

CURRENT TECHNOLOGY AND TECHNIQUES IN RE-MINERILZATION OF
WHITE SPOT LESIONS: A SYSTEMATIC REVIEW

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ABSTRACT

White Spot lesions are a common iatrogenic occurrence on patients who are treated with fixed orthodontic appliances. There is a dynamic chemical interaction between enamel and saliva at the tooth surface that allow a lesion to have phase changes involving demineralization of enamel and remineralization. This is due to calcium and phosphate dissolved in saliva that is deposited onto the tooth surface or removed depending on the surrounding pH. Caseinphosphopeptide-amorphous calcium phosphate (CPP-ACP) is gaining popularity in dentistry as a way to increase the available level of calcium and phosphate in plaque and saliva to improve the chemical gradient so that it favors remineralization. The aim of our investigation is to search the available current literature and formulate a recommendation for use of CPP-ACP in orthodontics.

Publications from the following electronic databases were searched: PubMed, Web of Science, Cochrane Library and Science Direct. Searches from August 2010 to April 1st 2012 were performed under the terms “MI Paste OR Recaldent OR caseinphosphopeptide-amorphous calcium phosphate OR CPP-ACP or tooth mousse”. The searches yielded 155 articles, These were reviewed for relevance based on inclusion and exclusion criteria. Articles with inappropriate study design or no outcome measures at both baseline and end point were also excluded. 13 articles were deemed of relevance with a high quality study design and were included in this study for evaluation.

The current literature suggests a preventative treatment regimen in which MI Paste Plus is used. It should be delivered once daily prior to bed after oral hygiene for 3 minutes in a fluoride tray, throughout orthodontic treatment. It should be recommended

for high risk patients determined by poor oral hygiene, as seen by the inability to remove plaque from teeth and appliances. This protocol may prevent or assist in the remineralization of enamel white spot lesions during and after orthodontic treatment.

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CHAPTER 1: INTRODUCTION

Orthodontic patients commonly refer in their chief complaint that they would like to improve their smile. We change lives and improve smiles with our orthodontic appliances. After a patient undergoes orthodontic treatment often times we find some marring evidence of treatment. We find the dreaded white spot lesion caused in part by a patients inability to remove oral plaque. Because this is a wide spread problem in orthodontics, we would like to present an option to patients that would improve their smile esthetics.

The chemical exchange at the surface of enamel is a dynamic interchange that allows white spot lesions to form. This chemical interaction also allows for minerals to be re-deposited at the surface. This exchange leads researchers to believe that treatments can be used to enhance the remineralization of enamel. Fluoride has been used in dentistry for decades to improve caries rates. Its ability to enhance esthetics of lesions is questionable. The ability to intercept an early lesion and improve its esthetic results would be beneficial for all our patients.

The aim of our investigation into the literature is twofold. First we would like to review the best mode of treatment of white spot lesions. We would also like to formulate a recommendation for use of CPP-ACP in orthodontics.

CHAPTER 2: REVIEW OF LITERATURE

2.1 Incidence of White Spot Lesions

White spot lesions can be categorized as well defined opacities on dentition not related to fluoride/fluorosis (Russell, 1961). These milky white opacities are often located on smooth surfaces of teeth created by subsurface enamel porosity from carious demineralization (Summitt JB, 2006). Orthodontic patients are at a greater risk for developing white spot lesions than the general population due to plaque retentive sites of fixed appliances. The buccal aspects of mandibular molars are at the greatest risk for lesions in the general and orthodontic population. This is believed to occur due to relative location and quantity of salivary flow in the oral cavity. Orthodontic patients also show this esthetic problem on mandibular canines, premolars and maxillary lateral incisors (Ogaard B. , 1989) (Gorelick, Geiger, & Gwinnett, 1982). Frequency of white spot lesions after fixed orthodontic therapy can range from 2 and 96 percent (Gorelick, Geiger, & Gwinnett, 1982) (Mitchell, 1992). White spot lesions can be induced clinically within a four week period of time with orthodontic treatment (B Ogaard, 1988) (M O'Reilly, 1987). White spots do not disappear after de-bonding (Al-Khateeb, 1998), however, their appearance can improve within 2-3 weeks (Willmot, 2008) (Ogaard B. , 1989) (Monique van der Veen, 2007). Mattousch's recent study has shown that 40 percent will improve without treatment, 45 percent will remain the same and 15 percent will progress to more severe lesions. The greatest magnitude of changes in remineralization is in the first 6 months after orthodontic de-bonding (T Mattousch, 2007). Depth matched studies of active and inactive lesions confirm these findings. They

also show that active lesions exhibited a more porous surface layer than inactive lesions. White spot lesions are highly variable in depth, width and mineral content all of which affect their optical appearance (Cochrane N. , An X-ray Microtomographic study of Natural White-spot Enamel Lesions, 2012).

2.2 Chemistry of Enamel Microstructure

Enamel is the hardest structure in the human body. It is comprised 80-90 percent by volume of carbonated calcium hydroxyapatite crystals, the remaining 10-20 percent is a proteinaceous fluid (C. Robinson, 2000). The stoichiometric formula for hydroxyapatite being $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ (Kay, 1964) . The crystals can be up to 100 μm long, 50nm wide and 25nm thick (Johnson N. , 1967). Crystals are arranged into bundles of about 1000 called enamel prisms. Cross-sectionals of these prisms show a circular keyhole-shape arrangement (Arends, 1981). At the periphery of the prism is an intercrystalline space (Boyde, 1989). There are extraneous materials found in enamel including fluoride, carbonate, magnesium and other minor organic and inorganic components (C. Robinson, 2000). Figure 1 shows hydroxyapatite chemical structure. Figure 2a. shows, Saliva, Enamel, Dentin schematic with the prism and interprismatic shape. Figure 2.b, shows a schematic representation of enamel at the prism direction along the C-axis (Arends, 1981).

