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Is there a Role for Casein Phosphopeptide–Amorphous Calcium Phosphate (CPP-ACP) in Paediatric Dentistry?

Abstract: In the age of minimally invasive dentistry, products with the ability to prevent and reverse common dental diseases are becoming increasingly popular. Casein phosphopeptide–amorphous calcium phosphate (CPP–ACP) contains the compounds casein, phosphate and calcium, which all have the ability to remineralize enamel. Dental caries, visible demineralization following removal of orthodontic appliances, non-carious tooth surface loss and dentine hypersensitivity due to structural anomalies are frequently seen in children and young people. The evidence for CPP–ACP and fluoride-containing CPP–ACP is positive for managing dental caries and non-carious tooth surface loss, specifically erosion, but is less clear in the management of visible demineralization following orthodontic appliance removal and dentine hypersensitivity owing to structural anomalies. When recommending CPP–ACP-containing products, dental practitioners should be aware of medical and social contra-indications that preclude its use.

CPD/Clinical Relevance: CPP–ACP may have a role in the management of common paediatric dental conditions.

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Casein phosphopeptide–amorphous calcium phosphate (CPP–ACP) is a calcium-based phosphate system that aids enamel remineralization through promoting apatite formation.[1] The CPP–ACP complex (Recaldent) was developed at the School of Dental Science at the University of Melbourne, Victoria, Australia and is marketed in the UK as GC Tooth Mousse or GC MI Paste Plus, which also contains fluoride. A varnish containing both CPP–ACP and fluoride (GC MI varnish) is available, as is a glass ionomer cement with added CPP–ACP (GC Fuji VII EP, GC, Japan), although the latter is currently only available in Australia. Another formulation that incorporates Recaldent is chewing gum (available through BreezeCare UK online).

Calcium, phosphate and the protein casein, which are found in milk products, have the potential to remineralize enamel, but large volumes are required.[1] CPP is formed when casein is digested by the enzyme trypsin, then aggregated with calcium phosphate and purified using ultrafiltration.[2] While ACP has the potential to remineralize enamel, it is unstable and rapidly crystallizes out, promoting the formation of dental calculus. When CPP is combined with ACP, the multiple phosphoseryl residues from casein bound in CPP stabilize ACP by preventing its precipitation into a crystalline phase. The resulting CPP–ACP complex forms a stable remineralization compound.[1]

Mechanism of action

CPP–ACP is readily soluble in saliva and attaches itself to dental plaque and tooth surfaces.[2,3] When subjected to a drop in pH, the attached CPP–ACP releases calcium and phosphate ions, leading to a state of supersaturation, which decreases enamel demineralization and

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promotes remineralization.[1,3] This action leads clinicians to consider using CPP-ACP in a variety of clinical applications, including the management of caries, visible demineralization following removal of orthodontic appliances, non carious tooth surface loss (erosion) and dentine hypersensitivity. The evidence for which is discussed in further detail below, and summarized in Table 1.

Clinical application for CPP–ACP	Summary of evidence
Dental caries	Both a systematic review and a randomized controlled trial demonstrate effectiveness of CPP-ACP in preventing caries.[3,8] Evidence from another systematic review suggests CPP–ACP has a limited effect in treating dental caries.[9] A separate meta-analysis concluded that CPP–ACFP remineralizes early occlusal enamel lesions.[15]
Orthodontic-related demineralization	Inconclusive evidence from systematic reviews and *in vivo* studies, although there is an indication that CPP–ACP has a superior effect in remineralizing enamel over fluoride-containing products.[22,23,25]
Erosion	*In vitro* studies suggest CPP–ACP reduces erosive potential of drinks and increases microhardness of teeth.[32,33]
Dentine hypersensitivity	Systematic reviews conclude there is insufficient or low-quality evidence that CPP–ACP reduces symptoms of dentine hypersensitivity.[37–39]

Table 1. Summary of evidence for the use of CPP–ACP in different clinical applications

