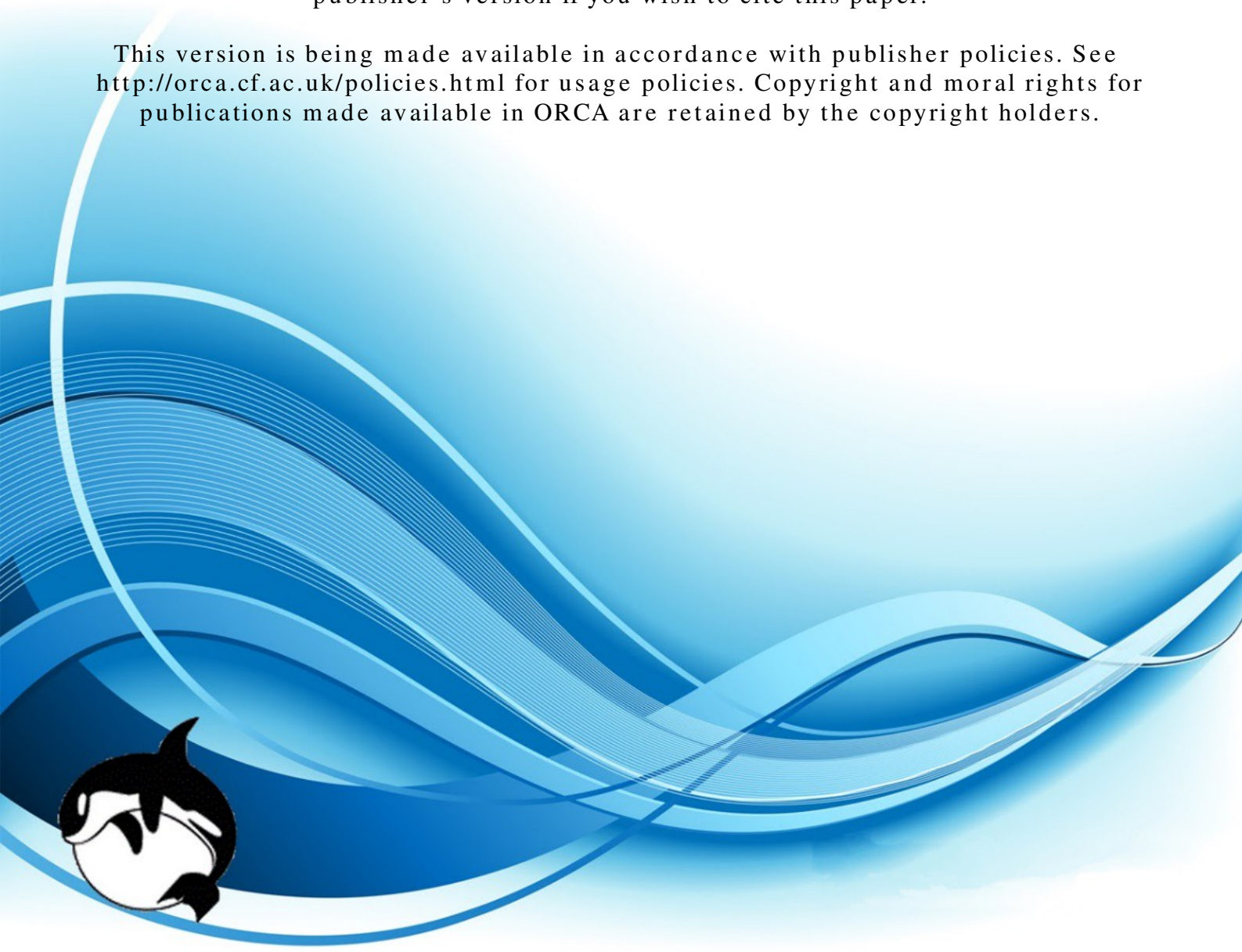

Mineralising agents to manage early carious lesions – part II: clinical application

Abstract

The successful commercialisation of mineralisation technologies used for the primary and secondary prevention of early carious lesions, provides several clinical options for the oral healthcare team using the minimum intervention oral care (MIOC) delivery framework. These new technologies are available in many different forms, with different properties and can be used in a variety of clinical scenarios. This paper is the second in a series providing a review on the clinical efficacy of new technologies and products available as well as clinical guidance for their use.

Clinical relevance

Many mineralising agents have been released in addition to “gold-standard” fluoride therapy, each having different active ingredients, modes of action and clinical uses. Clinicians must have an appreciation of these agents and related guidelines so that they can use these topical agents appropriately in order to maximise the clinical benefits for their patients as well as managing their expectations.

Objectives

The reader should be aware of the currently available remineralisation agents and choose the appropriate option on the basis of the clinical evidence and the case scenario.

INTRODUCTION

The prevalence of dental caries worldwide has seen a steady decline in the past 50 years, largely due to the wide use of fluoride[1]. Typically, early carious lesions (white spot lesions) are present on tooth surfaces most commonly missed during oral hygiene, and where plaque accumulates easily – proximal (Figure 1) and cervical margin (Figure 2). Fluoridated products are still considered the most efficient way to prevent and remineralise carious lesions. However, fluoride on its own does not remineralise carious lesions. It requires the presence of other mineral ions present within the oral cavity. With advances in the understanding of the mechanisms of carious lesion formation and progression and the chemistry of remineralisation / mineral deposition, new therapies have been developed. Their remineralisation chemistry has been investigated comprehensively in laboratory studies and discussed in Part 1 of this review. Some of these new technologies have been commercialised with various clinical benefits claimed by the manufacturers.

The aim of this second article is to provide an overview of clinical evidence of currently available remineralisation technologies and guidelines on related interventions in primary care practice.

CLINICAL EVIDENCE FOR REMINERALISATION

Tables 1 to 6 summarise the findings from some of the key clinical studies on current remineralisation approaches.

Fluoride

The introduction of fluoride is considered an important cornerstone in the prevention of dental caries. Its remineralisation effectiveness has been supported by numerous clinical studies. Fluoride is added as the main active ingredient in both consumer (toothpastes and

mouthrinses) and professional products (varnishes, topical gels and restorative materials) as well as in foodstuffs such as salt and dairy products, especially when public water fluoridation is not feasible[1]. Retrospective analysis of clinical data from a 3-year trial suggests that the use of fluoride toothpaste can reverse early caries through remineralisation[2] and this effect could be enhanced by additional application of fluoride mouthrinse after toothbrushing or by fluoride varnish[3–5]. Marinho et al. reviewed the Cochrane database regarding topical fluoride application in preventing dental caries and found that the efficacy was positively associated with the intensity of fluoride application and concentration; therefore, the impact of fluoride is dose-dependent[6].

Considering the dose-response feature of fluoride, it seems rational to increase the concentration of fluoride in different modalities to maximise its clinical benefits, for those patients at risk. In recent years, some high-F toothpastes such as 5000 ppm (Duraphat™5000; Colgate-Palmolive, New York, USA) have been used to manage adult high caries risk patients; these products are only available via prescription by a medical or dental professional. Clinical studies have revealed high fluoride toothpaste intervention can effectively improve remineralisation[7,8].

Despite the significant clinical benefits, concerns regarding fluoride use should not be overlooked. Since the first report in 1993, dental fluorosis caused by fluoride application has been under the spotlight[1]. Contradicting clinical results were reported in the past regarding the prevalence of fluorosis after self-applied fluoride use[9]. In a more recent Cochrane review, an increased risk of mild fluorosis was observed when toothpastes with 1000 ppm fluoride were administrated to children aged 5-6 years, though this was mitigated by the beneficial caries prevention effect[10]. Fluoride concentration in toothpaste has been limited to 1000-1450 ppm by regulatory authorities in most consumer markets, with even lower concentration recommended for children under 6 years old (European Academy of Paediatric Dentistry:

1000 and 500 ppm for 2-6 years old 6 months-2 years, respectively[11,12]). The reason for the restriction of paediatric toothpaste formulation is to mitigate the systemic impact of ingested toothpaste which occurs inevitably when children use toothpaste.

