had no superiority over the control group. However, Stafford (27) and Lopatiene et al. (15) reported that varnish application was effective; however, they evaluated patients after the completion of orthodontic treatment. Thus, enhanced adherence to oral hygiene measures may explain the difference in the results. A more recently published paper by Flynn et al. (28) reported that fluoride varnish had no superior advantage in reducing WSLs during orthodontic treatment. A recent systematic review conducted on the efficacy of fluoride varnish for treating orthodontically-induced WSLs pointed to this controversy and stated that adequate data are not available to draw a definite conclusion (29).

Pairwise comparisons showed that the mean WSLs score reduction in the MI Paste Plus group was higher than that in the varnish group by 0.17 units at six months in the current study; however, this difference was not significant. In the study by Huang et al. (12), the difference between the MI Paste Plus and varnish was insignificant (12). However, Llena et al. (14) demonstrated that MI Paste Plus was more effective than varnish. Nevertheless, this difference was only significant in the first four weeks of the 12-week study period. The superior efficacy of MI Paste Plus compared with fluoride varnish can be due to the presence of calcium and phosphate ions along with fluoride because fluoride requires six phosphate ions and 10 calcium ions for the formation of fluorapatite. Therefore, in the case of

only using fluorinated compounds, these ions may not be available in adequate amounts (30).

Also, in fluorinated products, the precipitation of calcium fluoride on the surface of WSLs may inhibit the passage of ions into the deeper, more affected layers (30). On the other hand, when CPP-ACP is used, neutral ions such as  $\text{CaHPO}_4$  are produced, localized on the tooth surface, and subsequently diffuse deep into the body of WSLs; accordingly, remineralization occurs throughout the entire body of WSLs (31).

The mean saliva pH in the control group was 6.8 at baseline and 6.45 after the intervention. The mean pH was 6.35 before and 6.45 after the intervention in the varnish group. In the MI Paste Plus group, the mean pH was 6.45 before and 6.35 after the intervention. However, in general, no significant difference was noted in pH after the intervention compared with baseline. In a study by Heshmat et al. (32), the saliva pH in the MI Paste Plus group did not change significantly after the intervention compared with baseline. Another study reported the saliva pH increase after the intervention; this result may be due to patients' oral hygiene and diet (33). Different results regarding the saliva pH in different studies may be due to the tools used to measure pH. Also, a recent study comparing the efficacy of CPP-ACP with/without fluoride reported that exercise and innate metabolic differences might affect the pH (34). In the present study, a pH-meter (Merck, Germany) was used, which was not digital and could not measure changes smaller than one unit. The groups were not fundamentally different in terms of mean age, gender, education level, plaque index, DMFT, or WSLs score at baseline. Thus, these factors had no significant confounding effect on the results.

As mentioned earlier, most previous studies had been conducted in the short term (12, 14, 22, 24, 26) and had an in vitro design or conducted on patients after completing their orthodontic treatment. However, the current study was unique as it evaluated patients during orthodontic treatment. However, in the present study, patients had different levels of cooperation due to their decreased motivation over time. This was especially true in the last months of the study. Also, in the present study, clinical examination of oral cavity and dentition was performed with an explorer under unit light. This may explain the difference in the results compared with studies that performed clinical dental examinations using other tools. In general, scientific evidence supporting the remineralizing treatments of WSLs is not conclusive, and controlled clinical trials with long-term follow-ups are required to obtain more accurate results (35).

### 5.1. Conclusions

Under the limitations of this study, during orthodontic treatment, the number of WSLs in the control group slightly decreased following conventional oral hygiene. Both MI Paste Plus and fluoride varnish decreased the formation of WSLs in orthodontic patients. Besides, MI Paste showed superior results compared with fluoride varnish, but not significantly. Also, MI Paste Plus and fluoride varnish had no significant effect on the saliva pH.

### Footnotes

**Authors' Contribution:** Study concept and design: S.K and A.K; Acquisition of data: S.K and A.A; Analysis and interpretation of data: M.M; Drafting of the manuscript: S.K and S.K; Critical revision of the manuscript for important intellectual content: Y.S; Statistical analysis: M.M; Administrative, technical, and material support: A.K and S.K; Study supervision: S.K

**Clinical Trial Registration Code:** IRCT20170828035946N2.

**Conflict of Interests:** one of the authors of the article (Majid Mirmohammakhani) is the "associate editor" of the journal. Based on the journal policy, this author was completely excluded from any review process of this article.

**Ethical Approval:** IR.SEMUMS.REC.1396.58.

**Funding/Support:** The Semnan University of Medical Sciences supported this study.

**Informed Consent:** The patients were first briefed about the study, and written informed consent was obtained from them.

