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Effectiveness of Casein Phosphopeptide-Amorphous Calcium Phosphate on the Prevention of White Spot Lesions: A Systematic Review and Meta-Analysis

Defne Kecik[1,*]

[1]Associate Professor, Department of Orthodontics, Faculty of Dentistry, Istanbul Hospital, Baskent University, Istanbul, Turkey

[*]*Corresponding author*: Defne Kecik, Associate Professor, Department of Orthodontics, Faculty of Dentistry, Istanbul Hospital, Baskent University, Istanbul, Turkey. Tel: +90-5325643989, E-mail: defnekecik@gmail.com

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Abstract

Context: One of the most important aspects of dental profession is to consider the effectiveness of the preventive systems applied and maintain the good oral hygiene, oral health and minimize the risk of caries among the patients. A great spectrum of preventive activities and materials like fluoride applications, fissure sealants; also new technologies like Casein Phosphopeptide-Amorphous calcium phosphate (CCP-ACP) have a wide effect on preventing caries.

Objective: The objective of this systematic review with meta-analysis was to review systematically the clinical trials of CPP-ACP complex and determine the caries preventive effects on the remineralization process.

Data Sources: PubMed, Google Scholar, biomed central, cochrane oral health reviews, Cochrane library, directory of open access journals, Ovid Medline, Web of science and EMBASE were searched up to February 2016. Only articles in English were included. Trials that were considered clinically and methodologically homogeneous and reported on similar outcomes were pooled for meta-analyses. The clinical studies that inspected the effects of casein derivatives in dental practice were included. In vitro studies, case reports, case series, letters to the editors, editorials, review articles and commentaries were not included for the statistical analysis but evaluated to identify the potential outcomes of the further studies.

Study Selection: Of the 3859 studies screened 92 studies were assessed for eligibility, and 22 were selected for inclusion and 11 was in the final sample for meta-analysis. Systematic review was assessed and the remineralization effect of CPP-ACP was demonstrated compared to placebo in the meta-analysis.

Conclusions: The evaluated systematic review with meta-analyses, clinical trials showed the remineralization effect of CPP-ACP on early caries lesions mainly the white spot lesions (WSL's). In vivo RCT studies reveal a promising caries preventing effect, inducing remineralization and treating dentin hypersensitivity and dry mouth with the use of clinical CPP-ACP application.

Keywords: Remineralization, Decalcification, Caseine Phosphopeptide-Amorphous Calcium Phosphate, Meta-Analysis, White Spot Lesions

1. Context

Dental caries is a major public health problem among the whole world. It is becoming a controlled problem with fluoride enriched water and personal hygiene applications; however cariogenicity threatens the healthcare system to a greater extent compared to heart diseases, cancer, diabetes or hypertension (1, 2).

Caries lesions are the clinical manifestation of pathogenic process that may have been occurring on the dental surface over months or years. The first step of cariogenicity is that oral bacteria start to decay the food interacting with mucopolysaccarides like sucrose on the enamel surface. Dental plaque bacteria metabolize dietary sugars to produce organic acids that solubilize tooth enamel's hydroxyapatite crystals. During the exposure of the enamel to organic acids, solid calcium phosphate is solubilized to free calcium. This process is called demineralization and it is reversible to some point by the presence of salivary sodium bicarbonate aiding remineralization (3).

High risk of dental caries is dependent on the variables such as ethnicity and low socioeconomic status. These threatening epidemiologic variations had led the researchers and product developers search for products to reduce the prevalence of dental caries. Mainly the products that are convenient and easy to use for the customer such as chewing gums and sugar-free products that protects the tooth decay at a degree. Dental caries is still the predominant cause of tooth loss. One of the most effective approaches used to protect the populations from cavities have been leading them to consume dairy products and mostly milk, as they have been identified as one of the most

important cariostatic factors (3).

Milk is an excellent protein providing essential amino acids and organic nitrogen and containing anticariogenic properties like calcium, phosphate, lipids and caseine for humans of all ages. Dairy products were started to consume as a food group that is effective in preventing dental caries in the late 1950s (4). Researches have focused on isolating protective factors from milk to use as food additives or specific agents to reduce cariogenicity.