Another concern is that fluoride is most effective at the surface of the carious lesion leading to surface remineralisation, whilst there is minimal remineralisation within the body of the lesion[12]. Full remineralisation is therefore difficult to achieve using topically applied fluoride, regardless of the product. The benefits of high fluoride application are limited up to a point and may cause lesion lamination[13]. There is a growing market of acidulated phosphate fluoride (APF) products attempting to tackle this issue. These products are present in mouthrinse, gel or foam that have low pH (~3.0) to create pathways for fluoride and mineral ion ingress through the less porous enamel lesion surface, into the body of the carious lesion[14]. Its remineralisation effect on carious lesions is challenged by some in-situ studies and randomised clinical controlled trials (RCTs) which found no additional benefits in addition to standard fluoride toothpaste[15,16], whilst discolouration and etching of restorative materials as well as dentine hypersensitivity due to their acidity, may increase especially when used frequently[13].

Casein phosphopeptide-amorphous calcium phosphate (CPP-ACP)

CPP-ACP and its combination with fluoride, CPP-ACFP, are found in different forms and formulations; creams, mouthwashes and chewing gum. The aim of CPP-ACP use is to remineralise incipient enamel lesions at both the surface and subsurface level (an example of its clinical application is depicted in Figure 3). Its clinical efficacy has been evidenced by an increasing body of RCTs[17]. Studies have suggested that CPP-ACP could deliver significantly better remineralisation of WSLs in children and adolescents when compared to conventional fluoride products including toothpaste, mouthwash or fluoridated hydroxyapatite[18–26]. However, conflicting results have been reported, concluding that clinical remineralisation

efficacy of CPP-ACP was not superior and may even be inferior to fluoride therapies[27–29]. Several RCTs indicated that CPP-ACP failed to show greater remineralising benefits over placebo pastes [30–32]. There is also great variety present in literature and systematic reviews, with some supporting the significant caries remineralising and prevention effects of CPP-ACP whilst others claim its long-term or synergistic effect with fluoride is limited[33–35].

The disparity and contradiction from clinical trials can be attributed to many factors, including lesion type, duration, the form of the applied agents and the evaluation methodologies. In the study of Llena et al., pit and fissure lesions showed limited remineralisation, probably due to insufficient penetration of CPP-ACP in these areas[18]. It is also noted that in many studies additional oral hygiene measures such as use of fluoride toothpaste or antimicrobial mouthwash are included, so introducing more variables to the study and masking the actual efficacy of the target intervention. Another limitation of the published clinical trials is the patient type, which primarily focused on children and adolescents below 18-years-old; only a few took adults or older adult patients into consideration[29,36]. Therefore, the clinical efficacy of CPP-ACP remains uncertain in the adult and older adult populations. In addition, subjects with different susceptibility to caries may also introduce risk of bias to the trials. For example, remineralising effects maybe limited on orthodontic patients as the appliances reduce the efficiency of oral hygiene but more obvious on dental students who are better aware of oral hygiene[33,37]. More well-designed, long-term RCTs with broader patient and indication types are warranted.

Self-assembling peptides (SAP)

SAP P11-4 promotes enamel remineralisation by diffusing into the subsurface zone and providing a matrix for oriented crystal growth. It has been commercialised in some countries since 2013 (Curodont™ Repair; Credentis AG, Windisch, Switzerland). There have been several

small-scale clinical trials to investigate its clinical efficacy in remineralising incipient occlusal[38,39], buccal/labial[40–42], proximal[43], or post-orthodontic[44] WSLs. All observed significant regression of caries and improved appearance of the WSLs after P11-4 intervention compared to placebos or fluoride varnishes, implying superior subsurface remineralisation. Its combination with fluoride varnish, however, did not offer any obvious added effect[41]. Neither adverse effects nor severe adverse effects were reported, except Burton et al. found possible P11-4-related adverse effects of hypersensitivity in two cases [45].

It is worth mentioning that most studies were single-blinded RCTs due to modality reasons. In addition, Credentis AG (manufacturer of Curodont™ Repair) either funded or had employees listed as co-authors in most of these studies, which raises the question of potential research bias. The split-mouth nature of some studies may have crossover effects influencing the results[40,41,44]. The short duration of these studies, ranging from 6 to 12 months, limits the medium and long term potential of using SAP and further clinical research is required.

One concern regarding SAP technology is its clinical application that requires several steps, including meticulous preparation of the materials and tooth preparation by conditioning and etching[42]. The fact that SAP remineralisation is driven by saliva, might limit its efficacy in patients with poor saliva quality or in those with poor compliance[46]. Nevertheless, the ability of SAP in guided enamel remineralisation on the subsurface level defines progress in non-invasive caries therapy. More well-designed RCTs are necessary.

Calcium sodium phosphosilicate – bioactive glass

Calcium sodium phosphosilicate, invented by Prof. Hench in the late 1960s and in clinical use since 1985, was originally indicated for use in bone regeneration[47]. NovaMin™ is the trademark of a bioglass formulation designed for oral care purposes. Currently available dental products using NovaMin™ technology are produced by GlaxoSmithKline and include Sensodyne™ Protect & Repair Toothpaste (GlaxoSmithKline, Brentford, UK). The most noted

effect of NovaMin™ is its effect on dentine hypersensitivity[48]. Its clinical efficacy as a remineralising agent remains questionable. RCTs on the remineralisation potential of NovaMin™ are sparse with one being conducted by Hoffman et al. who investigated the prevention of NovaMin™ against WSLs and gingivitis during orthodontic treatment[49]. The results showed the NovaMin™-containing toothpaste exhibiting similar remineralisation as fluoride toothpaste. However, one cannot extrapolate that NovaMin™ possesses a similar prevention efficacy against WSLs as fluoride, because in addition to NovaMin™, the tested toothpaste also incorporated 5000 ppm sodium fluoride which on its own, is also capable of remineralisation. Recently, a new formulation of bioglass, BioMinF™, has emerged to aid remineralisation. This incorporates fluoride into the glass matrix as a soluble additive. In-vitro investigations suggest better remineralisation than NovaMin™ due to accelerated yet sustained dissolution of glass, enhanced concentration of phosphate and a reduced wash-off of fluoride[50,51]. However, no clinical studies are published yet to prove its clinical benefits. In general, bioglass as a remineralisation agent seemingly holds a promise, but more RCTs are required before any definitive conclusion can be drawn.

Functionalised-Tricalcium Phosphate (f-TCP)

f-TCP is an end product of β-TCP by mechanochemical ball-milling with organics, tailored to boost the activity of fluoride ions during remineralisation. It has been patented by 3M (Minnesota, USA) and launched in some markets in various forms, including cream (Clinpro™ Tooth Crème, 950 ppm fluoride), toothpaste (Clinpro™ 5000 Anti-Cavity Toothpaste, 5000 ppm fluoride) and varnish (Clinpro™ White Varnish, 22600 ppm fluoride). Previous studies failed to show significant remineralisation of the WSLs treated by f-TCP, which seem to imply a limited long-term remineralisation potential [52,53]. More recent clinical trials, however, demonstrated significant improvement of WSLs after f-TCP applications and the efficacy was

similar to or marginally better than that by other agents such as CPP-ACP, nano-hydroxyapatite and self-assembly peptide[42,54–57]. Nonetheless, the transient nature of f-TCP might hinder it from being effective, as in the study of Kau et al. participants were instructed not to rinse but to expectorate so that active constituents from the f-TCP cream were not cleared out immediately. The disparity within the published clinical trials suggest f-TCP needs more well-designed RCTs before clinical recommendation.