Dental caries

Enamel is constantly undergoing cycles of demineralization and remineralization. Dental plaque contains bacteria, notably *Streptococcus mutans*, that metabolize fermentable carbohydrate (sugar) to produce lactic acid, which is responsible for subjecting enamel to a drop in pH and leading to demineralization. When conditions in the oral cavity promote enamel demineralization, the dental caries process begins. As mineral is lost, a white spot lesion starts to develop. If this lesion is left to progress, the enamel surface may cavitate, allowing bacteria to infiltrate the dentine with ease. Bacteria can travel along the dentine tubules to reach the pulp and periapical tissues, which in turn causes pain and infection.[4]

Although the overall prevalence of dental caries in this country is decreasing, 23.3% of children in England still have experience of dental decay, with marked inequalities in the distribution and impact.[5] In 2015–2016, approximately 57,485 children and young people under the age of 19 were admitted to hospital for a dental general anaesthetic to treat a primary diagnosis of dental caries. This represents the most common reason for this age group to require a hospital admission with an estimated cost of £39 million to the NHS.[6] If detected early, preventive interventions can be implemented and the caries process reversed, reducing the need for operative treatment and its associated costs. Along with effective plaque control, reduction of fermentable carbohydrate in the diet and increased fluoride availability, CPP–ACP may have a role to play in the remineralization of enamel.

Through its incorporation into the dental pellicle, CPP–ACP can inhibit the adherence of cariogenic bacteria. This in turn reduces the production of acid from fermentable carbohydrate and the subsequent drop in pH that leads to demineralization of the enamel.[1] This preventive effect was investigated through a high-quality randomized controlled trial involving a sample of 2720 children over a 24-month period. The researchers demonstrated an 18% reduction in caries in children chewing sugar-free gum containing 54 mg CPP–ACP compared to the control group who chewed sugar-free gum with no added CPP–ACP.[7] These findings were corroborated by a systematic review by Yengopal and Mickenautsch, that further considered the preventive effect of CPP–ACP in chewing gum in a meta-analysis of five randomized controlled trials. The authors reported a significant improvement (P=0.00001) in the remineralization of lesions exposed to 18.8 mg or 10.0 mg CPP–ACP delivered by sugar-free chewing gum compared to controls who chewed sugar-free gum with no added CPP–ACP. However, it should be noted that the sample sizes of the included studies were small (n=10), the studies were conducted on adults only and the length of exposure to CPP–ACP was short (<15 days).[3]

A subsequent systematic review by Raphael and Blinkhorn not only considered the preventive effect of CPP–ACP, but also its potential role in the treatment of early carious lesions in adolescents. Of the 12 included studies, three investigated the role of cream containing CPP–ACP (Tooth Mousse) in the prevention of dental caries, and concluded that there was no benefit of using CPP–ACP over fluoride toothpaste. Interestingly, in the treatment of early dental caries, four studies favoured the use of CPP–ACP while three showed there was no statistical difference among the control groups who carried out twice-daily brushing with fluoride toothpaste only. The authors of this review concluded that there did appear to be some benefit of using CPP–ACP-containing cream in treatment of early dental caries, but found the quality of evidence to be limited owing to short observation times and small sample sizes.[8] These findings corroborate an earlier systematic review by Li and co-workers of the preventive effect in children, which determined that CPP–ACP has a long-term remineralization effect on early carious and white spot lesions. None the less, the authors of this review advise caution with this conclusion because the majority of studies had a high risk of bias.[9]

While CPP–ACP has been shown to have a preventive effect, it appears to be less effective than fluoridated dentifices. A series of systematic reviews by Marinho and co-workers reported fluoridated toothpaste (≥1000ppm), mouthrinse and varnish produced a reduction in decayed, missing and filled tooth surfaces of permanent teeth of 24%, 27% and 43%, respectively, when compared with

Figure 1. Orthodontic-related demineralization affecting labial surfaces.

Figure 2. Tooth surface loss (erosion) affecting palatal surfaces of maxillary incisors.

Figure 3. Tooth surface loss (erosion) affecting the occlusal surface of a restored primary second molar.

a placebo or no treatment.[10–12] As both CPP–ACP and fluoride have been shown to prevent caries, the possibility of combining the two in order to enhance the preventive effect of these interventions has been considered.