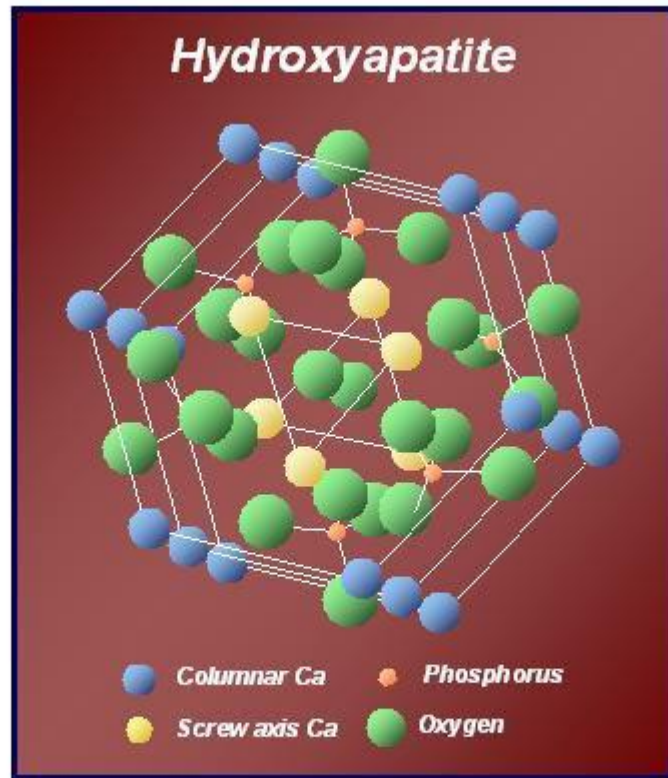


Figure 1. Structure of hydroxyapatite

(Elliot, 1994) Figure 1. Structure of hydroxapatite

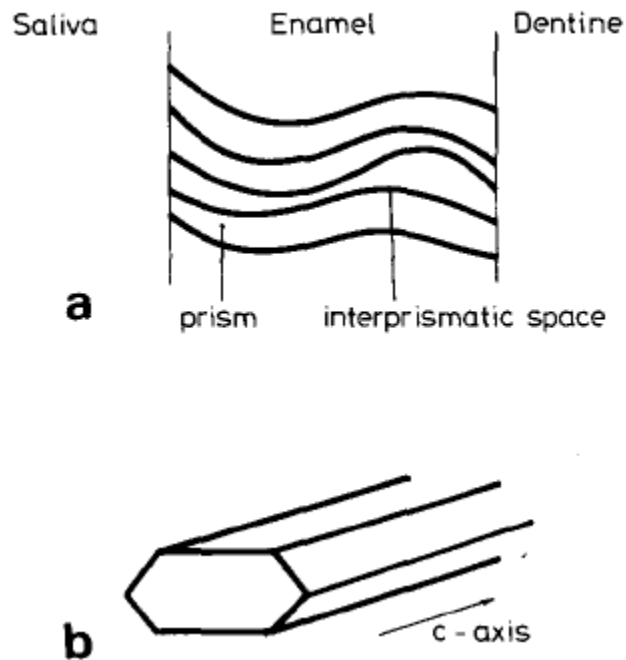


Figure 2 (a) Saliva, Enamel, Dentin Schematic with the Prism and Interprismatic Shape

(b) Schematic of Enamel and the Prism Direction along the C-axis

2.3 Histopathology of White Spot Lesions

Acidogenic bacteria accumulate on plaque retentive surfaces. They create an acidic environment in the mouth which is cyclic and buffered by saliva (Bishara s. a., 2008). Should the pH in saliva drop below the threshold of 5.5, demineralization of enamel will occur (M Larsen, 2003). The periphery of the prisms in the intercrystalline space is the most accessible and soluble thus being the first to demineralize (C. Robinson, 2000).

Darling describes four porosity-related zones in a caries lesion. The innermost zone is the Translucent Zone. It consists of 1-2 percent mineral loss derived from interprismatic and intercrystalline regions. The succeeding stage is the positively

birefringent (dark) zone. The porosity in this zone is 5-10 percent. It is comprised of both larger pores and smaller pores, the smaller pores may represent the occurrence of remineralization (C. Robinson, 2000). Once the porosity reaches 25-50 percent, the body of the lesion, will continue to enlarge until cavitations (Darling, 1961). The surface zone is an intact zone at the surface which continues until the occurrence of either cavitation or remineralization. The surface zone has 1-2 percent mineral loss similar to the translucent zone (C. Robinson, 2000). The surface zone is important as it is the basis for the interfacial chemistry between plaque and enamel and salivary ions (Gorelick, Geiger, & Gwinnett, 1982).

There are two subdivisions of enamel demineralization. Surface softening which is the initial preferential removal of interprismatic minerals at the enamel surface, which occurs at pH 2-4 over a short period of time. The second is the subsurface lesion. The area of dissolution occurs mainly in the deeper part of enamel. A mineral-rich layer intact layer covers a porous layer. The pH of this dissolution phenomenon involves ranges from 4.5-6.5 over a longer period of time (Arends, 1981). This distinction is important because surface softened lesions remineralize faster and more completely than more traditional lesions. White spot lesions associated with orthodontic appliances are more likely to be surface softened lesions (B Ogaard, 1988). This can be seen in Figure 3, Schematic represents A-Normal Enamel, B- Etched Enamel, C- Surface softened enamel and D-for Subsurface lesion (Arends, 1981).

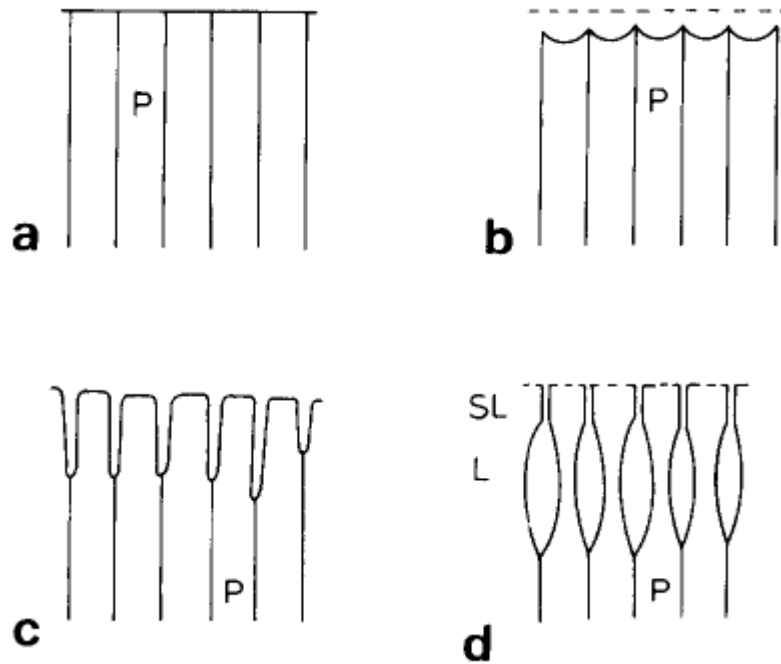


Figure 3 **Schematic Representation of a) Normal Enamel b) Etched Enamel c) Surface-softened Enamel d) Subsurface Lesion**

2.4 Kinetics of Enamel Re-mineralization/Demineralization

The surface zone is free of cavitation and continuously undergoes re-mineralization/demineralization this is similar to the appearance of sound enamel (Darling, 1961). This condition is due to the redeposition of minerals such as calcium, phosphate and fluoride is occurring after its initial loss (C. Robinson, 2000); representing a dynamic exchange between the enamel surface and plaque. The normal presence of the pellicle can act as a reservoir and permselective barrier for minerals (Gray, 1977). Minerals can also be recruited from the chemical gradient created from within the active lesion. Penetration of acid and protons into the enamel microstructure can cause crystal

dissolution, which in turn causes a high concentration gradient of minerals away from the advancing lesions front. This increased concentration of minerals causes the advancing edge of the lesion to slow and allows for remineralization at the surface (C. Robinson, 2000). The dynamics of the equilibrium of mineral concentration and pH will decide whether the enamel becomes stable to the acid attack or succumbs to dissolution (C. Robinson, 2000).

2.5 Efficacy of Fluoride Treatments on White Spot Lesions

Fluoride is a member of the halogen group on the periodic table. It has been used in dentistry for decades to help control caries. Fluoride incorporates into hydroxyl vacancies of enamel creating fluoridated apatite (C. Robinson, 2000). The fluoridated crystals require a lower pH of 4.3 to dissolve hydroxyapatite (M Larsen, 2003). This chemical behavior is crucial to the importance of fluoride in caries prevention and control (C. Robinson, 2000). Fluoridated minerals' lower solubility also allow it to precipitate readily and mainly at the enamel surface. The fluoride molecule will also occlude the surface porosities where previous demineralization has occurred, thus causing the repair process to be restricted to the surface layer. As a result, one can hypothesize that fluoride is less effective at facilitating remineralization than inhibiting demineralization, since its remineralizing activity would not lead to repair deeper portions of the lesion (C. Robinson, 2000). This conclusion is demonstrated clinically in areas with drinking water fluoridation. The number of white spots being remineralized is decreased. In epidemiological studies both lesion repair and deterioration were significantly less pronounced (Arends, 1981). It would be beneficial if an optimum fluoride value could be

found that would slow lesion formation and speed lesion repair (Christoffersen & Christoffersen, 1984).