Other calcium phosphate remineralisation agents

Amorphous Calcium Phosphate (ACP) is a technology developed in 1999 utilising unstabilised calcium phosphate to boost remineralisation. It has been incorporated into toothpaste, gel and varnish products. Evidence of ACP on remineralising caries is mostly limited to in-situ and laboratory studies using in-vitro or animal models[58,59]. The only double-blinded RCTs were conducted by Papas et al. on patients with high caries risk who received therapeutic radiation therapy due to head and neck cancer[60,61]. Significantly reduced net yearly increment was described for root caries of participants in the ACP group (Enamelon™; Premier Dental Products Co., Pennsylvania, USA). However, its unstable nature could induce intra-oral precipitation of calcium phosphates which might increase the risk of dental calculus, reducing bioavailable calcium and phosphate ions. Furthermore, fluorapatites are formed when fluoride ions are present, which may also reduce its bioavailability, hence potentially limiting the efficacy intra-orally.

Synthetic hydroxyapatite (HA) has been used in toothpaste in 1980s by Sangi Co. Ltd. (Saitama, Japan). Since then, toothpastes have emerged incorporating HA[62]. In recent years, HA-related anticaries products have been gaining research interest. Clinical evidence of the treatment of the WSLs by hydroxyapatite has been reported in some RCTs ranging from 6 weeks to 12 months, with results indicating that nano-HA had caries remineralising capabilities are similar

to fluoride toothpastes or mouthwashes[63–67]. More well-designed RCTs are a prerequisite before any clinical recommendations.

CLINICAL GUIDANCE

In the UK there are two main guidelines that outline the prevention and management of dental caries in adults and children, The Delivering Better Oral Health Toolkit 2021 (DBOHv4; Public Health England (Office for Health Improvement and Disparities)[68], and Prevention and Management of Dental Caries in Children 2018 (SDCEP, Scotland)[69]; both outline the use of different oral care products in the management of caries, whether they are over the counter, prescription-only, or professionally applied.

The DBOHv4 document dedicates two chapters to the management of dental caries (Chapter 4)[70] and the use of fluorides (Chapter 9)[71], with an overview/summary of their recommendations for prevention of dental caries in children and adults found in Chapter 2[72]. In the summary guidance tables from DBOHv4, only fluoride use is mentioned at length and detail whilst there is no mention of other non-fluoride agents. Table 7 outlines specific recommendations of fluoride use for different populations according to their age and risk of caries. In Chapter 4, a brief mention is made of topical remineralising agents and are suggested to be effective in remineralising early enamel lesions in high-risk patients, these typically consisting of casein phosphopeptide (CPP-ACP).

The Scottish Dental Clinical Effectiveness Programme (SDCEP) guidelines for the Prevention and Management of Dental Caries in Children was published in 2018[69]. These guidelines specifically mention fluoride and no other non-fluoride agent. All children receive standard prevention appropriate to their age, and those with increased risk of caries receive enhanced prevention until their risk reduces. These recommendations are summarised in Table 8.

It is important to note in both sets of guidelines there is no mention of non-fluoride based products in their main clinical strategies for remineralisation due to the fact there is a limited high level evidence-base. However, this does not mean that these products are automatically without merit in targeted populations.

CONCLUSIONS

Delivering better oral health, specifically caries, should be focused on primary and secondary prevention delivered using the minimum intervention oral care (MIOC) framework[73–76]. As part of this, is the need for development of new remineralisation technologies and products. Although fluoride products remain the most effective in remineralising enamel caries, their benefit may have plateaued and certain negative perceptions such as risk to health and dental fluorosis may hinder their further clinical application. Among other technologies, CPP-ACP is a promising therapy, despite some contradictory findings from clinical studies. SAP might the next generation of remineralisation for its ability in structuring guided enamel remineralisation. Calcium sodium phosphosilicate, f-TCP, ACP and synthetic HA demonstrate some remineralisation capability, however the level of clinical evidence is limited. Although these non-fluoride technologies hold promise, more well-designed RCTs are vital to clarify their actual clinical benefits over traditional gold-standard fluoride, especially in higher risk, vulnerable patient groups where these adjunctive therapies would have most benefit. The two main UK-based guidelines outline extensively and in detail the fluoride preparations that can be used for the management of dental caries based on the level of risk of caries development; neither provide guidance on the use of non-fluoride preparations in the management of caries.

REFERENCES

1 Whelton HP, Spencer AJ, Do LG, Rugg-Gunn AJ. Fluoride revolution and dental caries: Evolution of policies for global use. *J Dent Res* 2019; **98**: 837–846.

2 Biesbrock AR, Faller R V, Bartizek RD, Court LK, McClanahan SF. Reversal of incipient and radiographic caries through the use of sodium and stannous fluoride dentifrices in a clinical trial. *J Clin Dent* 1998; **9**: 5–10.

3 Duckworth RM, Horay C, Huntington E, Mehta V. Effects of flossing and rinsing with a fluoridated mouthwash after brushing with a fluoridated toothpaste on salivary fluoride clearance. *Caries Res* 2009; **43**: 387–390.

4 ten Cate JM. Contemporary perspective on the use of fluoride products in caries prevention. *Br Dent J* 2013; **214**: 161–167.

5 Memarpour M, Fakhraei E, Dadaein S, Vossoughi M. Efficacy of fluoride varnish and casein phosphopeptide-amorphous calcium phosphate for remineralization of primary teeth: A randomized clinical trial. *Med Princ Pract* 2015; **24**: 231–237.

6 Marinho VC, Higgins JP, Logan S, Sheiham A. Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev* 2003; : CD002782.

7 Nordström A, Birkhed D. Preventive effect of high-fluoride dentifrice (5,000 ppm) in caries-active adolescents: A 2-year clinical trial. *Caries Res* 2010; **44**: 323–331.

8 Mannaa A, Campus G, Carlén A, Lingström P. Caries-risk profile variations after short-term use of 5000 ppm fluoride toothpaste. *Acta Odontol Scand* 2014; **72**: 228–234.

9 Stookey GK. Review of fluorosis risk of self-applied topical fluorides: dentifrices, mouthrinses and gels. *Community Dent Oral Epidemiol* 1994; **22**: 181–186.

10 Wong MC, Glenny A-M, Tsang BW, Lo EC, Worthington H V, Marinho VC. Topical fluoride as a cause of dental fluorosis in children. *Cochrane Database Syst Rev* 2010; : CD007693.

11 Guidelines on the use of fluoride in children: an EAPD policy document. *Eur Arch Paediatr Dent* 2009; **10**: 129–135.

12 Lynch RJM, Smith SR. Remineralization agents – New and effective or just marketing hype? *Adv Dent Res* 2012; **24**: 63–67.

13 Amaechi BT. Remineralisation - The buzzword for early MI caries management. *Br Dent J* 2017; **223**: 173–182.

14 Darvell BW. Surfaces. In: *Materials Science for Dentistry*. Elsevier, 2018, pp 292–336.

15 Paes Leme AF, Dalcico R, Tabchoury CPM, Del Bel Cury AA, Rosalen PL, Cury JA. In situ effect of frequent sucrose exposure on enamel demineralization and on plaque composition after APF application and F dentifrice use. *J Dent Res* 2004; **83**: 71–75.