Casein is the most important phosphoprotein in bovine milk with a 80% of the concentration (5). Several studies have evaluated the low cariogenity and the cariostatic activity of the dairy products such as milk, casein and cheese (5-10). Casein phosphopeptides (CPP) can stabilize calcium phosphate in state-forming CPP- amorphous calcium phosphate (ACP) complex (11, 12). The CPP-ACP complex was patented by the University of Melbourne, Australia and the Victorian diary industry authority, Abbotsford, Australia and the trademark is Recaldent, owned by Bonlac foods limited. The commercial names of CPP-ACP are labeled as MI Paste and MI paste plus or GC tooth mousse or tooth mousse plus varying according to the marketing region. It is used primarily as abrasive prophylaxis paste and secondarily for the treatment of tooth sensitivity. The use of the CPP-ACP for remineralization of the enamel and dentin and the prevention of dental caries is the other major application alternative. Since CPP has a more anticariogenic activity compared to casein, it can be used as an anticariogenic additive to food and toothpaste (12). According to Reynolds et al. (11, 13) CCP-ACP binds readily to tooth surface and to the bacterial plaque around the tooth. Thus, CCP-ACP deposits a highly concentrated ACP around the tooth surface and the localized CPP-ACP buffers the free calcium and phosphate ions increasing the level of calcium phosphate in plaque; therefore maintain a state of supersaturation inhibiting enamel demineralization and enhancing remineralization. Rose (14) stated that CPP-ACP binds well to dental plaque providing a large calcium reservoir inhibiting the demineralization and providing remineralization. It is also demonstrated that enamel remineralized by CPP-ACP is relatively more acid-resistant than normal tooth enamel (15, 16).

Roberts (17) have stated that treatment of enamel swabs in vitro with CPP inhibits acid preparation via stimulating the reminaralization by calcium uptake into enamel (18). This mechanism could control acid formation in dental plaque and reducing hydroxyapatite dissolution from tooth enamel (19).

CPP also has the capability to bind the cell walls of the potential dental pathogens such as Streptococcus sobrinus and Streptococcus sangius resulting in another possible mechanism for anticariogenicity.

2. Objective

The purpose of this meta-analysis is to evaluate the clinical efficacy of CPP-ACP and systematically review the clinical usage and benefits of CPP-ACP when introduced to oral environment; this meta-analysis aimed to answer the question: Does topical CPP-ACP application induce remineralization of the enamel and enhance the white spot lesions.

3. Data Sources

3.1. Search Criteria

The literature search involved the electronic databases: PubMed, Google Scholar, Biomed central, Cochrane oral health reviews, Cochrane library, directory of open access Journals, Ovid Medline, Web of science and EMBASE. The search terms were identified as MI Paste, Recaldent, Caseine phosphopeptide-amorphous calcium phosphate, CPP-ACP, Tooth Mousse.

3.2. Inclusion and Exclusion Criteria

Randomized controlled clinical trials or controlled clinical trials using topical CCP-ACP in any form such as toothpaste, mouth rinses, tooth mousse and chewing gum were included. Case reports, editorials, case series, in vitro studies were excluded.

3.3. Participants

Humans with white spot lesions on enamel surface was included.

3.4. Outcomes

The main outcome measure was the decrease in white spot lesions and caries prevention indicated by improvement in DMFT/DMFS/DFS scores or a remineralization percentage. A change in the number of white spot lesion was one of the outcomes.

3.5. Intervention and Control

Only studies that compared the following strategies were included:

- Noninvasive treatment: remineralization with the agents containing CPP-ACP such as chewing gums, tooth pastes, tooth mousse, topical creams.

- Control: no active treatment or placebo application.

3.6. Data Extraction and Quality Assessment

Of the screened 3859 articles, 92 were reviewed and resulted in 22; which is eligible for systematic review (15, 16, 20-30, 31-39); finally 11 were eligible for meta-analysis (20, 23-28). The primary outcome of these studies was the reduction in caries increment (an improvement in DMTF/DMFS/DFS scores) and the change in proportion of the white spot lesions (remineralization percentage) (31, 33-37). The following data was collected: authors and publication year, number and age of participants, intervention and control details, check-time points, method of assessment, reported outcomes. Each study was evaluated by the method described in Cochrane handbook of systematic reviews of interventions 5.1.0; which is the official guideline describing in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of healthcare interventions. The evaluation was done in random sequence generation, blinding, allocation concealment and selective outcome reporting.