2.6 Efficacy of Casein Derivatives on White Spot Lesions

Bioactive properties in milk have been seen in the literature for use in many diseases such as heart disease, cancer and dental caries. It has been observed that dairy products can lower the incidence of caries in epidemiological studies. Caseins account for 80 percent of the total protein in bovine milk. This protein exists as a calcium phosphate stabilized micellular complex that is thermodynamically stable. Industry has phosphorylated these proteins in vitro, however this process is done naturally in vivo within the intestinal tract. The phosphorylated casein-derived peptides are known as (CPP) Caseinophosphopeptides. In dentistry, Caseinophosphopeptides-colloidal amorphous calcium phosphate (CPP-ACP) is used as a bioactive peptide that substantially increases the level of amorphous calcium phosphate in plaque, thus depressing enamel demineralization and enhancing remineralization. Casein derivatives allow for a reservoir of calcium and phosphate ions to maintain a super saturation with respect to tooth enamel without precipitation thus promoting remineralization of tooth structure (Aimutis, 2004).

The active sequence of CPP is –Ser(P)-Ser(P)-Ser(P)-Glu-Glu (Reynolds E. , 2009). Please note that Ser(P) refers to the phosphorylated form of the amino acid serine. The mechanism of action for CPP-ACP results from the formation of amorphous electroneutral nanocomplexes with a hydrodynamic radius of about 1.5nm. The size and electroneutrality of the nanocomplexes allow it to enter porosities in enamel and diffuse

down concentration gradients (Reynolds, Cai, Cochrane, & Shen, 2008). The CPPs have a high binding affinity for apatite thus bind to a more thermodynamically favored surface on the apatite crystal. The demineralized enamel crystals voids have shown to occlude with CPP-ACP. CPP-ACP acts as a reservoir in plaque for calcium, phosphate and fluoride ions, and this reservoir stays stable throughout pH cycling. Casein has also been shown to be hydrolyzed by bacteria, the ammonia formed by the process increases pH further inhibiting demineralization and promote remineralization (Cochrane, Cai, Huq, & Burrow, 2010).

2.7 Current Methods of Prevention of White Spot Lesions

Incidence of white spot lesions can be directly correlated with plaque. Individual oral hygiene encouragement should be given during treatment as a primary way of preventing lesions (Artun & Brobakken, 1986). A commonly recommended addition to brushing with fluoridating antiplaque dentifrice (Marcoeli, Simplicio, & Cury, 2006) and regular flossing is use of low concentration of sodium fluoride rinse (Geiger, Gorelick, & Gwinnett, The effect of a fluoride program on white spot formation during orthodontic treatment, 1988) (M O'Reilly, 1987). The fluoride rinse has been show to significantly reduce formation of white spot lesions (Geiger A. , Gorelick, Gwinnett, & Benson, 1992). Daily application of Stannous fluoride gel by the patient has also shown to be effective in preventing white spot lesions (Stratemann & Shannon, 1974) (Collins M. , 2011).

Some orthodontists utilize techniques that have not yet proven effective by evidence-based analysis. Fluoride varnish has not shown significant advantages from a

quantitative point of view in the literature (Vivaldi-Rodrigues, Demito Carina, & Ramos, 2006). Fluoride-releasing Adhesives and Antimicrobial/Fluoride-releasing self-etching primers are products that attempt to improve white spot lesions in the non-compliant patient (Korbmacher, Huck, & Kahl-Nieke, 2006) (Bishara, Raed, & Warren, 2002). These types of fluoride releasing bonding systems have not proven to be effective in improving white spot lesions, however, they have not demonstrated any clinical ramifications such as increasing clinical debonds of bonded brackets or patient harm (Trimpeneers & Dermaut, 1996).

Glass ionomer cements leach fluoride over prolonged periods of time and can be recharged with outside sources of fluoride (Johnson N. , 2000). Glass ionomer cement may be effective in preventing decalcification but the evidence in the literature is weak (Rogers, B, & E, Fluoride-containing orthodontic adhesives and decalcification in patients with fixed appliances: A systematic Review, 2010) (Sudjalim, 2007).

Elevated fluoride products shift the balance of demineralization as found in 5000ppm fluoride dentifrice vs 1500pm (ten Cate, Buijs, Miller, & Exterkate, 2008). Caution should be exercised when using concentrated fluoride agents since it will arrest the lesion but prevent complete remineralization repair. This is because high levels of fluoride create a surface layer of sound enamel that occludes and prevents nanoparticles access to the subsurface part of the lesion (Ogaard B. , 1988). This is important as some orthodontists regularly prescribe these toothpastes to their patients.

The FDA has approved CPP-ACP for use as prophylactic tool and as a treatment for tooth sensitivity. Its use as a remineralizing agent is an off-label application

(Azarpazhooh, 2008). Orthodontists have found success with remineralizing white spot lesions when using it in chewing gum, (Cai, Manton, Walker, & Cross, 2007) (Morgan, Adams, Bailey, Fishman, & Reynolds, 2008) (Shen, Cai, Nowicki, & Vincent, 2001) lozenges (Cai, Shen P, & Reynolds, Remineralization of enamel subsurface lesions in situ by sugar-free lozenges containing casein phosphopeptide-amorphous calcium phosphate, 2003) and as an additive in toothpaste (Rao, Bhat, & S, 2009).

The most current recommendations for preventing white spot lesions are good oral hygiene, daily rinsing with 0.05percent sodium fluoride mouth rinse (Benson, Milett, Dyer, & Parkin, 2005). An Orthodontist would be prudent to use a glass ionomer cement in patients with poor oral hygiene over the conventional composite resin (Rogers, Chadwick, & Treasure, Fluoride-containing orthodontic adhesives and decalcification in patients with fixed appliances: A Systematic Review, 2010) (Benson, Milett, Dyer, & Parkin, 2005). Short term used of CPP-ACP has shown evidence of remineralization and long term use suggests preventative caries effects, however there are no firm recommendations found in the literature that recommend a protocol for use (Veerasamy & Mickenautsh, 2009).

There is evidence that a combination of Fluoride and CPP-ACP might deliver mineral to white spot lesions and improve esthetics (Mayne, Cochrane, Cair, & Woods, 2011). Casein phosphopeptide amorphous calcium fluoride phosphate (CPP-ACFP) supplies a reservoir of ions to drive diffusion of these ions leading to the formation of hydroxyapatite or, when fluoride is also present, fluorapatite. (Cochrane, Saranathan, & Cai, Enamel Subsurface Lesioin Remineralisation with Casein Phosphopetide stabilised

solutions of Calcium, Phosphate and Fluoride, 2008). This combination may be able to utilize the chemical properties of remineralization better than either fluoride or CPP-ACP could alone. (Reynolds, Cai, Cochrane, & Shen, 2008).

2.8 Conservative Treatment Options for White Spot Scars

Obviously as clinicians, we optimally wish to try to prevent white spot lesions. When they do occur we have options to salvage the esthetics of our patients with conservative treatment options. Tooth Whitening can possibly camouflage the white spot lesion and should be considered first (Bishara s. a., 2008). Microabrasion and home treatment of CCP-ACP are often performed under the supervision of a dentist as a minimally invasive technique (Ardu, 2007) (Milnar, 2007). Enamel microabrasion corrects the surface coloration defects by removing approximately 100 μm of the surface enamel (Ng, 2007).