16 Bonow MLM, Azevedo MS, Goettems ML, Rodrigues CRMD. Efficacy of 1.23% APF gel applications on incipient carious lesions: a double-blind randomized clinical trial. *Braz Oral Res* 2013; **27**: 279–285.

17 Reynolds EC. Casein phosphopeptide-amorphous calcium phosphate: The scientific evidence. *Adv Dent Res* 2009; **21**: 25–29.

18 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**: 181–6.

19 Fredrick C, Krithikadatta J, Abarajithan M, Kandaswamy D. Remineralisation of occlusal white spot lesion with a combination of 10% CPP-ACP and 0.2% sodium fluoride

evaluated using Diagnodent: a pilot study. *Oral Health Prev Dent* 2013; **11**: 191–6.

20 Andersson A, Sköld-Larsson K, Hallgren A, Petersson LG, Twetman S. Effect of a dental cream containing amorphous cream phosphate complexes on white spot lesion regression assessed by laser fluorescence. *Oral Health Prev Dent* 2007; **5**: 229–33.

21 Morgan MV, Adams GG, Bailey DL, Tsao CE, Fischman SL, Reynolds EC. The anticariogenic effect of sugar-free gum containing CPP-ACP nanocomplexes on approximal caries determined using digital bitewing radiography. *Caries Res* 2008; **42**: 171–184.

22 Bailey DL, Adams GG, Tsao CE, Hyslop A, Escobar K, Manton DJ *et al.* Regression of post-orthodontic lesions by a remineralizing cream. *J Dent Res* 2009; **88**: 1148–1153.

23 Rao SK, Bhat GS, Aradhya S, Devi A, Bhat M. Study of the efficacy of toothpaste containing casein phosphopeptide in the prevention of dental caries: a randomized controlled trial in 12- to 15-year-old high caries risk children in Bangalore, India. *Caries Res* 2009; **43**: 430–435.

24 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 Dentofac Orthop* 2011; **140**: 660–668.

25 Güçlü ZA, Alaçam A, Coleman NJ. A 12-week assessment of the treatment of white spot lesions with CPP-ACP paste and/or fluoride varnish. *Biomed Res Int* 2016; **2016**: 1–9.

26 Heravi F, Ahrari F, Tanbakuchi B. Effectiveness of MI Paste Plus and Remin Pro on remineralization and color improvement of postorthodontic white spot lesions. *Dent Res J (Isfahan)* 2018; **15**: 95.

27 Bröchner A, Christensen C, Kristensen B, Tranæus S, Karlsson L, Sonnesen L *et al.* Treatment of post-orthodontic white spot lesions with casein phosphopeptide-

stabilised amorphous calcium phosphate. *Clin Oral Investig* 2011; **15**: 369–373.

28 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 Dentofac Orthop* 2013; **143**: 31–41.

29 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**: 35–40.

30 Sitthisettapong T, Phantumvanit P, Huebner C, DeRouen T. Effect of CPP-ACP paste on dental caries in primary teeth. *J Dent Res* 2012; **91**: 847–852.

31 Sitthisettapong T, Doi T, Nishida Y, Kambara M, Phantumvanit P. Effect of CPP-ACP paste on enamel carious lesion of primary upper anterior teeth assessed by quantitative light-induced fluorescence: A one-year clinical trial. *Caries Res* 2015; **49**: 434–441.

32 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**: 610–617.

33 Li J, Xie X, Wang Y, Yin W, Antoun JS, Farella M *et al.* Long-term remineralizing effect of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) on early caries lesions in vivo: A systematic review. *J Dent* 2014; **42**: 769–777.

34 Fontana M. Enhancing fluoride: clinical human studies of alternatives or boosters for caries management. *Caries Res* 2016; **50**: 22–37.

35 Wang Y, Li J, Sun W, Li H, Cannon RD, Mei L. Effect of non-fluoride agents on the

prevention of dental caries in primary dentition: A systematic review. *PLoS One* 2017; **12**: e0182221.

36 Hay KD, Thomson WM. A clinical trial of the anticaries efficacy of casein derivatives complexed with calcium phosphate in patients with salivary gland dysfunction. *Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontology* 2002; **93**: 271–275.

37 de Oliveira PRA, Schubach da Costa Barreto L, Tostes MA. Effectiveness of CPP-ACP and fluoride products in tooth remineralization. *Int J Dent Hyg* 2021; : idh.12542.

38 Alkilzy M, Tarabaih A, Santamaria RM, Splieth CH. Self-assembling peptide P11-4 and fluoride for regenerating enamel. *J Dent Res* 2018; **97**: 148–154.

39 Doberdoli D, Bommer C, Begzati A, Haliti F, Heinzel-Gutenbrunner M, Juric H. Randomized clinical trial investigating self-assembling peptide P11-4 for treatment of early occlusal caries. *Sci Rep* 2020; **10**: 4195.

40 Bröseler F, Tietmann C, Bommer C, Drechsel T, Heinzel-Gutenbrunner M, Jepsen S. Randomised clinical trial investigating self-assembling peptide P11-4 in the treatment of early caries. *Clin Oral Investig* 2020; **24**: 123–132.

41 Kondelova PS, Mannaa A, Bommer C, Abdelaziz M, Daeniker L, di Bella E *et al.* Efficacy of P11-4 for the treatment of initial buccal caries: a randomized clinical trial. *Sci Rep* 2020; **10**: 20211.

42 Kobeissi R, Osman E, Badr SB. Effectiveness of self-assembling peptide P11-4 compared to tricalcium phosphate fluoride varnish in remineralization of white spot lesions: A clinical randomized trial. *Int J Clin Pediatr Dent* 2021; **13**: 451–456.

43 Schlee M, Schad T, Koch JH, Cattin PC, Rathe F. Clinical performance of self-assembling peptide P11-4 in the treatment of initial proximal carious lesions: A practice-based case series. *J Investig Clin Dent* 2018; **9**: e12286.

44 Welk A, Ratzmann A, Reich M, Krey KF, Schwahn C. Effect of self-assembling peptide P11-4 on orthodontic treatment-induced carious lesions. *Sci Rep* 2020; **10**: 6819.

45 Brunton PA, Davies RPW, Burke JL, Smith A, Aggeli A, Brookes SJ *et al.* Treatment of early caries lesions using biomimetic self-assembling peptides – a clinical safety trial. *Br Dent J* 2013; **215**: E6–E6.

46 Schlee M, Rathe F, Huck T, Schad T, Koch JH, Tjaden A *et al.* Klinischer Effekt biomimetischer Mineralisation bei Approximalkaries. *Stomatologie* 2014; **111**: 175–181.

47 Hench LL. The story of Bioglass®. *J Mater Sci Mater Med* 2006; **17**: 967–978.

48 Wefel JS. NovaMin ® : Likely Clinical Success. *Adv Dent Res* 2009; **21**: 40–43.

49 Hoffman DA, Clark AE, Rody WJ, McGorray SP, Wheeler TT. A prospective randomized clinical trial into the capacity of a toothpaste containing NovaMin to prevent white spot lesions and gingivitis during orthodontic treatment. *Prog Orthod* 2015; **16**: 25.

50 Bakry A, Abbassy M, Alharkan H, Basuhail S, Al-Ghamdi K, Hill R. A novel fluoride containing bioactive glass paste is capable of re-mineralizing early caries lesions. *Materials (Basel)* 2018; **11**: 1636.

51 Ramadoss R, Padmanaban R, Subramanian B. Role of bioglass in enamel remineralization: Existing strategies and future prospects—A narrative review. *J Biomed Mater Res Part B Appl Biomater* 2021; : jbm.b.34904.