3.7. Risk of Bias Assessment

Selection bias (allocation concealment, sequence generation) performance and detection bias (blinding of participants, examiners), attrition bias (follow-up loss or missing values of participants) and reporting bias (selective reporting, missing outcomes) were evaluated according to Cochrane's guidelines (40).

4. Results

4.1. Results of the Search

Throughout the electronic databases 3859 were related with this subject. Following the elimination of the case reports, case series, editorials, letters to the editor and in vitro studies, 92 eligible studies were evaluated full-text. 22 of them were included in the systematic review and 11 RCT in situ studies with homogenous data allocation were selected for meta-analysis.

The treatment procedures and the style of study design for all the evaluated articles included in the systematic review were shown in Table 1.

4.2. Pooling Data for Meta-Analysis

Clinically and methodologically homogenous data were pooled for meta-analysis.

The caries preventive effect of the applied agents with and without CPP-ACP reveals that the weighed mean difference had a significant value in favor of CCP-ACP group.

Figure 1 provides information on the overall weight of evidence for the remineralization and caries-preventive effect of CPP-ACP. All studies had a crossover in situ design with similar intervention style. 8 studies (20, 23-25, 28, 31, 33, 35) showed a significant remineralization effect ($P < 0.01$ and $P < 0.001$) whereas 3 studies (34, 36, 37) showed no difference of remineralization between groups ($P > 0.05$).

The mean differences were calculated to reflect the size of the treatment effect between the intervention and control groups.

The cumulative weight of evidence for the caries-preventive effect of CPP-ACP (delivered via sugar-free gum) when compared to that of sugar-free gum without CPP-ACP showed an increase. The data sets, from 8 trials (Figure 1) with individual weighted mean differences (WMDs) for control and intervention groups showed an increase, whereas 3 studies did not show a meaningful remineralization.

The results showed a significant regression in white spot lesions with the use of clinical inspection of the lesions via visual scoring on a scale, ICDAS Criteria, DMFS index, Laser fluorescence reading (DIAGNOdent), or QLF assessment.

5. Discussion

The aim of this systematic review with meta-analysis was to identify the caries preventive effect of CPP-ACP via the published randomized clinical trials and clinically controlled trials. All the studies used in this meta-analysis were in situ randomized controlled trials with a crossover component.

Concerning the white spot and caries lesions exposed to CPP-ACP were inspected to have a significant improvement in remineralization compared to control group lack of CPP-ACP. The results obtained from this meta-analysis suggest that a long-term exposure to CPP-ACP is favorable for an even greater treatment effect in terms of the caries preventive activity. The study design with percentage outcomes is not an ideal method however can be justified; since the measurable amount of remineralization requires sectioning of the tooth in which the orthodontic cases requiring extraction would give the exact amount for remineralization. Thus, well designed randomized controlled trials had added weight of evidence indicating the efficacy of CPP-ACP (28, 31). The follow-up time of studies varied from 3 months to 2 years. For the observation of the demineralization / remineralization process the follow-up period; at least 3 months' time is needed (34, 40, 41) in addition the observation period needed to determine the clinical changes created by CPP-ACP requires a long period of time (31), thus the significant results obtained from this study suggested that long term exposure to CPP-ACP suggests an evidence of greater treatment effects in caries