A new treatment that is being used to treat white spot lesions is resin infiltration (Soviero, 2010). This treatment involves hydrochloric acid etch to open the porosities in enamel so that a high penetration of a low viscosity resin could be used to fill the demineralized areas and prevent further demineralization from occurring (Mendes, 2010). Short term studies show acceptable esthetic results (Paris, 2010). Long term studies are needed to prove efficiency of treatment (Martignon, 2010). The unfilled, low-viscosity, light-cured resin material used as the infiltrant in this technique (product is produced and marketed by DMG Gmbh, Germany) contains predominately the resin monomer tetraethylglycerol dimethacrylate (TEGDMA), which is know to enhance water sorption in resin composite materials. Questions arise that the resin restoration may absorb water

and stain, long term in an oral environment compared to other treatment options (Phark, 2010). Composite or Porcelain veneers could also be used to improve patient esthetics. Full Coverage crowns should be the last option utilized by the dentist (Bishara s. a., 2008).

2.9 Future Treatment

The future of treatment with regard to white spot lesions may include iontophoresis, nanoparticles and smart peptides. Iontophoresis is [process](#) where electricity is utilized to assist the drug delivery to the site of action. In dentistry a current application is in treatment of hypersensitive teeth using NaF penetration into enamel (Surender, 2011). The electrical pressure utilized in iontophoresis has been shown to penetrate into dental tubules (Brahmbhatt, 2011). Nanoparticles have been used as carriers for therapeutic modalities in tissues. For example, it is used in cancer treatment to improve bioavailability, efficacy and reduce side effects of the therapeutic agent. Nanoparticles that have been studied as nano-carriers include many types of materials such as lipids, polymers, iron oxide, gold, calcium phosphate (YuLing Han, 2011). Perhaps the calcium phosphate nano-carrier could be used to remineralize enamel and dentin. Smart peptides may be able to stabilize the calcium phosphate in mammalian body fluids so that it can be integrated into tissues more effectively (Attard, 2009). These types of technology could be used to drive ions back into caries lesions to remineralize enamel and dentin on a “powered level.” One of these technologies may reshape dentistry as we now know it.

CHAPTER 3: AIMS OF THE INVESTIGATION

The aim of our investigation is to search the available current literature and formulate a recommendation for use of CPP-ACP in orthodontics.

CHAPTER 4: MATERIALS AND METHODS

4.1 Information Sources

To identify publications the following electronic databases were searched: PubMed, Web of Science, Cochrane Library and Science Direct. In order to search databases, search terms that are relevant must be used so that articles in the databases can be identified. The terms that we have chosen were used previously by Yengopal in a meta-analysis for CPP-ACP. These terms were found to yield the most significant studies available as identified in the literature review (Veerasamy & Mickenautsh, 2009). It was felt that an expansion of searches from August 2010 to April 1st 2012 would allow for more recent literature to be found. Terms used are “MI Paste OR Recaldent OR caseinphosphopeptide-amorphous calcium phosphate OR CPP-ACP or tooth mousse”. Thus with these search terms we hope to answer the question on recommendations for CPP-ACP in Orthodontics.

4.2 Inclusion and Exclusion Criteria

The literature search will encompass all databases in the English language for publications for the selected search terms after August 2008. Publications will be selected based on relevance from title/abstracts. The studies that will be included must be able to deal with the question of clinical relevance to answer clinical questions of efficacy of CPP-ACP in any mode of delivery. Therefore, Studies must be randomized (RCT) or quasirandomized (CCT), in situ or in vivo, or be a systematic or meta-analysis review. The studies that comprise case reports, editorials, case series, in-vitro studies, animal studies and review papers will be excluded. Where only a relevant title without an

abstract was available, a full copy of the publication will be found and assessed for inclusion. Where multiple reports cover the same trial only one report will be included. All duplicates from each database will be discarded.

4.3 Study Quality

The study will be divided into three stages. The first stage will involve reviewing all titles and abstracts by reviewer SP, to determine whether each article meets the inclusion and exclusion criteria. If, with the information available, it will be determined that an article definitely did not meet the inclusion criteria, then it was excluded. If the article was borderline then the opinion of a second reviewer will be attained. In stage 2, the quality assessment of the included studies will be undertaken by two reviewers. The study design, study quality, consistency and directness will be the key elements considered (Grade, 2004). Articles with inappropriate study design or no outcome measures at both baseline and end point will be excluded. For all included studies notes will be formed for flaws in the study design. Stage 3, all included articles will be read and discussed. A detailed summary will be formulated including the study design, study quality, consistency and directness of importance outcomes from the evidence. The amount of high quality articles reviewed will determine the strength of recommendations for the review (Grade, 2004). Disagreements will be resolved through discussion and consensus between reviewers.

CHAPTER 5: RESULTS

5.1 Stage 1: Database Results

PubMed database was searched for clinical trials, meta-analysis, Randomized control trials, in Humans, in English from the dates of Aug 1st 2008 to April 1st 2012. An example of the Mesh terms and Query Translation can be seen in Table 1. Twenty-one articles were found. Four excluded based on title and abstract because they were in-vitro studies. Three were excluded because the focus of the study was not related to white spots.

Science Direct was searched with the terms “MI Paste OR Recaldent OR caseinphosphopeptide-amorphous calcium phosphate OR CPP-ACP or tooth mousse” for dates 2008-2012. The search yielded 10 articles. 1- duplicate. One in-vitro study was discarded. Five articles were discarded due to topics that were not related to this study. One animal study was discarded.

Web of Science was searched with the terms “MI Paste OR Recaldent OR caseinphosphopeptide-amorphous calcium phosphate OR CPP-ACP or tooth mousse” for dates Aug 2008-2012. The search yielded 101 articles. Thirty-seven were discarded due to topic relevance, 36 were discarded due to in-vitro study design, 7 were discarded as non-human studies, 2 were discarded because the full article was written in Chinese, 2 articles were discarded as they were commentary articles and 15 studies were discarded as duplicates of studies already obtained.

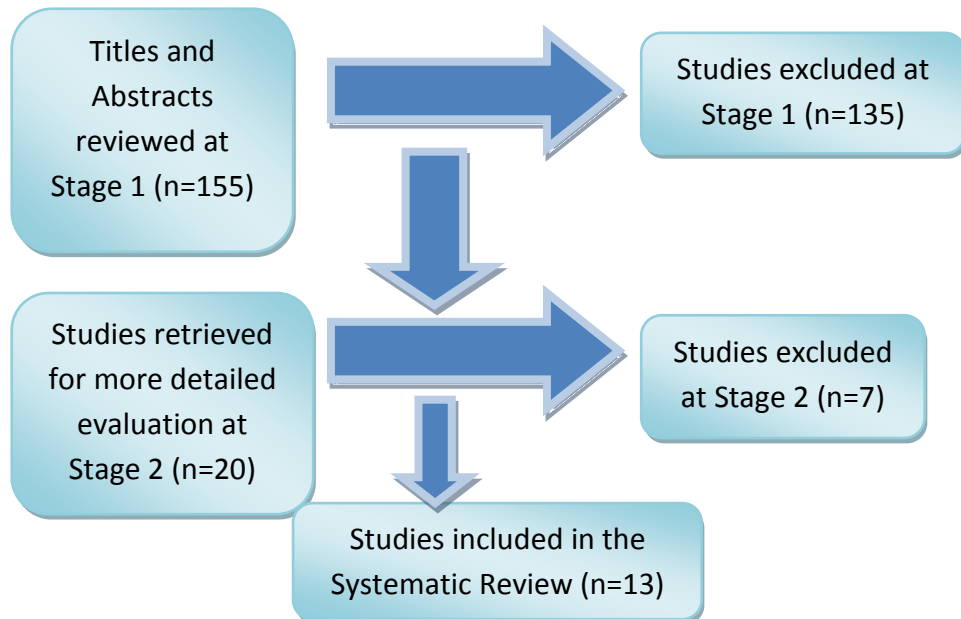
The Cochrane Library was searched with the terms “MI Paste OR Recaldent OR caseinphosphopeptide-amorphous calcium phosphate OR CPP-ACP or tooth mousse” for dates 2008-2012. Twenty-four articles were found. Seven were duplicates previously found. Nine were not pertinent to answer the aim of this study. Five were in-vitro studies that were also discarded.