52 Pascual A, Muñoz C, Silva A, Martínez-Beneyto Y, Ruiz A. Effects of fluoride and calcium phosphate-based varnishes on pH, lactic acid, and trace elements in saliva: A randomized clinical trial. 2020. doi:10.21203/rs.3.rs-33730/v2.

53 Thaper R, Karlinsey RL. Clinical observations on the remineralization of stage 1 enamel

caries lesions using a traybased protocol: A case report. *Int J Dent Oral Heal* 2016; **2**: 1–4.

54 Damyanova DD, Angelova DS, Targova-Dimitrova DT. Clinical study remineralization effect of mineralization varnish. *IOSR J Dent Med Sci* 2016; **15**: 134–136.

55 Badr S, Ragab H. The effectiveness of a nano-hydroxyapatite paste and a tri-calcium phosphate fluoride varnish in white spot lesions remineralization (randomized clinical trial). *Egypt Dent J* 2018; **64**: 2757–2765.

56 Kau CH, Wang J, Palombini A, Abou-Kheir N, Christou T. Effect of fluoride dentifrices on white spot lesions during orthodontic treatment: A randomized trial. *Angle Orthod* 2019; **89**: 365–371.

57 AlFeel J, Laflouf M, AlKurdi S, Alkhouli M. Evaluating the effect of Clinpro Tooth Crème on remineralization of pre-carious white spot lesions in anterior primary teeth: Randomized controlled clinical trial. *Pediatr Dent J* 2021; **31**: 152–158.

58 Thompson A, Grant LP, Tanzer JM. Model for assessment of carious lesion remineralization, and remineralization by a novel toothpaste. *J Clin Dent* 1999; **10**: 34–9.

59 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**: 26–9.

60 Papas A, Russell D, Singh M, Stack K, Kent R, Triol C *et al.* Double blind clinical trial of a remineralizing dentifrice in the prevention of caries in a radiation therapy population. *Gerodontology* 1999; **16**: 2–10.

61 Papas A, Russell D, Singh M, Kent R, Triol C, Winston A. Caries clinical trial of a remineralising toothpaste in radiation patients. *Gerodontology* 2008; **25**: 76–88.

62 Chen L, Al-Bayatee S, Khurshid Z, Shavandi A, Brunton P, Ratnayake J. Hydroxyapatite in oral care products—A review. *Materials (Basel)* 2021; **14**: 4865.

63 Makeeva IM, Polyakova MA, Avdeenko OE, Paramonov YO, Kondrat'ev SA, Pilyagina AA. Effect of long term application of toothpaste Apadent Total Care Medical nano-hydroxyapatite. *Stomatologiya* 2016; **95**: 34–6.

64 Hegazy SA, Salama RI. Antiplaque and remineralizing effects of Biorepair mouthwash: A comparative clinical trial. *Pediatr Dent J* 2016; **26**: 89–94.

65 Paszynska E, Pawinska M, Gawriolek M, Kaminska I, Otulakowska-Skrzynska J, Marczuk-Kolada G *et al.* Impact of a toothpaste with microcrystalline hydroxyapatite on the occurrence of early childhood caries: a 1-year randomized clinical trial. *Sci Rep* 2021; **11**: 2650.

66 Schlagenhauf U, Kunzelmann K, Hannig C, May TW, Hösl H, Gratza M *et al.* Impact of a non-fluoridated microcrystalline hydroxyapatite dentifrice on enamel caries progression in highly caries-susceptible orthodontic patients: A randomized, controlled 6-month trial. *J Investig Clin Dent* 2019; **10**: e12399.

67 Grocholewicz K, Matkowska-Cichocka G, Makowiecki P, Droździk A, Ey-Chmielewska H, Dziewulska A *et al.* Effect of nano-hydroxyapatite and ozone on approximal initial caries: a randomized clinical trial. *Sci Rep* 2020; **10**: 11192.

68 No Title. https://www.gov.uk/government/publications/delivering-better-oral-health-an-evidence-based-toolkit-for-prevention (accessed 25 Oct2021).

69 No Title. https://www.sdcep.org.uk/wp-content/uploads/2018/05/SDCEP-Prevention-and-Management-of-Dental-Caries-in-Children-2nd-Edition.pdf.

70 No Title. https://www.gov.uk/government/publications/delivering-better-oral-health-an-evidence-based-toolkit-for-prevention/chapter-4-dental-caries (accessed 25

Oct2021).

71 No Title. https://www.gov.uk/government/publications/delivering-better-oral-health-an-evidence-based-toolkit-for-prevention/chapter-9-fluoride (accessed 25 Oct2021).

72 No Title. https://www.gov.uk/government/publications/delivering-better-oral-health-an-evidence-based-toolkit-for-prevention/chapter-2-summary-guidance-tables-for-dental-teams (accessed 25 Oct2021).

73 Banerjee A. 'Minimum intervention' – MI inspiring future oral healthcare? *Br Dent J* 2017; **223**: 133–135.

74 Banerjee A. Minimum Intervention (MI) Oral Healthcare Delivery Implementation – Overcoming the Hurdles. *Prim Dent J* 2017; **6**: 28–33.

75 Martignon S, Pitts NB, Goffin G, Mazevet M, Douglas GVA, Newton JT *et al.* CariesCare practice guide: consensus on evidence into practice. *Br Dent J* 2019; **227**: 353–362.

76 Banerjee A. Minimum intervention oral healthcare delivery - is there consensus? *Br Dent J* 2020; **229**: 393–395.

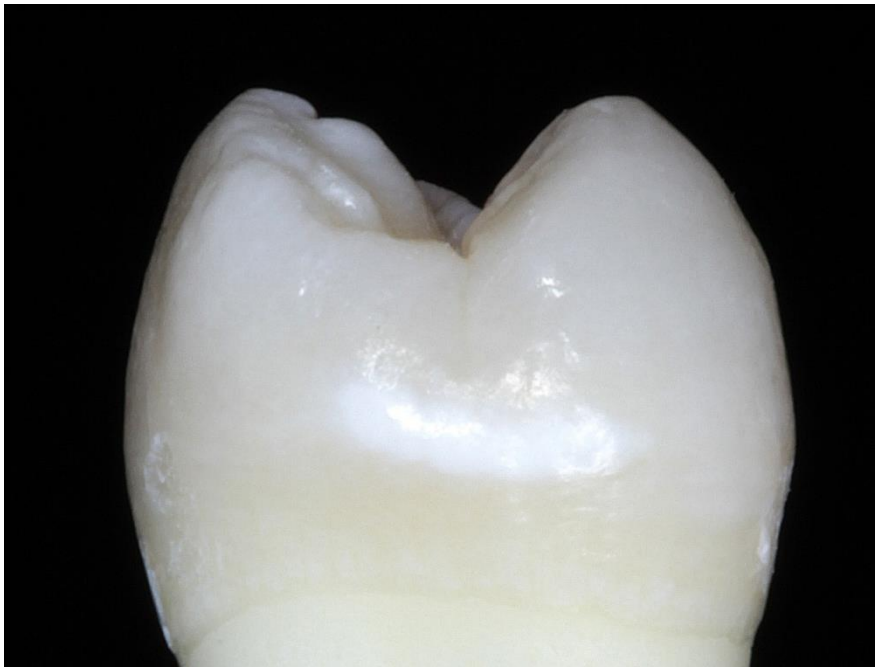

Figure 1. Example of white spot lesion on the proximal surface of a mandibular premolar – the lesion itself is formed beneath the contact point where plaque accumulation occurs and is commonly missed during routine oral hygiene. Photo courtesy of L. Mackenzie.