### References

- Furuta M, Yamashita Y. Oral Health and Swallowing Problems. *Curr Phys Med Rehabil Rep.* 2013;**1**:216–22. doi: [10.1007/s40141-013-0026-x](https://doi.org/10.1007/s40141-013-0026-x). [PubMed: [24392281](https://pubmed.ncbi.nlm.nih.gov/24392281/)]. [PubMed Central: [PMC3873078](https://pubmed.ncbi.nlm.nih.gov/PMC3873078/)].
- Rafeian Kupaeni N, Jazaeri M, Rezaei Soufi L, Faradmal J, Abdolsamadi H, Shokri Y. Evaluation of the Relationship between Salivary Albumin Level and Dental Caries. *Avicenna J Clin Med.* 2013;**20**(2):101–6.
- Jo SY, Chong HJ, Lee EH, Chang NY, Chae JM, Cho JH, et al. Effects of various toothpastes on remineralization of white spot lesions. *Korean J Orthod.* 2014;**44**(3):113–8. doi: [10.4041/kjod.2014.44.3.113](https://doi.org/10.4041/kjod.2014.44.3.113). [PubMed: [24892024](https://pubmed.ncbi.nlm.nih.gov/24892024/)]. [PubMed Central: [PMC4040358](https://pubmed.ncbi.nlm.nih.gov/PMC4040358/)].
- Noble J, Cassolato S, Karaikos N, Wiltshire WA. My patient is receiving orthodontic treatment, and her oral hygiene has taken a turn for the worse. What preventive and interceptive measures are available for improving and maintaining good oral hygiene and cariogenic control in orthodontic patients? *J Can Dent Assoc.* 2009;**75**(6):441–3.
- Choi YY. Relationship between orthodontic treatment and dental caries: results from a national survey. *Int Dent J.* 2020;**70**(1):38–44. doi: [10.1111/ijdj.12515](https://doi.org/10.1111/ijdj.12515). [PubMed: [31441042](https://pubmed.ncbi.nlm.nih.gov/31441042/)].
- Sudjalim TR, Woods MG, Manton DJ. Prevention of white spot lesions in orthodontic practice: a contemporary review. *Aust Dent J.* 2006;**51**(4):284–9. quiz 347. doi: [10.1111/j.1834-7819.2006.tb00445.x](https://doi.org/10.1111/j.1834-7819.2006.tb00445.x). [PubMed: [17256301](https://pubmed.ncbi.nlm.nih.gov/17256301/)].
- Walsh LJ, Healey DL. Prevention and caries risk management in teenage and orthodontic patients. *Aust Dent J.* 2019;**64** Suppl 1:S37–45. doi: [10.1111/adj.12671](https://doi.org/10.1111/adj.12671). [PubMed: [31144319](https://pubmed.ncbi.nlm.nih.gov/31144319/)].
- Heymann GC, Grauer D. A contemporary review of white spot lesions in orthodontics. *J Esthet Restor Dent.* 2013;**25**(2):85–95. doi: [10.1111/jerd.12013](https://doi.org/10.1111/jerd.12013). [PubMed: [23617380](https://pubmed.ncbi.nlm.nih.gov/23617380/)].
- Goswami M, Saha S, Chaitra TR. Latest developments in non-fluoridated remineralizing technologies. *J Indian Soc Pedod Prev Dent.* 2012;**30**(1):2–6. doi: [10.4103/0970-4388.95561](https://doi.org/10.4103/0970-4388.95561). [PubMed: [22565510](https://pubmed.ncbi.nlm.nih.gov/22565510/)].
- Chambers C, Stewart S, Su B, Sandy J, Ireland A. Prevention and treatment of demineralisation during fixed appliance therapy: a review of current methods and future applications. *Br Dent J.* 2013;**215**(10):505–11. doi: [10.1038/sj.bdj.2013.1094](https://doi.org/10.1038/sj.bdj.2013.1094). [PubMed: [24264666](https://pubmed.ncbi.nlm.nih.gov/24264666/)].
- Haghighi HS, Skandarinejad M, Abdollahi AA. Laser application in prevention of demineralization in orthodontic treatment. *J Lasers Med Sci.* 2013;**4**(3):107.
- Huang GJ, Roloff-Chiang B, Mills BE, Shalchi S, Spiekerman C, Korpak AM, et al. Effectiveness of MI Paste Plus and PreviDent fluoride varnish for treatment of white spot lesions: a randomized controlled trial. *Am J Orthod Dentofacial Orthop.* 2013;**143**(1):31–41. doi: [10.1016/j.ajodo.2012.09.007](https://doi.org/10.1016/j.ajodo.2012.09.007). [PubMed: [23273358](https://pubmed.ncbi.nlm.nih.gov/23273358/)]. [PubMed Central: [PMC411089](https://pubmed.ncbi.nlm.nih.gov/PMC411089/)].