A summary of our findings in stage 1 can be seen in Table 2. 155 total articles were found by the described search terms. The articles abstracts and titles were reviewed by author, SP, and 135 studies were excluded. The studies excluded were in-vitro (46), non-human (8), Topic relevance (54), Language (2), Commentary (2), and duplicates (27).

Table 1: Search Terms.

Query Translation:
<pre>"mi paste"[ALL Fields] OR "recaldent"[ALL Fields] OR ("casein phosphopeptide-amorphous calcium phosphate nanocomplex" [Supplementary Concept] OR "casein phosphopeptide-amorphous calcium phosphate nanocomplex"[All Fields] OR "tooth mousse"[All Fields]) AND ("humans"[MeSH Terms] AND (Clinical Trial[ptyp] OR Meta-analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Controlled Clinical Trial[ptyp])) AND English[lang] AND ("2010/08/01"[PDAT] : "2012/04/01"[PDAT]))</pre>
<input type="button" value="Search"/> <input type="button" value="URL"/>
Result:
12
Database:
PubMed
User query:
<pre>"mi paste"[ALL Fields] OR "recaldent" [ALL Fields] OR ("casein phosphopeptide-amorphous calcium phosphate nanocomplex" [Supplementary Concept] OR "casein phosphopeptide-amorphous calcium phosphate nanocomplex"[All Fields] OR "tooth mousse"[All Fields]) AND ("humans"[MeSH Terms] AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Controlled Clinical Trial[ptyp])) AND English[lang] AND ("2010/08/01"[PDAT] : "2012/04/01"[PDAT]))</pre>

Table 2: Study Flow Diagram.



5.2 Stage 2: Article Review

In stage 2, the twenty (20) remaining articles were reviewed carefully for study type, study design, study quality by both SP and SJ. After discussing literature it was decided that 7 articles would be excluded, these can be seen in Appendix A. A detailed evaluation can be seen in the subsequent paragraphs.

After reviewing “The evaluation of fluorescence changes after application of casein phosphopeptides (CPP) and amorphous calcium phosphate (ACP) on early carious lesions” by Altenburger, we excluded it because it studied carious pits and fissures not smooth surfaces. It was felt that articles must relate to smooth surfaces so that conclusions could be formulated for orthodontic treatment.

After reviewing “The clinical application of surface pH measurements to longitudinally assess white spot enamel lesions” by Kitasako it was excluded because the study lacked a sufficient sample size to make it statistically relevant. The conclusion was that pH could be used to measure white spot lesion activity.

After reviewing “MIH supplementation strategies: Prospective Clinical and Laboratory Trial” by Baroni, we excluded it because its topic was focused on mineralization and porosity rather than remineralization technique. This paper also utilized molar replicas to visualize mineralization in-vitro with scanning electron microscopy microphotographs.

After reviewing “Salivary pH level and Bacterial plaque evaluation in orthodontic patients treated with Recaldent products” by Marchisio, we excluded it because it did not have any statistical analysis.

After reviewing “The effect of casein and calcium containing paste on plaque pH following a subsequent carbohydrate challenge” by Caruana, we excluded it because of topic. The paper did not discuss remineralization or white spot lesions. The paper concluded that CPP-ACP contributed a buffering effect to plaque pH following a sucrose challenge inferring that this led to a reduced amount of demineralization.

After reviewing “Casein Phosphopeptide-Amorphous Calcium Phosphate Incorporated into Sugar Confections Inhibits the Progression of Enamel Subsurface Lesions in situ” by Walker, we excluded it because it is an unsuitable application technique. It is felt that this confection is not commercially available and could not be implemented into an orthodontic regimen at this time. The paper does show that sugar + 1.0% CPP-ACP does have a significantly greater remineralization effect than a control and sugar-free confection.

After reviewing “Consumption of milk with added casein phosphopeptide-amorphous calcium phosphate remineralizes enamel subsurface lesions in situ” by Walker, it was excluded because it is an unsuitable application technique. It is felt that this CPP-ACP addition to milk is not commercially available and could not be implemented into an orthodontic regimen at this time. The paper did show that the remineralizing effect of CPP-ACP in milk was dose dependent and that 0.3% CPP-ACP

produced a 164% increase in mineral content of subsurface lesions when compared to the milk control.

5.3 Stage 3: Articles Included

The 13 included studies as seen in appendix B used different methodologies and reporting strategies making a meta-analysis impossible. High quality articles were chosen so that orthodontic recommendations could be extrapolated for use by the clinician.

Included articles include one meta-analysis, 2 systematic review papers, and 10 Randomized Controlled Trials (RCT). A summary of included trials can be seen in Table 3.

The article by Veerasamy Yengopal was a meta-analysis “caries preventive effect of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP): a meta-analysis”. It evaluated 12 articles and concluded that the studies it reviewed indicated a short term remineralization effect of CPP-ACP. It also suggested that further RCTs were needed to confirm a long-term caries preventative effect. Details of its included studies can be seen in Table 4.

A review article by Llena “Anticariogenicity of casein phosphopeptide-amorphous calcium phosphate: a review of the literature” reviewed 31 articles. It concluded that CPP-ACP remineralized white spot lesions to a clinically significant manner. Details of included studies can be seen in Table 5. The second review article by Gupta “CPP-ACP Complex as a New Adjunctive Agent for remineralization: A Review” reviewed 16 articles. It concluded that calcium

phosphate based remineralization technologies showed effectiveness in caries prevention and lesion reversal.

Table 3: Included Studies

Author, Year, Study design	Intervention	Control	Study assessment	Time of intervention	Outcomes
Yengopal, 2009, meta-analysis	CPP-ACP vs other intervention vs control	12 articles reviewed all have controls	Varies per article	Varies per article	Short term remineralization effect shown for CPP-ACP. It also suggested that further RCT were needed to confirm a long-term caries preventative effect.
Gupta, 2011, Review	CPP-ACP complex in clinical studies	16 articles reviewed	Varies per article	Varies per article	CPP-ACP remineralized white spot lesions to a clinically significant manor
Llena, 2009, Review	CPP-ACP role in invivo and invitro studies	31 articles reviewed	Varies per article	Varies per article	calcium phosphate based remineralization technologies showed effectiveness in caries prevention and

Table 3, continued.					lesion reversal
Uysal, 2010, Randomized Control Trial	Topical application of CCP-ACP gel or fluoride gel	Yes	Cross-sectional microhardness	60 days	CPP-ACP and fluoride containing agents successfully inhibited caries around orthodontic brackets
Uysal, 2010, Randomized Control Trial	Brackets bonded with an ACP-containing orthodontic composite	Yes (resin-based orthodontic composite)	Superficial-microhardness	30 days	ACP-containing orthodontic composite for bonding orthodontic brackets successfully inhibited demineralization in vivo
Cai, 2009, Randomized Control Trial	Chewing one of 4 gums: Trident Xtra Care (CCP-ACP added), Orbit Professional (calcium carbonate added), Orbit, and Extra	Yes (two sugar-free gums: Orbit and Extra)	Mineral level determined by microradiography	14 days per gum, 1 week washout period between gum type	Chewing Trident Xtra Care (contains CCP-ACP) resulted in significantly higher remineralization than chewing Orbit Professional, Orbit, or Extra
Bailey, 2009, Randomized Control Trial	Use of a remineralizing cream containing casein phosphopeptide-amorphous calcium phosphate	Yes	Clinical assessments using ICDAS II criteria	12 weeks	Significantly more post-orthodontic white-spot lesions regressed with the remineralizing cream compared to the placebo
Shen	Slurry of	Yes	Mineral content	10 days	Placebo < 1000