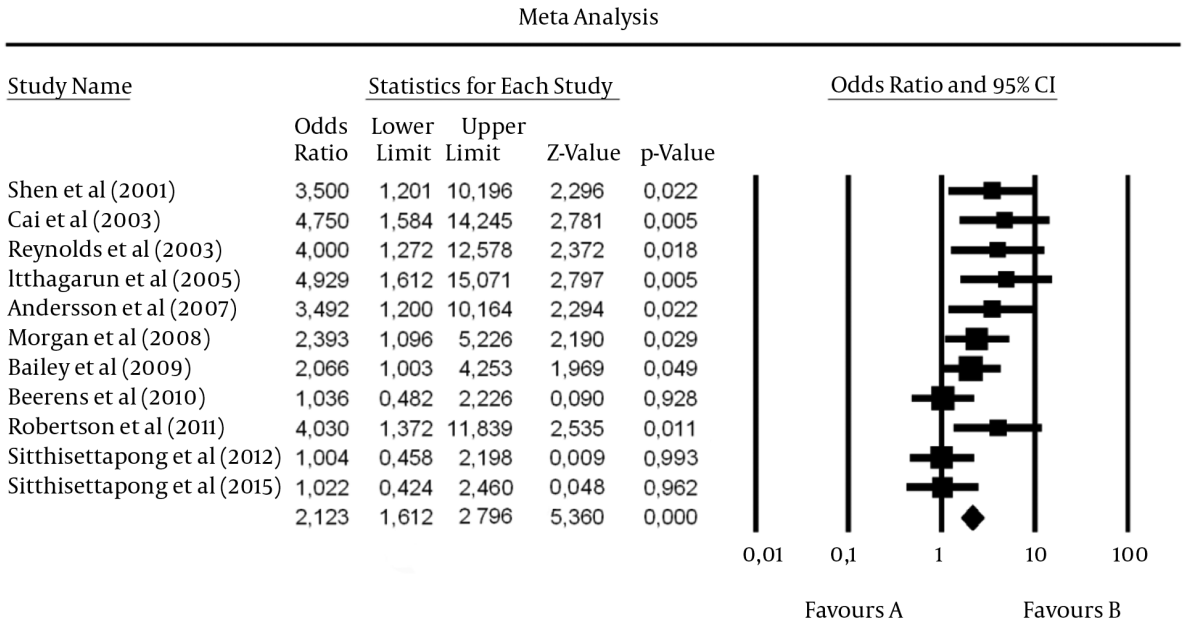

Figure 1. Data Were Synthesized With Random Effects Meta-Analysis, With Odds Ratios (OR) and 95% Confidence Intervals Being Calculated

preventive efficacy. According to another trial, the long-term usage of CPP-ACP reveals a beneficial affect considering remineralizaiton (28). This study is compatible with Reynolds et al. (12) who developed the CPP-ACP application for remineralization providing independent information.

Various methods have been introduced to inspect caries lesions with clinical examination and radiography; and when these methods are used in conjunction with clinical indices like DS/DMFS index the outcomes may be stronger (32). Fluorescence-based devices have recently been introduced for the detection of early caries lesions; such as laser fluorescence (DIAGNOdent) that can detect the lesions at dentine level (42, 43); and Quantitative Light-induced Fluorescence (QLF) which is able to detect the secondary caries, smooth surface caries and demineralization adjacent to orthodontic brackets (44, 45).

The potential side effects of CPP-ACP should be taken into consideration. The studies assessing the clinical safety of CPP-ACP showed no significant difference between CPP-ACP groups and control groups concerning the dental calculus formation, allergies or other side effects (31-33, 36).

The meta analysis with systematic reviews are powerful ways for achieving meaningful conclusions of the data collected from the studies; however the weakness caused by heterogeneity and small sample size should be taken into consideration.

To summarize, this meta-analysis has provided the evidence that usage of CPP-ACP increases remineralization and enhances white spot lesions. The effective doses of CPP-ACP concentrations ranged between 10.0 mg to 56.4 mg in sugar free gum. The results of in situ trials support the effect of CPP-ACP for remineralization and caries prevention.

5.1. Conclusions

According to this systematic review, CPP-ACP has a remineralization effect on early caries lesions. In vivo randomized clinical trials provide promising results for the long-term use of CPP-ACP for caries prevention. With the Well-designed randomized controlled trials on the outcome of caries prevention is guaranteed.

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Table 1. Evidence OF Clinical Efficiency AND Efficacy of CPP-ACP