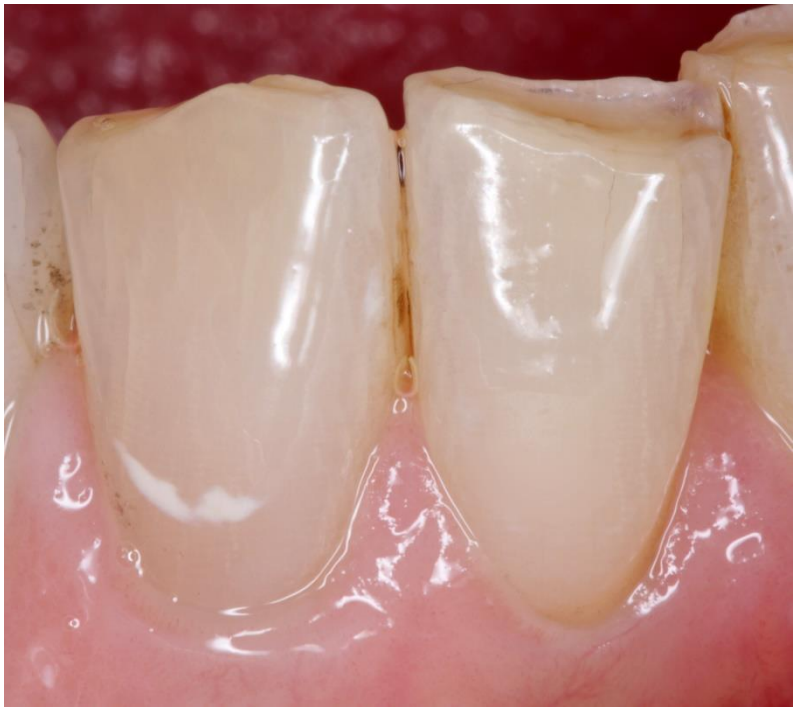

Figure 2. A clinical example of a white spot lesion around the cervical aspect of a mandibular incisor. Courtesy of L. Mackenzie.

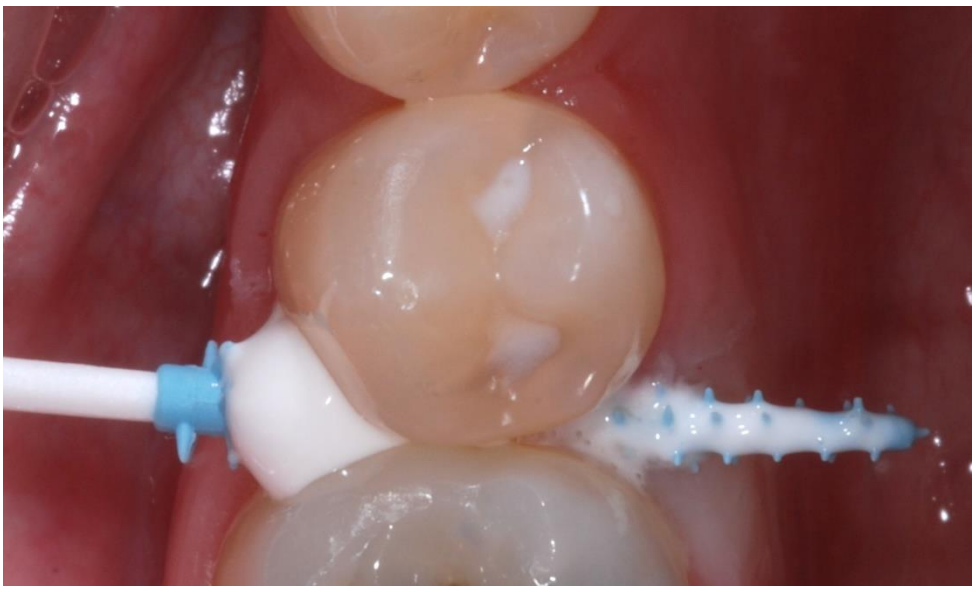

Figure 3. Clinical application of CPP-ACP paste using an appropriately sized interdental applicator. Courtesy of L. Mackenzie.

Table 1 Summary of clinical studies for fluoride

Authors	Study type	Sample characteristics	Duration	Interventions	Outcome
Biesbrock et al.[2]	Retrospective, double-blinded RCT	Not specified	3 years	i) 0.243% sodium fluoride dentifrice ii) 0.4% stannous fluoride/ calcium pyrophosphate dentifrice iii) non-fluoridated placebo/ calcium pyrophosphate dentifrice	Sodium fluoride delivered greater remineralisation to reverse caries than stannous fluoride, although no significant difference was found between the two treatments.
Bonow et al.[16]	Double-blinded RCT	59 subjects (7-12yo)	8 weeks	i) DFL gel (1.23% APF) ii) Placebo gel Fluoridated toothpaste (1100 ppm) was used in all groups	1.23% APF gel failed to demonstrate extra benefits in treating the WSLs in addition to the placebo when exposure to fluoride was present in both groups.
Duckworth et al.[3]	Single-blinded randomised crossover trial	20 subjects (18-55yo)	120 min	i) Rinsing with water ii) Dental floss iii) Dental floss then rinsing with fluoride mouthwash (226mg/L) Brushing with fluoride toothpaste (1450 ppm) was applied before each regime	Fluoridated mouthwash after professional flossing generated more fluoride retention in the saliva which might provide better caries remineralisation and prevention benefits.

Mannaa et al.[8]	Not specified	34 subjects (mean age: children: 14.5yo; mothers: 38.4yo)	6 weeks	i) Clinpro™ 5000 toothpaste (5000 ppm fluoride)	Short-term application of 5000 ppm fluoride demonstrated clear reduction of caries risk.
Memarpour et al.[5]	Parallel, double-blinded RCT	140 children (1-3yo)	1 year	i) Placebo ii) Oral hygiene iii) DuraShield™ varnish (5% fluoride) + oral hygiene iv) CPP-ACP + oral hygiene	Oral hygiene with CPP-ACP was the most effective in decreasing the size of the WSLs due to remineralisation, followed by oral hygiene with 5% fluoride varnish.
Nordström et al.[7]	Single-blinded RCT	211 subjects (14-16yo)	2 years	i) Duraphat™ toothpaste (5000 ppm fluoride) ii) Pepsodent™ Superfluor toothpaste (1450 ppm fluoride)	5000 ppm fluoride demonstrated significantly lower caries lesion progression and incidence than 1450 ppm fluoride.

Table 2 Summary of clinical studies for casein phosphopeptide-amorphous calcium phosphate

Authors	Study type	Sample characteristics	Duration	Interventions	Outcome
Andersson et al.[20]	RCT	26 subjects (12-16yo)	1 year	i) CPP-ACP cream + 1100ppm fluoride toothpaste ii) 0.05% fluoride mouthwash + 1100ppm fluoride toothpaste	CPP-ACP showed aesthetical improvement of WSLs than NaF mouthwash. No additional clinical benefits could be identified.
Bailey et al.[22]	RCT	45 subjects (12-18yo)	3 months	i) Tooth Mousse™ cream (10% CPP-ACP) ii) Placebo cream	CPP-ACP significantly enhanced regression of WSLs than placebo.
Beerens et al.[32]	RCT	54 subjects (12-19yo)	3 months	i) MI Paste™ Plus (0.2% CPP-ACP + 900 ppm fluoride) ii) Ultradent™ toothpaste (fluoride-free + calcium)	No difference was found between CPP-ACFP and placebo in QLF assessments.
Bröchner et al.[27]	RCT	50 subjects (13-18yo)	1 month	i) Tooth Mousse™ cream (CPP-ACP) + Colgate toothpaste (1100 ppm fluoride) ii) Colgate toothpaste (1100 ppm fluoride)	CPP-ACP was not superior to fluoride toothpaste, although it reduced the area of the post-orthodontic WSLs.