- Raphael S, Blinkhorn A. Is there a place for Tooth Mousse in the prevention and treatment of early dental caries? A systematic review. *BMC Oral Health.* 2015;**15**(1):113. doi: [10.1186/s12903-015-0095-6](https://doi.org/10.1186/s12903-015-0095-6). [PubMed: [26408042](https://pubmed.ncbi.nlm.nih.gov/26408042/)]. [PubMed Central: [PMC4583988](https://pubmed.ncbi.nlm.nih.gov/PMC4583988/)].
- Llena C, Leyda AM, Forner L. CPP-ACP and CPP-ACFP versus fluoride varnish in remineralisation of early caries lesions. A prospective study. *Eur J Paediatr Dent.* 2015;**16**(3):181–6.
- Lopatiene K, Borisovaite M, Lapenaite E. Prevention and Treatment of White Spot Lesions During and After Treatment with Fixed Orthodontic Appliances: a Systematic Literature Review. *J Oral Maxillofac Res.* 2016;**7**(2). et. doi: [10.5037/jomr.2016.7201](https://doi.org/10.5037/jomr.2016.7201). [PubMed: [27489605](https://pubmed.ncbi.nlm.nih.gov/27489605/)]. [PubMed Central: [PMC4970501](https://pubmed.ncbi.nlm.nih.gov/PMC4970501/)].
- Singh S, Singh SP, Goyal A, Utreja AK, Jena AK. Effects of various remineralizing agents on the outcome of post-orthodontic white spot lesions (WSLs): a clinical trial. *Prog Orthod.* 2016;**17**(1):25. doi: [10.1186/s40510-016-0138-9](https://doi.org/10.1186/s40510-016-0138-9). [PubMed: [27480987](https://pubmed.ncbi.nlm.nih.gov/27480987/)]. [PubMed Central: [PMC4969265](https://pubmed.ncbi.nlm.nih.gov/PMC4969265/)].
- Duraisamy V, Xavier A, Nayak UA, Reddy V, Rao AP. An in vitro evaluation of the demineralization inhibitory effect of F(-) varnish and casein phosphopeptide-amorphous calcium phosphate on enamel in young permanent teeth. *J Pharm Bioallied Sci.* 2015;**7**(Suppl 2):S513–7. doi: [10.4103/0975-7406.163521](https://doi.org/10.4103/0975-7406.163521). [PubMed: [26538909](https://pubmed.ncbi.nlm.nih.gov/26538909/)]. [PubMed Central: [PMC4606651](https://pubmed.ncbi.nlm.nih.gov/PMC4606651/)].
- Lin YANG, Min ZOU. Remineralization of enamel promoted by casein phosphopeptide-amorphous calcium phosphate with different concentration of fluorin. *Shanghai J Stomatol.* 2013;**22**(5):533.
- Mayne RJ, Cochrane NJ, Cai F, Woods MG, Reynolds EC. In-vitro study of the effect of casein phosphopeptide amorphous calcium fluoride phosphate on iatrogenic damage to enamel during orthodontic adhesive removal. *Am J Orthod Dentofacial Orthop.* 2011;**139**(6):e543–51. doi: [10.1016/j.ajodo.2010.09.027](https://doi.org/10.1016/j.ajodo.2010.09.027). [PubMed: [21640866](https://pubmed.ncbi.nlm.nih.gov/21640866/)].
- Wang Y, Mei L, Gong L, Li J, He S, Ji Y, et al. Remineralization of early enamel caries lesions using different bioactive elements containing toothpastes: An in vitro study. *Technol Health Care.* 2016;**24**(5):701–11. doi: [10.3233/THC-161221](https://doi.org/10.3233/THC-161221). [PubMed: [27233091](https://pubmed.ncbi.nlm.nih.gov/27233091/)].
- Yap J, Walsh LJ, Naser-Ud Din S, Ngo H, Manton DJ. Evaluation of a novel approach in the prevention of white spot lesions around orthodontic brackets. *Aust Dent J.* 2014;**59**(1):70–80. doi: [10.1111/adj.12142](https://doi.org/10.1111/adj.12142). [PubMed: [24528001](https://pubmed.ncbi.nlm.nih.gov/24528001/)].
- 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**(5):660–8. doi: [10.1016/j.ajodo.2010.10.025](https://doi.org/10.1016/j.ajodo.2010.10.025). [PubMed: [22051486](https://pubmed.ncbi.nlm.nih.gov/22051486/)].
23. Abdoli A. [Ability of CPP-ACP, CPPF-ACP and Flouride gel in remineralization of demineralized enamel around orthodontic brackets in vitro]. Qazvin University of Medical Sciences, Qazvin, Iran; 2013.
  24. Ballard RW, Hagan JL, Phaup AN, Sarkar N, Townsend JA, Armbruster PC. Evaluation of 3 commercially available materials for resolution of white spot lesions. *Am J Orthod Dentofacial Orthop.* 2013;**143**(4 Suppl):S78–84. doi: [10.1016/j.ajodo.2012.08.020](https://doi.org/10.1016/j.ajodo.2012.08.020). [PubMed: [23540640](https://pubmed.ncbi.nlm.nih.gov/23540640/)].