Table 3, continued.				using transverse microradiograp hy		ppm F = fTMP + 950 ppm F < 5000ppm < CPP-ACP < CPP-ACP + 900 ppm F
2011, Randomiz ed Control Trial	product (placebo, 1000ppmF, 5000ppm F, CPP-ACP, CPP-ACP + 900ppm F, fTCP + 950ppm F) rinsed for 60 seconds 4 times per day for 10 days					
Robertson 2011, Randomiz ed Control Trial	26 patients wear tray with CPP-ACP 3- 5 minutes after bushing, before bed for 3 months, pt checked at 4 week intervals, pt in active orthodontic treatment	yes	Enamel decalcification index	3 months	CPP-ACP decreased the number of white spot lesions, Placebo had no preventive effect, number of lesions increased	
Beerens 2010, Randomiz ed Control Trial	54 patients observed after removal of orthodontic appliances for Caries regression using CPP- ACFP	yes	Quantitive light induced fluorescence	3 months	No significant difference found between groups	
Brochner 2010, Randomiz ed Control Trial	CPP-ACP used once daily after removal of orthodontic appliances	yes	Quantitive light induced fluorescence	4 weeks	No significant difference found between groups	
Ferrazzano 2011,	40 patients used CPP-	yes	Scanning electron	1 month	CPP-ACP able to	

Table 3, continued			micrography		promote remineralization of early enamel lesions
Randomized Control Trial	ACP used on one side of mouth with placebo on other side once daily				
Srinivasan 2010, Randomized Control Trial	8 patients wearing 45 enamel samples using (CPP-ACP, after washout period CPP-ACP + 900 ppm F)	yes	Microhardness	2 days per group	CPP-ACP + 900 ppm F > CPP-ACP > Saliva

Table 4: Yengopal Meta-analysis Included Studies

Author/year	Population	Intervention	Comparative intervention/control	Outcome/s	Study design
Iijima et al., 2004 [7]	10 healthy subjects (mean age 32.3; SD ±7.9 years).	Two gum treatments: 1. Dental chewing gum in slabs containing CPP-ACP (18.8 mg); 2. Sugar-free gum in slabs without CPP-ACP.	Cross-over design with 14-day test period followed by 7-day washout between interventions. <i>In vitro</i> acid challenge of enamel slabs done for 8 and 10 h.	% subsurface remineralization [Δ%] (CPP-ACP vs Control). Three measures reported: 1. Mean Δ% (17.89±0.97 vs 9.02±0.74); 2. %R after 8 h acid challenge (12.43±0.90 vs 3.12±0.88); 3. %R after 16 h acid challenge (10.40±1.19 vs 1.08±1.02).	Double-blind RCT with crossover.
Ithaganum et al., 2005 [25]	12 healthy subjects (5 males, 7 females; age range 20–47 years).	Three types of sugar-free gum containing: 1. 30 mg urea, 2. 30 mg urea + 25 mg dicalcium phosphate dehydrate, 3. 30 mg urea + 4.7 mg CPP-ACP.	Cross-over design with 21-day test period for each type of gum followed by 5-day washout after each test period.	Two outcomes reported: 1. Mean % change in lesion depth of the samples. 2. Mean % remineral content of the samples.	Double-blind RCT with crossover.
Shen et al., 2001 [24]	30 healthy subjects (30±7.53±7 and 34±6 years).	Three types of gum: 1. Sorbitol-based pellet gum containing four different doses of CPP-ACP. 2. Sorbitol-based slab gum containing four different doses of CPP-ACP. 3. Xylitol-based pellet gum containing four different doses of CPP-ACP. Doses in mg of CPP-ACP were 0, 0.19, 1.8, 8 and 56.4 mg.	Cross-over design with 14-day test period for each type of gum followed by at least 1 week washout period between interventions.	For mouthrinse trial: calcium and phosphate levels in plaque, gingival fluid, and saliva. For chewing gum trial: % remineralization, %R, and level of CPP in plaque.	Double-blind crossover design in design; gum has in component.
Reynolds et al., 2003 [6]	30 healthy adults (age range 22–44 years).	Constituting of two parts: A. Mouth-rinse trial with four interventions tested: 1. 2% CPP-ACP, 2. 6% CPP-ACP, 3. Calcium + phosphate slurry mixed as mouth rinse, 4. Deionized water. B. Chewing gum trial containing a calcium additive either in pellet or slab form contained a calcium additive CaCO ₃ or CaHPO ₄ /CaCO ₃ or CPP-ACP (two types of gum with three different additives). 2. Subjects chewed gum pellets containing 9.5 mg CPP-ACP for 4 days without using any other oral hygiene methods.	Mouth-rinse trial: crossover in design; treatment period 4 weeks between interventions. Chewing gum trial: crossover in design; no washout period stated; <i>in situ</i> study.	1. % Subsurface remineralization. 2. % Remineralization after 16-h acid challenge.	Double-blind RCT with crossover.
Cai et al., 2007 [3]	10 healthy subjects (7 males, 3 females; age range 23–46 years).	Three treatments: 1. Sugar-free pellet gum containing 20 mg citric acid + 18.8 mg CPP-ACP. 2. Gum with 20 mg citric acid. 3. Gum with neither citric acid nor CPP-ACP.	Cross-over trial with 2-week treatment periods followed by 7-day washout.	% subsurface remineralization (%R).	Double-blind RCT with crossover.
Walker et al., 2006 [9]	10 healthy adults.	Three treatments: 1. 200 ml milk containing 2.0 g CPP-ACP. 2. 200 ml milk containing 5.0 g CPP-ACP. 3. 200 ml milk containing no CPP-ACP.	Cross-over trial with 15-day treatment period followed by 7-day washout.	% subsurface remineralization (%R).	Double-blind RCT with crossover.
Cai et al., 2003 [12]	10 healthy subjects (6 males, 4 females; mean age 34±6.6 years).	Four treatments consisting of 1.75 g lozenge with: 1. 18.8 mg CPP-ACP. 2. 56.4 mg CPP-ACP. 3. No CPP-ACP. No lozenge; no treatment; control.	Cross-over design with 14-day test period for each type of lozenge (4× daily use) followed by at least 1 week washout period between interventions.	% subsurface remineralization (%R).	Double-blind RCT with crossover.
Manton et al., 2009 [8]	10 healthy subjects (6 males, 4 females).	Three types of gum: 1. Sorbitol/xylitol-based 2.0 g slab gum containing 9.5 mg CPP-ACP. 2. 2.0 g slab pellet (x2) gum containing no CPP-ACP. 3. Two gum pellets containing 10 mg CPP-ACP.	Cross-over design with 14-day test period for each type of gum (4 times daily use) followed by 7-day washout period between interventions.	% subsurface remineralization (%R).	Double-blind RCT with crossover.
Morgan et al., 2008 [4]	2720 healthy children randomized into test (<i>n</i> =1369) and control (<i>n</i> =1351).	Gum with 54 mg CPP-ACP chewed 3 times daily for 10 min per session. 926 children completed trial. 439 dropped out.	Sorbitol-based gum- chewed 3 times daily for 10 min per session. 894 children completed trial. 452 dropped out.	Caries progression or regression at 24 months. Approximal caries diagnosed via digital bitewing X-rays.	Double-blind RCT.
Reynolds et al., 2008	14 healthy subjects (7 males, 7 females; age range 21 to 45 years).	Two RCTs: A. Three mouthrinses containing either: 1. 2% w/v CPP-ACP + 450 ppm F as NaF in de-ionized water. 2. 450 ppm F as NaF in de-ionized water. 3. Placebo control rinse as de-ionized water. B. Toothpaste trial: each toothpaste slurry containing either: 1. Placebo. 2. 1100 ppm F as NaF. 3. 2800 ppm F as NaF. 4. 2% CPP-ACP. 5. 2% CPP-ACP + 1100 ppm F as NaF.	A. Cross-over trial with 15 min rinses 3 times daily for 4 days and once on the fifth day. No other oral hygiene method used in test period. Washout period was 4 weeks between interventions. B. Cross-over trial with 4 rinses per day for 14 days followed by 7-day washout between interventions. <i>In-vitro</i> acid challenge of enamel slabs done after <i>in situ</i> study.	1. Plaque fluoride levels. 2. % subsurface remineralization (%R). 3. % remineralization after acid challenge.	Double-blind RCT with crossover.
Andersson et al., 2007 [13]	26 healthy subjects (13 boys, 13 girls; mean age 14.6 years; age range 12–16 years; 60 teeth; 152 white spot lesions on canines and incisors) who were randomly assigned to fixed orthodontic treatment.	Test group consisted of 13 subjects: 70 sites. Treatment: Brushing twice daily with dental cream containing CPP-ACP for 3 months followed by use of 1100 ppm F toothpaste for 3 months.	Control group comprised 13 subjects: 82 sites. Treatment: 0.02% NaF mouthwash + 1100 ppm F toothpaste for 6 months.	Regression of white spot lesions diagnosed via visual inspection and laser fluorescence over 1, 3, 6 and 12 months.	RCT.