Fredrick et al.[19]	RCT	45 subjects (17-20yo)	1 month	i) Tooth Mousse™ Plus (10% CPP-ACP + 0.2% fluoride) ii) Tooth Mousse™ (10% CPP-ACP) iii) S-flo mouthrinse (0.5% fluoride)	CPP-ACP with or without 0.2% NaF was superior to 0.5% NaF in remineralising WSLs. Combination of CPP-ACP and fluoride did not show added efficacy over CPP-ACP alone.
Güçlü et al.[25]	Not specified	21 subjects (8-15yo)	3 months	i) Control ii) Flor-Opal™ varnish (5% fluoride) iii) Tooth Mousse™ paste (10% CPP-ACP) iv) Tooth Mousse™ paste (10% CPP-ACP) + Flor-Opal™ varnish (5% fluoride)	CPP-ACP paste improved aesthetic appearance and remineralisation of the WSLs as a supplement application with xylitol gum, antimicrobial mouthwash and fluoride toothpaste.
Hay et al.[36]	RCT	124 subjects with Sjögren syndrome or head/neck cancer (>25yo)	1 year	i) CD-CP mouthrinse ii) NaF mouthrinse (0.05% fluoride)	Coronal caries incidence was higher in the sodium fluoride group than in the CD-CP group, but the difference was not statistically significant.
Heravi et al.[26]	RCT	36 patients (13-23yo)	3 months	i) MI Paste™ Plus cream (CPP-ACPF) ii) ReminPro™ cream (Fluoridated HA) iii) No treatment control	CPP-ACFP was effective in reducing the size, increasing the mineral content and improving the appearance of post-orthodontic WSLs.

Huang et al.[28]	Single-blinded, 3-armed, active-controlled, parallel-group trial	115 subjects (12-20yo)	2 months	i) MI Paste™ Plus paste (CPP-ACPF) ii) PreviDent™ varnish (22600 ppm fluoride) iii) Usual home-care All interventions included 1100ppm fluoride toothpaste	MI Paste Plus and PreviDent interventions failed to demonstrate better effectiveness for improving the appearance of the WSLs than usual oral hygiene procedures.
Llena et al.[18]	Prospective, double-blinded trial	80 subjects (6-14yo)	3 months	i) Tooth Mousse™ paste (CPP-ACP) ii) MI Paste™ Plus paste (CPP-ACP + 900ppm fluoride) iii) Duraphat™ varnish (5% fluoride) iv) Non-fluoridated paste All interventions included 1100ppm fluoride toothpaste	CPP-ACFP were superior to fluoride varnish in remineralising WSLs. No difference was found between CPP-ACP and fluoride varnish.
Morgan et al.[21]	Parallel, double-blinded RCT	1749 subjects (11.5-13.5yo)	2 years	i) 3% CPP-ACP gum ii) Sorbitol-based gum	CPP-ACP chewing gum significantly controlled the progression and promoted remineralisation of the approximal caries.
Rao et al.[23]	Parallel, triple-blinded RCT	139 subjects (12-15yo)	2 years	i) 2% CPP toothpaste ii) 0.76% sodium mono-fluorophosphate (SMFP) toothpaste iii) Placebo toothpaste	CPP-containing toothpaste was similarly effective in preventing caries compared to 0.76% SMFP toothpaste.
Robertson et al.[24]	Prospective, double-blinded RCT	50 subjects (>12yo)	1 year	i) MI Paste™ Plus paste ii) Placebo paste	CPP-ACP significantly prevented the WSLs from progressing and reduced the numbers of the WSLs during orthodontic treatment compared to the placebo.

Singh et al.[29]	Double-blinded RCT	41 subjects (16-25yo)	i) Colgate total (1000 ppm fluoride) ii) 5% fluoride varnish iii) Tooth Mousse™ (CPP-ACP) containing 900 ppm fluoride All interventions included regular use of 1000 ppm fluoride toothpaste for toothbrushing	The severity of the WSLs was reduced by CPP-ACP, which was comparable with fluoride toothpaste alone. No additional clinical benefits to regular use of fluoride toothpaste were found for both fluoride varnish and CPP-ACP with 900 ppm fluoride in remineralising post-orthodontic WSLs.

Table 3 Summary of clinical studies for self-assembling peptides

Author(s)	Study type	Sample characteristics	Duration	Interventions	Outcome
Alkilzy et al.[38]	Single-blinded RCT	70 subjects (>5yo)	6 months	i) Curodont™ Repair (SAP) + Duraphat™ varnish (22600 ppm fluoride) ii) Duraphat™ varnish (22660 fluoride)	Significantly more regression of caries was found for P11-4 in combination with fluoride varnish compared to fluoride varnish alone.
Bröseler et al.[40]	Prospective, split-mouth, single-blinded RCT	37 subjects (13-16yo)	1 year	i) Curodont™ Repair (SAP) ii) Duraphat™ varnish (22600 ppm fluoride)	P11-4 is superior compared to fluoride varnish in remineralising early buccal caries.
Brunton et al.[45]	Non-controlled safety clinical trial	15 subjects (18-65yo)	6 months	i) P11-4 solution	The treatment of early caries lesions with P11-4 was safe, and that a single application is associated with significant enamel regeneration.
Doberdoli et al.[39]	Single-blinded RCT	90 subjects (6-15yo)	1 year	i) Curodont™ Repair (SAP) + Fluor Protector S varnish (7700 ppm fluoride) ii) Curodont™ Repair (SAP) + Curodont™ Protector (SAPM gel) iii) Fluor Protector™ S varnish (7700 ppm fluoride)	Treatment with P11-4 alone or with SAPM gel induced significantly more regression of early caries than that with fluoride varnish.

Kobeissi et al.[42]	Single-blinded RCT	9 subjects (7-17yo)	6 months	i) Clinpro™ White Varnish (TCPF) ii) Curodont™ Repair (SAP)	TCPF and SAP11-4 were both significantly effective in remineralising the WSLs with SAP11-4 being significantly better due to its guided enamel regeneration potential.
Kondelova et al.[41]	Quadruple-blinded split-mouth RCT	44 subjects (15-39yo)	9 months	i) Curodont™ Repair (SAP) ii) Placebo All subjects also received fluoride varnish treatment	SAP P11-4 treatment resulted in superior caries regression compared to placebo with fluoride varnish. Effects of fluoride varnish was not affected by SAP.
Schlee et al.[43]	Prospective uncontrolled case study	26 subjects (18-65yo)	1 year	i) Curodont™ Repair (SAP)	Initial proximal carious lesions could be remineralised by treatment with P11-4 SAP, but additional factors might influence the overall treatment outcome.
Welk et al.[44]	Single-blinded split-mouth RCT	21 subjects (12-18yo)	6 months	i) Curodont™ Repair (SAP)	WSLs treated with P11−4 SAP were significantly remineralised on the subsurface level compared with the control teeth.

Table 4 Summary of clinical studies for bioglass

Authors	Study type	Sample characteristics	Duration	Interventions	Outcome
Hoffman et al.[49]	Prospective, double-blinded RCT	48 subjects (12-25yo)	6 months	i) ReNew™ (5% NovaMin™ + 5000 ppm fluoride) ii) Crest (0.15% fluoride)	ReNew™ had effects in improving WSLs, plaque levels and gingival health similar to 0.15% fluoride containing toothpaste in orthodontic patients.