  25. Beerens MW, van der Veen MH, van Beek H, ten Cate JM. Effects of casein phosphopeptide amorphous calcium fluoride phosphate paste on white spot lesions and dental plaque after orthodontic treatment: a 3-month follow-up. *Eur J Oral Sci.* 2010;**118**(6):610–7. doi: [10.1111/j.1600-0722.2010.00780.x](https://doi.org/10.1111/j.1600-0722.2010.00780.x). [PubMed: [21083623](https://pubmed.ncbi.nlm.nih.gov/21083623/)].
  26. Clark MB, Slayton RL, Section on Oral H. Fluoride use in caries prevention in the primary care setting. *Pediatrics.* 2014;**134**(3):626–33. doi: [10.1542/peds.2014-1699](https://doi.org/10.1542/peds.2014-1699). [PubMed: [25157014](https://pubmed.ncbi.nlm.nih.gov/25157014/)].
  27. Stafford GL. Fluoride varnish may improve white spot lesions. *Evid Based Dent.* 2011;**12**(4):104–5. doi: [10.1038/sj.ebd.6400823](https://doi.org/10.1038/sj.ebd.6400823). [PubMed: [22193651](https://pubmed.ncbi.nlm.nih.gov/22193651/)].
  28. Flynn LN, Julien K, Noureldin A, Buschang PH. The efficacy of fluoride varnish vs a filled resin sealant for preventing white spot lesions during orthodontic treatment: A randomized clinical trial. *Angle Orthod.* 2021. doi: [10.2319/052521-418.1](https://doi.org/10.2319/052521-418.1). [PubMed: [34679162](https://pubmed.ncbi.nlm.nih.gov/34679162/)].
  29. Alrebdi A, Ericson D, Qasim SSB, Albahoth A, Al-Sulimani A, Baskaradoss JK. Efficacy of fluoride varnish in treating orthodontically-induced white spot lesions: a systematic review and meta-analysis. *Aust Orthod J.* 2021;**37**(2):147–56. doi: [10.21307/aoj-2021-016](https://doi.org/10.21307/aoj-2021-016).
  30. Cross KJ, Huq NL, Palamara JE, Perich JW, Reynolds EC. Physicochemical characterization of casein phosphopeptide-amorphous calcium phosphate nanocomplexes. *J Biol Chem.* 2005;**280**(15):15362–9. doi: [10.1074/jbc.M413504200](https://doi.org/10.1074/jbc.M413504200). [PubMed: [15657053](https://pubmed.ncbi.nlm.nih.gov/15657053/)].
  31. Vanichvatana S, Auychai P. Efficacy of two calcium phosphate pastes on the remineralization of artificial caries: a randomized controlled double-blind in situ study. *Int J Oral Sci.* 2013;**5**(4):224–8. doi: [10.1038/ijos.2013.67](https://doi.org/10.1038/ijos.2013.67). [PubMed: [24030557](https://pubmed.ncbi.nlm.nih.gov/24030557/)]. [PubMed Central: [PMC3967314](https://pubmed.ncbi.nlm.nih.gov/PMC3967314/)].
  32. Heshmat H, Banava S, Mohammadi E, Kharazifard MJ, Mojtahedzadeh F. The effect of recommending a CPP-ACPF product on salivary and plaque pH levels in orthodontic patients: a randomized cross-over clinical trial. *Acta Odontol Scand.* 2014;**72**(8):903–7. doi: [10.3109/00016357.2014.920515](https://doi.org/10.3109/00016357.2014.920515). [PubMed: [24856191](https://pubmed.ncbi.nlm.nih.gov/24856191/)].
  33. 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**(3):232–6. doi: [10.1111/j.1601-5037.2009.00374.x](https://doi.org/10.1111/j.1601-5037.2009.00374.x). [PubMed: [20624194](https://pubmed.ncbi.nlm.nih.gov/20624194/)].
  34. Ashour DG, Farid MR, Mosallam RS, Abouauf EA. Effect of CPP-ACP pastes with/without fluoride on white spot lesion progression, salivary pH, and fluoride release in high caries risk patients: A randomized clinical trial. *Int J Oral Health.* 2021;**13**(4):336.
  35. Sonesson M, Bergstrand F, Gizani S, Twetman S. Management of post-orthodontic white spot lesions: an updated systematic review. *Eur J Orthod.* 2017;**39**(2):116–21. doi: [10.1093/ejo/cjw023](https://doi.org/10.1093/ejo/cjw023). [PubMed: [27030284](https://pubmed.ncbi.nlm.nih.gov/27030284/)].