Table 5: Lena Review Article Included

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Uysal published a RCT : “The effects of different topical agents on enamel demineralization around orthodontic bracket: an in vivo and in vitro study”, in which 21 patients and 60 extracted premolars were randomly divided into three groups. One group received CPP-ACP gel, one group received Fluoride gel and a control group that did not receive an applied agent. Comparison of groups was done through microhardness tests. The study concluded that CPP-ACP and fluoride containing agents inhibited caries around orthodontic brackets compared to the control group.

Also published by Uysal was “In vivo effects of amorphous calcium phosphate-containing orthodontic composite on enamel demineralization around orthodontic brackets”, in which 14 patients were divided into two groups, one bonded with an ACP containing composite paste and a control with plain composite paste that did not contain fluoride. Comparison of groups was done through microhardness tests. The study, performed over a 30 day period, found that ACP-containing orthodontic paste successfully inhibited demineralization in-vivo compared to the control.

Cai published a randomized control trial titled “Remineralization of enamel subsurface lesions by chewing gum with added calcium” in 2009. Four types of sugar free gums were tested on subjects for two weeks. Chewing gums included were: Trident Xtra Care (CCP-ACP added), Orbit Professional (calcium carbonate added), Orbit (2% xylitol) , and Extra (control). Comparison of groups measured Mineral levels determined by microradiography. The Study found that Chewing Trident Xtra Care (contains CCP-

ACP) resulted in significantly higher remineralization than chewing Orbit Professional, Orbit, or Extra.

Another randomized control trial “regression of post-orthodontic lesions by a remineralizing cream” by Bailey showed significantly more post-orthodontic white spots were regressed compared to a placebo. The trial tested CCP-ACP (MI Paste) versus a control cream on 45 participants and 408 lesions for 12 weeks. The study measured the severity of the lesions with International Caries Detection Assessment System II (ICDAS II).

A randomized control trial by Shen “Effect of added calcium phosphate on enamel remineralization by fluoride in a randomized controlled in situ trial” tested 6 products on enamel appliances worn by volunteers. Each product was utilized 4 times per day for 60 seconds over 10 days. Slurry of product (placebo, 1000ppmF, 5000ppm F, CPP-ACP, CPP-ACP + 900ppm F, fTCP + 950ppm F). Comparison of the products tested was evaluated by measuring the enamel mineral content using transverse microradiography. The study concluded that from least effective to most effective was as follows: Placebo < 1000 ppm F = fTMP + 950 ppm F < 5000ppm < CPP-ACP < CPP-ACP + 900 ppm F.

A Randomized control study performed by Robertson “MI Paste Plus to prevent demineralization in orthodontic patients: A prospective randomized control trial” studied 60 patients in active orthodontic treatment can compared MI Paste Plue with placebo paste. Enamel decalcification index was used to compare lesions and patients were followed for 3 months. The patients were using the paste for 3-5min daily after brushing

their teeth each night before bed. The study concluded that the placebo paste had no preventive action while MI Paste plus reduced white spots at the gingival surface.

“The effects of casein phosphopeptide amorphous calcium fluoride phosphate past on white spot lesions and dental plaque after orthodontic treatment: a 3-month follow-up” was a randomized controlled trial post-orthodontic treatment by Beerens. Fifty-four (54) post-orthodontic patients were followed after appliance removal for 3 months. Subjects used CPP-ACP +F or a control paste after brushing their teeth before bed. Quantitative light induced fluorescence images were used to compare white spot lesions. The study found that there was no significant difference between groups. The authors concluded that there was no clinical advantage for use of CPP-ACFP paste supplementary to normal oral hygiene.

Another randomized control study using post-orthodontic patients was performed by Brochner titled “Treatment of post-orthodontic white spot lesions with casein phosphopeptide-stabilised amorphous calcium phosphate”. This study used 60 post orthodontic patient using CPP-ACP and a control over 4 weeks. The patient used the paste once daily after brushing before bed. The lesions were assessed using quantitative light induced fluorescence. The study found that the past was not superior to the “natural” regression following daily use of fluoride toothpaste.

A randomized control trial by Ferrazzano titled “In vivo remineralisation effect of GC Tooth Mousse on early dental lesions: SEM analysis” tested the remineralising potential of CPP’s on early enamel lesions. 40 patients were used, a control and a test group. The test group used a placebo on one side of the mouth and the MI Paste on the

other side for one month. The groups wore appliances with demineralized enamel. SEM analysis was used to compare enamel lesions. The study found that CPP was able to promote remineralisation of early enamel lesions.

The last randomized control trial included in the study was published by Srinivason, titled “Comparison of the remineralization potential of CPP-ACP and APP-ACP with 900ppm fluoride on eroded human enamel: An in situ study”. This study used 5 patients wearing 45enamel slab appliance over a test period of two days. CPP-ACP, APP-ACP + 900ppm and a placebo. The study concluded that both CPP-ACP and CPP-ACP plus fluoride remineralized softened enamel. The CPP-ACP with fluoride demonstrated higher remineralization of eroded enamel.

CHAPTER 6: DISCUSSION

The articles included in the study lacked homogeneity between methods of testing CCP-ACP. The variations between studies occurred in methods, some in-situ some in-vivo, the method of delivery of CPP-ACP and the length of time CPP-ACP was exposed to the lesions varied. These differences greatly affect the ability of this study to perform a meaningful meta-analysis and the significance that can be drawn from this study's conclusions need to be verified with more in-depth randomized control trials.

The review articles presented by Yengopal, Gupta, and Llena all support the use of CPP-ACP in our patients for preventative and remineralizations purposes of white spot lesions. These articles conclude that CPP-ACP is beneficial over other remineralization treatments or saliva alone. These articles do not mention how this should be delivered or how long duration of treatment is needed to obtain significant results. These questions will be explored further through extrapolation of data within the randomized control trials included in the study.

The included articles by Srinivason, Uysal, and Shen that compared CPP-ACP with and without small amounts of fluoride showed that fluoride increased the amount of remineralization. Fluorides ability to prevent caries is well known and documented. It appears that fluoride may have a synergistic effect with CPP-ACP improving the ability to remineralize a softened subsurface lesion in enamel. The by which this combination is delivered to patients is important because there is a level of ingestible fluoride that is not to be exceeded. For example, MI Paste Plus (CPP-ACP with 900ppm fluoride) is not recommended for children under the age of 6 by the manufacturer and is recommended

for use with supervision of a clinician. The use of the paste applied topically with the assistance of a fluoride tray for 3 minutes once a day (before bed) after tooth brushing (as recommended by the manufacture and utilized in various clinical trials) appears to be the most effective way to utilize the product.