Author,Year	Population	Intervention	Controls	Outcome	Conclusion	Study Design
Shen et al, 2001	30 adults (age: 23 - 40 years)	In situ, gum with 0.19, 10, 18.8, 56,4 mg CPP-ACP	Crossover washout 1 week	% subsurface remineralization	Dose-based increased in remineralization with CPP-ACP	RCT (Double-blind)
Hay and Thomson, 2002	124 subjects (age: 53 ± 14 years)	63 subjects, topical CD-CP mouthrinse. 3 times/day	61 subjects, 0,05%NaF mouthrinse. 3 times/day	Coronal caries prevention, bite wing radiographic screening, 12 months	CD-CP application successful for caries prevention in dry mouth	RCT (Double-blind unclear)
Hay and Morton, 2003	38 adults (age: older than 25 years)	CD-CP application for 2 weeks	Mouth moistening with spring water, chewing gum, artificial saliva	Questionnaire	CD-CP advantageous in oral moistening and caries prevention in xerostomia	Questionnaire
Cai et al, 2003	10 adults (age: 34 ± 6 years)	4 treatments with 1,75 g lozenge with: a-18,8mg CPP-ACP, b-56,4mgCPP-ACP, c-No CPP-ACP, d-Control	Crossover design with 14-day test period. 4xdaily usage of test materials followed by 1 week washout	%subsurface remineralization	CPP-ACP increases enamel remineralization via lozenge.	RCT (Double blind, crossover, in situ)
Reynolds et al, 2003	30 adults (age: 22 - 44 years)	2 parts: 1-Mouth rinse: a-2%CPP-ACP, b-6% CPP-ACP, c-$Ca^{+}PO_4$ mouth rinse, d-Deionized water, 2-Gum (pellet or swab) with, a-$CaCO_3$ or $CaHPO_4/CaCO_3$ or CPP-ACP, b-gum pellets with 9,5 mg CPP-ACP	Crossover: mouthrinse washout: 4 weeks	Mouthrinse: plaque Ca and inorganic PO_4 levels; Gum: %subsurface remineralization	CPP leading ACP to tooth surface and stabilization	RCT (Double-blind, crossover, chewing gum in situ)
Iijima et al, 2004	10 adults (age: 32,3 ± 7,9 years)	2 gums: 1-sugar-free gum with 18,8 mg CPP-ACP, 2-Sugar-free gum without CPP-ACP	Control: sugar-free gum without CPP-ACP	% subsurface remineralization	Sugar-free gum with CPP-ACP is effective in remineralization	RCT (Double-blinded, crossover, short washout, small sample size)
Itthagarun et al, 2005	12 adults (age: 20 - 47 years)	3 gums: 1-with 30 mg urea, 2 - 30 mg urea + 25mg dicalcium phosphate dehydratre; 3 - 30mg urea + 47 mg CPP-ACP	Crossover design with 21-day test period for each type of gum followed by 5 day washouts after test	2 outcomes: 1- mean percentage change in lesion depth; 2-mean percentage change in mineral content	Potential of caries prevention with gum containing urea, dicalcium phosphate or CPP-ACP	RCT (Double-blinded, crossover, in situ)
Kowalczyk et al, 2006	13 adults (age: 23 - 48 years)	GC tooth mousse applied to 101 teeth for 3 minutes	None	Pain intensity following GC tooth mousse application	Short term therapeutic effect in pain removal	Uncontrolled cohort study,. No blinding, no control.
Walker et al, 2006	10 adults	In situ: 200 mL test milk or control milk with 2 or 5 g CPP-ACP/L	Control: crossover, washout 1 week	% subsurface remineralization	Remineralizing activity with milk containing CPP-ACP	RCT (Double-blinded, crossover, short washout, small sample size)
Andersson et al, 2007	26 adolescents-60 teeth (age: 14, 6 years)	60 teeth, 70 WSL's. CPP-ACP application 3 months-12 months follow-up	13 controls 62 WSL's. Daily topical CPP-ACP cream	Blind essessment for 1, 3, 6, 12 months	Both CPP-ACP and NaF reversed WSL's	RCT (Single-blinded) Small sample, no power analysis, no significant difference with laser fluorescence
Cai et al, 2007	10 subjects (age: 23 - 46 years)	Sugar-free pellet gum with 20 mg cirtic acid + 18, 8 mg CPP-ACP; gum with citric acid; gum with no citric acid and no CPP-ACP	Crossover washout for 2 weeks followed by one week washout	Percentage of subsurface remineralization	CPP-ACP significantly effective on enamel mineralization	RCT (Double - blinded, crossover, in situ)
Reynolds et al, 2008	14 subjects (age: 21 - 45 years)	2 Trials: 1 - 3 mouthrinses containing; a-2% CPP-ACP + 450 ppm F, b-450 ppm F, c-placebo, 2-Toothpaste	Mouthrinse:Crossover washout 4 days/ 3 times daily for 15 days; Toothpaste, Crossover trial with 4 rinses/day for 14 days followed by 7	Approximal caries screened by bitewing radiographs. % subsurface remineralization and plaque calcium	CPP is important for the stabilization of ACP on tooth surface	RCT (Double blinded, crossover, in situ)