CPP–ACP can be combined with fluoride to produce casein phosphopeptide–amorphous calcium fluoride phosphate, henceforth referred to as CPP–ACFP (GC MI Paste Plus, GC, Japan). Studies have suggested that this complex has a greater remineralization effect on enamel than CPP–ACP alone.[13,14] Srinivasan and co-workers concluded that CPP–ACP with 900ppm fluoride exhibited greater remineralization potential than CPP–ACP alone.[14] In this study, the participants wore a removable appliance with embedded specimens of human teeth eroded with a cola drink to compare CPP–ACP with CPP–ACFP. However, while the CPP–ACFP complex has the benefit of calcium, phosphate and fluoride in one product, the *in situ* study did not entirely mimic all the factors to which the oral cavity is subjected because participants were advised to remove the test appliance while eating and drinking, then to rinse the mouth with water and wait 10 minutes before re-inserting. Similarly, an *in vitro* study by Cochrane and co-workers also found CPP–ACFP solutions produced greater remineralization than the CPP–ACP solutions at pH 5.5 and below.[13] A recent meta-analysis by Yan and co-workers concluded that when both CPP–ACP and fluorides are used, the remineralization effect was statistically significant in early enamel occlusal lesions, but had less effect on smooth surface lesions. However, it should be noted that this meta-analysis comprised a small sample of 10 studies with early carious lesions and comment cannot be made about the effect of these interventions on prevention of caries.[15]

While there is evidence to support the use of CPP–ACP/CPP–ACFP for both caries prevention and treatment, there are limitations within the studies and therefore well-designed, *in vivo*, randomized controlled trials are required.

Orthodontic-related demineralization

Fixed orthodontic brackets create areas of plaque stagnation due to their irregular surfaces,[16] and white spot lesions, the first sign of the caries process, can be seen on smooth surfaces following bracket removal in patients who have not maintained a high level of oral hygiene (Figure 1).[17] The prevalence of white spot lesions following orthodontic treatment, commonly referred to as post-orthodontic demineralization, ranges from 26% to 89% worldwide.[18] It has been suggested that visible enamel defects in children, including post-orthodontic demineralization, may negatively affect their oral health-related quality of life. One study reported that children with visible enamel defects may experience a higher incidence of negative judgements from their peers compared with children without enamel defects.[19]

While topical fluorides are an effective way to reduce the incidence of white spot lesions in patients undergoing fixed appliance orthodontic treatment,[20,21] using CPP–ACP as an adjunct to fluoride toothpaste may result in a superior outcome.[22] A review of five studies by Bergstrand and Twetman concluded that CPP–ACP cream was beneficial in reducing the visual appearance of post-orthodontic white spot lesions following removal of the brackets.[22]

Conversely, a subsequent systematic review by Chen and co-workers concluded that there was limited clinical evidence for using CPP–ACP in the management of post-orthodontic demineralization, particularly since the seven studies included were at high risk of bias.[23] Similar findings were reported in a more recent study by Singh and co-workers, who compared 1000ppm fluoride toothpaste alone and in combination with 5% sodium fluoride varnish or CPP–ACFP cream and found them all to be equally effective, indicating that CPP–ACFP cream provided no added benefit in the treatment of post-orthodontic white spot lesions.[24] Interestingly, Karabekiroğlu and co-workers found that 10% w/v CPP–ACP cream, when applied twice daily as an adjunct to 1450ppm fluoride toothpaste over 36 months, significantly reduced laser fluorescence readings in white spot lesions, indicating remineralization of the carious lesion subsurface.[25] However, the authors acknowledged that this finding does not always equate to a clinically significant reduction of white spot lesions, nor was there a statistically significant difference in effectiveness when compared to the control group who used 1450ppm fluoride toothpaste only.