Table 5 Summary of clinical studies for functionalised tri-calcium phosphate (f-TCP)

Authors	Study type	Sample characteristics	Duration	Interventions	Outcome
AlFeel et al.[57]	Double-blinded RCT	18 subjects (3-5yo)	6 weeks	i) Clinpro™ Tooth Creme (950 ppm fluoride + f-TCP)	f-TCP showed significantly better remineralisation effect on the WSLs than control, despite no improvement of clinical appearance was found.
Badr et al.[55]	Double-blinded RCT	20 subjects (12-16yo)	6 months	i) Desensibilize Nano P (nano-HA) ii) Clinpro™ White Varnish (f-TCP)	Both nano-HA and f-TCP were effective in remineralisation of the WSLs after orthodontic treatment. Nano-HA demonstrated better stability of remineralisation effect than f-TCP.
Damyanova et al.[54]	Not specified	100 subjects (4-6yo)	1 year	i) Clinpro™ White Varnish (f-TCP)	f-TCP was effective in reducing demineralisation on the subsurface level.
Kau et al.[56]	Randomised trial	100 subjects (>12yo)	4 months	i) Clinpro™ 5000 (5000 ppm fluoride) ii) Clinpro™ Tooth Creme (950 ppm fluoride + f-TCP) iii) MI Paste™ Plus (CPP-ACP + 0.2% fluoride)	All three therapies could prevent WSL formation, but high-dose fluoride was marginally better than f-TCP and CPP-ACP.

Kobeissi et al.[42]	Single-blinded RCT	9 subjects (7-17yo)	6 months	i) Clinpro™ White Varnish (f-TCP) ii) Curodont™ Repair (SAP)	f-TCP and SAP were both significantly effective in remineralising WSLs with SAP11-4 being significantly better due to its guided enamel regeneration potential.
Pascual et al.[52]	Double-blinded RCT	58 subjects (4-12yo)	12 months	i) MI Varnish (CPP-ACP) ii) Clinpro™ White Varnish (f-TCP)	Significant reduction of phosphorous was only found in the placebo group. Change of calcium concentration was not significant in experiment groups, though CPP-ACP had higher than f-TCP which may suggest better mineralising potential.

Table 6 Summary of clinical studies for other calcium-phosphate agents

Authors	Study type	Sample characteristics	Duration	Interventions	Outcome
Grocholewicz et al.[67]	RCT	92 subjects (20-30yo)	6 months treatment with follow-up at 1 and 2 year	i) ApaCare & Repair™ (10% nano-HA) ii) Ozone therapy iii) Apacare & Repair™ + Ozone therapy	Nano-HA demonstrated subsurface remineralisation potential at 1 year, which was significantly less effective than ozone therapy and the combination. Further demineralisation was observed for all groups at the 2-year follow-up.
Hegazy et al.[64]	Double-blinded RCT	76 subjects (7-12yo)	6 weeks	i) Biorepair™ mouthwash (nano-HA) ii) Listerine mouthwash (0.02% fluoride) iii) Peridex™ mouthwash (0.12% chlorhexidine)	Significant remineralisation of the WSLs was observed from 1 week in nano-HA and fluoride groups. No difference in remineralisation effectiveness was found between nano-HA fluoride mouthwashes at all follow-up periods.
Makeeva et al.[63]	Not specified	30 subjects (17-25yo & 35-44yo respectively for 2 study groups)	3 months	i) Apadent Total Care™ toothpaste (nano-HA)	Long-term application of nano-HA containing toothpaste promoted remineralisation of initial carious lesions.
Papas et al.[60]	Double-blinded RCT	50 subjects (>18yo)	1 year	i) Enamelon™ toothpaste (ACP + 1150 ppm fluoride) ii) Conventional toothpaste (1150 ppm fluoride)	ACP-containing toothpaste helped prevent and remineralise tooth coronal and root caries.

Papas et al.[61]	Double-blinded RCT	44 subjects (>18yo)	1 year	i) Enamelon™ toothpaste (ACP + 1100 ppm fluoride) ii) Conventional toothpaste (1100 ppm fluoride)	ACP-containing toothpaste was significantly better at controlling root caries than conventional fluoride toothpaste. More remineralisation of coronal caries was found in the ACP group albeit no statistical significance.
Paszynska et al.[65]	Double-blinded RCT	177 subjects (3-7yo)	1 year	i) Kinder Karex™ toothpaste (10% microcrystalline HA) ii) Elmex™ Kinder toothpaste (500 ppm fluoride)	HA demonstrated enamel caries remineralising capabilities not inferior to conventional fluoride toothpaste.
Schlagenhauf et al.[66]	Multicentre, prospective, parallel-group, two-arm, double-blinded RCT	133 subjects (11-25yo)	6 months	i) Karex™ toothpaste (10% microcrystalline HA) ii) Meridol™ toothpaste (1400ppm fluoride)	Regular use of fluoride-free HA toothpaste had similar impact on controlling caries progress to fluoride toothpaste in highly caries-active orthodontic subjects.

Table 7 Summary of the recommendations for remineralisation strategies from the Delivering Better Oral Health Toolkit 2021, PHE.

Age of Patients (yrs)	Caries Risk Category	Remineralisation Strategy	Delivery Method	Concentration	Frequency
0 – 3	Any	Fluoride	Toothpaste	≥ 1000 ppm	Twice Daily
	High	Fluoride	Toothpaste	1350 – 1500 ppm	Twice Daily
3 – 6	Any	Fluoride	Toothpaste Varnish	≥ 1000 ppm 22600 ppm	Twice Daily Twice Yearly
	High	Fluoride	Toothpaste Varnish	1350 – 1500 ppm 22600 ppm	Twice Daily Twice Yearly
7 – 18	Any	Fluoride	Toothpaste Varnish	1350 – 1500 ppm 22600 ppm	Twice Daily Twice Yearly
	High	Fluoride	Toothpaste Toothpaste Toothpaste Mouth rinse Varnish	1350 – 1500 ppm 2800 ppm (10+ yrs) 2800 or 5000 ppm (16+ yrs) 230 ppm (8+ yrs) 22600 ppm	Twice Daily Twice Daily Twice Daily Daily Twice Yearly
18+ (adult)	Any	Fluoride	Toothpaste	1350 – 1500 ppm	Twice Daily
	High	Fluoride	Toothpaste Toothpaste Mouth rinse	1350 – 1500 ppm 2800 or 5000 ppm 230 ppm	Twice Daily Twice Daily Daily

Table 8 Summary of the recommendations for remineralisation strategies from the SDCEP – Prevention and Management of Dental Caries in Children Edition 2018 (Denotes info from SDCEP Drug Prescribing for Dentistry guidance, and not explicitly written in the Prevention and Management of Dental Caries in Children guidance)

Age of Patients (yrs)	Caries Risk Category	Remineralisation Strategy	Delivery Method	Concentration	Amount	Frequency
0-3	Standard	Fluoride	Toothpaste	1000 – 1500 ppm	Smear	Twice Daily
			Varnish	22600 ppm (≥ 2 yrs)	0.25 mL	Twice Yearly
	Increased	Fluoride	Toothpaste	1350 – 1500 ppm	Pea-sized	Twice Daily
			Varnish	22600 ppm (≥ 2 yrs)	0.25 mL	Four Yearly
3 – 18	Standard	Fluoride	Toothpaste	1000 – 1500 ppm	Pea-sized	Twice Daily
			Varnish	22600 ppm	0.4 mL (5 – 7 yrs)	Twice Yearly
	Increased	Fluoride	Toothpaste	1350 – 1500 ppm (≤ 10 yrs)	Pea-sized	Twice Daily
			Toothpaste	2800 ppm (10 – 16 yrs)	Pea-sized	Twice Yearly
			Varnish	22600 ppm	0.4 mL (5 – 7 yrs)	Four Yearly
			Mouth rinse	230 ppm* (≥ 6 yrs)	10 mL*	Once Daily*