Cai published an article using CPP-ACP within chewing gum. This method of delivery is highly tolerable by teenage patients most of whom chew gum regardless of recommendations. Fluoride can not be added to the chewing gum because of ingestible fluoride limits. CPP-ACP is a protein derivative of milk and is safe to consume. The results of this study were highly effective in reducing white spot lesions.

Studies published by Robertson and Uysal were performed during active orthodontic treatment. These studies showed that CPP-ACP was helpful in preventing white spot lesions compared to controls. The chemistry of an enamel lesion formation supports the theory that treatment would be most effective while a surface softened lesion was actively forming. This occurs within 4 weeks of orthodontic treatment. Once a lesions surface has remineralized, the subsurface lesion is then harder to access thus more difficult to fully treat.

The studies performed by Brochner and Beerens on patients post-orthodontic treatment both showed that there was no significant difference between natural regression of lesions in a control group and reminerlization with a catalysist of CPP-ACP. Both studies measured this using quantitative light induced fluorescence. This is important because it indicates that for CPP-ACP to be effective that it must be utilized while the lesions are active. One study post-orthodontic treatment by Bailey did show that CPP-

ACP improved the esthetics of the white spot lesion. This study differed from Brochner and Beerens in that it used CPP-ACP protocol twice daily and utilized ICDASII to score lesions. These differences may have enhanced the results of this study compared to the respective studies by Brochner and Beerens which used the product once daily and used quantitative measurements to score changes in white spot lesions.

CPP-ACP has been shown to be effective when used in as little as two days as shown by Srinivasan utilizing microhardness tests. Ferrazzano further demonstrated remineralization after one month with scanning electron microscope analysis.

The goal of remineralization is one that returns the enamel to a state of health and esthetics. CPP-ACP is a product that is safe and can be used repeatedly over time. Average orthodontic treatment time is twenty-four months. This technology is best utilized while a patient is in fixed appliances to combat the difficulties that fixed appliances have on plaque retention. This treatment approach would allow a supersaturation of calcium and phosphate to be present in plaque and allow for remineralization to occur. This product should be used in conjunction with small amounts of fluoride throughout fixed treatment if the patient is able to comply.

CHAPTER 7: CONCLUSION

The included articles did allow the authors the ability to summarize current literature and make current recommendations as follows to prevent and improve white spot lesions during orthodontic treatment is as follows:

The current literature suggests a preventative treatment regimen in which MI Paste Plus is used for our patients. It should be delivered once daily prior to bed after oral hygiene for 3 minutes in a fluoride tray, throughout orthodontic treatment. It should be recommended for high risk patients determined by poor oral hygiene, as seen by the inability to remove plaque from teeth and appliances. This protocol may prevent or assist in the remineralization of enamel white spot lesions during and after orthodontic treatment.

CHAPTER 8: ENVOI

CPP-ACP future may prove to be as useful in improving caries rate as fluoride. Further studies are needed that explore its use during active lesion formation and active orthodontic treatment; the standard may shift from fluoride to CPP-ACP. This will need to be proven with additional randomized control trials and application of techniques. Also systematic review studies including meta-analysis to establish the validity of the available scientific evidence is needed. Additionally, new technologies incorporating advances in biotechnology and nanotechnology may well improve the clinicians ability to remineralize carious lesions at various stages of development. These future advances will also require both laboratory and clinical evaluation to demonstrate their efficacy and effectiveness.

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APPENDICES

APPENDIX A: LIST OF EXCLUDED TITLES

1. Am J Dent. 2010 Aug;23(4):188-92. The evaluation of fluorescence changes after application of casein phosphopeptides (CPP) and amorphous calcium phosphate (ACP) on early carious lesions. Altenburger MJ, Gmeiner B, Hellwig KT, Schirrmeyer JF. **Exclude- Does not evaluate smooth surface lesions**
2. J Dent Res. 2011;90(3):371-376. MIH Supplementation Strategies: Prospective Clinical and Laboratory Trial. Baroni C, Marchionni S. **Exclude- Topic**
3. Int J Dent Hygiene. 2010;8:232-236. Salivary pH level and bacterial plaque evaluation in orthodontic patients treated with Recaldent[®] products. Marchisio O, Esposito MR, Genovesi A. **Exclude- No statistical analysis**
4. J Dent. 2010 Jul;38(7):584-590. The clinical application of surface pH measurements to longitudinally assess white spot lesions. Kitasko Y, Cochrane NJ, Khairul M, Shida K, Adams GG, Burrow MF, Reynolds EC, Tagami J. **Exclude- Not enough subjects**
5. J Dent. 2009;37:522-526. The effect of casein and calcium containing paste on plaque pH following a subsequent carbohydrate challenge. Caruana PC, Al Mulaify S, Moazzez R, Bartlett D. **Exclude- Topic**
6. Aust Dent J. 2009;54:245-249. Consumption of milk with added casein phosphopeptide-amorphous calcium phosphate remineralizes enamel subsurface lesions in situ. Walker GD, Cai F, Shen P, Bailey DL, Yuan Y, Cochrane NJ, Reynolds C, Reynolds EC. **Exclude- Unsuitable application technique**
7. Caries Res. 2010;44:33-40. Casein Phosphopeptide-Amorphous Calcium Phosphate Incorporated into Sugar Confections Inhibits the Progression of Enamel Subsurface Lesions in situ. Walker GD, Cai F, Shen P, Adams GG, Reynolds C, Reynolds EC. **Exclude- Unsuitable application technique**

APPENDIX B: LIST OF INCLUDED TITLES

1. Australian Dent J. 2010; 55:268-274. Effects of different topical agents on enamel demineralization around orthodontic brackets: an in vivo and in vitro study. Uysal, Amasyali, Koyuturk
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5. Act Odontologica Scandinavica. 2009;67:321-332. Caris preventive effect of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP):a meta-analysis
6. J Dent. 2011;39:518-523. Effect of added calcium phosphate on enamel remineralization by fluoride in a randomized controlled in situ trial. Shen, Manton, Cochrane, Walker, Yuan, Reymolds
7. AJO-DO. 2011;140:600-668. MI Paste Plus to prevent demineralization in orthodontic patients: A prospective randomized controlled trial. Robertson, Kau English
8. I Dent J. 2011;61:210-216. In vivo remineralising effect of GC Tooth Mousse on early dental enamel lesions: SEM analysis. Ferrazzano, Amato, Cantile
9. E J Oral Sci. 2010. 118:610-617. Effects of casein phosphopeptide amorphous calcium fluoride phosphate paste on white spot lesions and dental plaque after orthodontic treatment: a 3-month follow-up
10. Clin Oral Invest. 2011. 15:369-373. Treatment of post-orthodontic white spot lesions with casein phosphopeptide-stabilised amorphous calcium phosphate. Brochner, Christensen
11. Archives of Oral Bio. 2010. 55:541-544. Comparison of the remineralization potential of CPP-ACP and ACP-ACP with 900 ppm fluoride on eroded human enamel: An in situ study
12. J Dent. 2009. 37: 763-768. Remineralization of enamel subsurface lesions by chewing gum with added calcium. Cai, Shen, Walker, Reynolds
13. J of contemporary dent practice. 2009:1-9. Anticariogenicity of casein phosphopeptide-amorphous calcium phosphate: a review of the literature. Llana, Carmen; Forner, Leopoldo