Both fluoride and CPP–ACP treatments aim to enhance the biological repair process, although the evidence appears inconclusive as to which produces the greatest benefit in improving the appearance of post-orthodontic demineralization. None the less, a young person may find it less easy to adhere to a new treatment, such as the incorporation of CPP–ACP into their daily routine, while most orthodontic patients will already be used to brushing twice daily with fluoridated toothpaste. However, despite

Figure 4. An affected lower right permanent molar in a young patient with molar–incisor hypomineralization (MIH).

Figure 5. A hypocalcifed phenotype of amelogenesis imperfecta, with heavy calculus deposits surrounding the mandibular incisors.

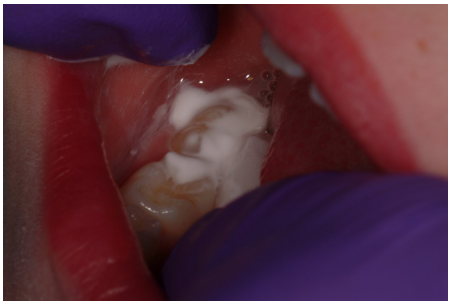

Figure 6. Professional demonstration of Tooth Mousse application to affected molar using gloved finger.

use of these topical therapies, it is important to note that post-orthodontic white spot lesions are not easily remineralized, and hence other treatments may be required in order to achieve acceptable aesthetics.[25] Micro-abrasion, resin infiltration systems and vital bleaching techniques are increasingly considered as minimally invasive methods to address aesthetic concerns.[26]

Non-carious tooth surface loss: erosion

Frequent contact with extrinsic and intrinsic sources of acid can lead to the irreversible loss of enamel through erosion. Exposure to acidic foods, carbonated drinks, sports energy drinks and gastric acids in particular, can erode enamel, causing thinning, pitting and sensitivity (Figures 2 and 3).[27] The prevalence of erosion in children and young people is high. The 2013 Children's Dental Health Survey found 5 year olds experienced tooth surface loss on 57% of lingual surfaces of the primary upper incisors. Around 43% of 15 year olds had tooth surface loss affecting the lingual surfaces of the upper permanent incisors, and almost one-third had experienced tooth surface loss on the first permanent molars.[28] Management of erosion includes early diagnosis, recording, identification of risk factors, dietary counselling, oral hygiene instruction and restorative treatment where indicated.[29]

As well as the ability to remineralize enamel,[1,3] CPP–ACP has also been shown to have anti-erosive properties.[30,31] In an *in vitro* study, Manton and co-workers found that adding 0.2% w/v CPP–ACP to carbonated sugared and sugar-free drinks significantly reduced their erosive potential compared to control drinks with no additions. Remarkably, the erosivity of the CPP–ACP-containing drinks was not found to be significantly different to that of de-ionized water.[30] These findings were corroborated by Ramalingam and co-workers, who found that the addition of CPP–ACP significantly reduced the erosive potential of a sports drink, and interestingly, it did not affect the taste.[32]

In addition to adding CPP–ACP into beverages, the literature suggests that topically applied CPP–ACP can reduce the effects of erosive beverages.[31,33] Piekarz and co-workers noted a significant 30% reduction in enamel and dentine erosion depths when 10% v/w CPP–ACP was topically applied after an acidic challenge *in vitro*.[31] To further investigate this, Rallan and co-workers tested the microhardness of enamel in primary incisors, which were demineralized in a sugary carbonated drink, following application of topical CPP–ACP, CPP–ACFP or fluoride toothpaste. They concluded that microhardness of teeth treated with CPP–ACFP was significantly higher compared to the other groups and CPP–ACFP produced the best remineralization effect.[33] Another *in vitro* study, by Somani and co-workers, comparing the CPP–ACP and CPP–ACFP remineralization effects on premolars subjected to demineralization in a carbonated drink, similarly concluded that CPP–ACFP had significantly better ($P<0.05$) remineralization abilities compared to CPP–ACP alone.[34]

The evidence clearly supports the use of CPP–ACP and CPP–ACFP in both the prevention and management of erosion in children and young people. There are barriers to this management strategy including persuading manufacturers to incorporate CPP–ACP into beverages that would lead to increased production costs. Furthermore, there are patient acceptability issues with the addition of another preventive product into their daily routine. More patient-centred research is required to assess the acceptability of adding CPP–ACP into drinks, and also the cost-effectiveness of this management strategy to prevent dental erosion.

Dentine hypersensitivity and structural anomalies

While symptoms arising from erosion can arise during childhood, particularly if severe, a more common reason for a child to report sensitivity is due to a structural dental defect. Teeth with porous and brittle hypomineralized enamel can be hypersensitive, particularly if the enamel layer breaks away following eruption; a condition known as post-eruptive breakdown. This is a feature of molar–incisor hypomineralization (MIH) (Figure 4),[35] and some phenotypes of amelogenesis imperfecta (AI) (Figure 5). Characterized by a short, sharp pain, multiple stimuli, such as thermal or tactile, can initiate dentine hypersensitivity in teeth.[36] Children with MIH and hypocalcified forms of AI often report avoiding cold foods, such as ice cream, and tend to brush their teeth using warm water. Young patients with hypersensitivity arising from AI in particular, frequently present with extensive calculus[37] deposits around their lower anterior dentition in particular, which inadvertently serves as a de facto barrier to these stimuli (Figure 5).

While more definitive treatment options are available to manage these conditions, some may not be appropriate for young patients, while in the developing dentition,

and, hence, interventions are necessary to help reduce the sensitivity during the interim period. Desensitizing agents, such as specially formulated toothpastes and CPP–ACP creams, have been suggested for this purpose (Figure 6).

A systematic review by West and co-workers concluded that self-administered toothpastes containing stannous fluoride, calcium sodium phosphosilicate and strontium are effective in reducing dentine hypersensitivity pain.[38] When discussing effectiveness of CPP–ACP-containing products in reducing dentine hypersensitivity, they concluded that the quality of evidence was low and insufficient to recommend the use of CPP–ACP. Furthermore, two other systematic reviews concluded CPP–ACP had insufficient efficacy in treating dentine hypersensitivity.[39,40] Despite the lack of high-quality evidence for its use, CPP–ACP creams are used by dentists around the world for managing these patients, perhaps due to the anecdotal evidence of effectiveness, the ease of application and the acceptability had by the products.

Clinical considerations

Where few teeth are involved, a pea-sized amount of CPP–ACP can be rubbed onto the affected area, using a clean finger, following toothbrushing at night (Figure 6). Where multiple teeth require treatment, a custom-made tray, similar to a bleaching tray, may provide a more suitable method of delivery.

Both CPP–ACP (GC Tooth Mousse) and CPP–ACFP (GC MI Paste Plus) are derived from milk casein and should not be used in patients who are vegan, have a proven or suspected milk protein allergy and/or have a sensitivity or allergy to benzoate preservatives. CPP–ACP is safe to ingest but caution should be taken with CPP–ACFP owing to the additional fluoride content in its formulation. If consumed in large amounts, CPP–ACP can have a laxative effect. It is generally accepted that chewing gum is not accepted for use in children who cannot reliably spit. Carers should be encouraged to support children when applying CPP–ACP formulations.

Furthermore, when recommending the use of CPP–ACP products to patients, it is important to acknowledge that they may not be easily accessible to all. Currently CPP–ACP products are predominantly available through dental practitioners (without prescription), rather than over-the-counter from pharmacies. None the less, the online market is providing another option, allowing patients to purchase the product directly, with GC Tooth Mousse currently retailing at £15.99 (Source: Amazon.co.uk; price correct on 23 January 2021).

Summary

In addition to other preventive regimens advocated by Public Health England,[41] children and young people with dental caries and erosion may benefit from the application of CPP–ACP. Furthermore, high-quality clinical trials are required to determine the effectiveness of CPP–ACP in managing post-orthodontic white spot lesions and children experiencing dentine hypersensitivity owing to enamel hypomineralization.

Compliance with ethical standards

Conflict of interest: the authors declare no conflict of interest.

Informed Consent: Informed consent was obtained from all individual participants included in the article.

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