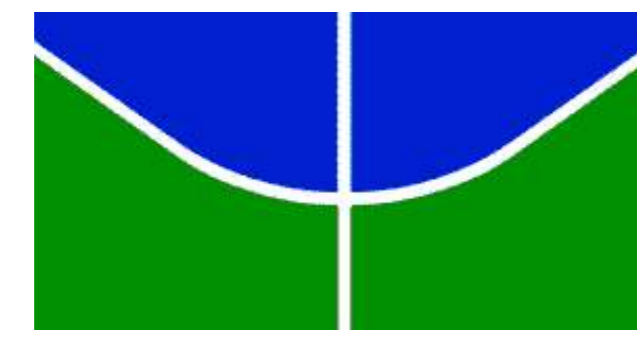


# Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP) a Systematic Review



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## Introduction

Casein phosphopeptide - amorphous calcium phosphate (CPP-ACP) is a casein derived peptide, with added calcium and phosphate, which acts as a calcium and phosphate reservoir when incorporated into dental plaque and on the tooth surface. The CPP-ACP nano complexes release calcium and phosphate ions via a pH or concentration gradient mechanism to maintain a supersaturated environment with respect to hydroxyapatite, therefore reducing demineralization and enhancing remineralization. Casein Phosphopeptide Amorphous Calcium Phosphate (CPP-ACP) nanocomplexes have been demonstrated to have anticariogenic potential in laboratory, animal, and human *in situ* experiments.

The ability of CPP-ACP to remineralise white spot lesions of enamel both *in vitro* and *in situ* has been widely reported. In a recent randomized clinical trial, CPP-ACP incorporated to either sorbitol- or xylitol-based gum resulted in a dose-related increase in enamel remineralization, with 0.19, 10.0, 18.8, and 56.4mg of CPP-ACP producing an increase in enamel remineralization of 9, 63, 102 and 152% respectively, relative to the control gum, independent of gum weight or type. In other studies, the addition of low concentrations (<1.0%) of CPP-ACP to acidic sports drink has been shown to reduce erosive potential without significantly altering taste. The inclusion of fluoride into CPP-ACP (known as CPP-ACFP) forms a novel material with fluoride incorporated into the nano-complex. Clinically, CPP-ACP can be delivered to the tooth surface in several vehicles: chewing gum, lozenge, topical crème, mouthrinse, toothpaste and added to glass ionomer cement (GIC) restorative material. This systematic review forms part of comprehensive review project with the focus on the current evidence base for the concept of minimal intervention (MI) dentistry. MI is a philosophy of professional care, concerned with the risk, earliest detection and earliest possible treatment of disease on micro (molecular) levels, followed by the most minimally invasive and patient-friendly options to repair irreversible damage caused by such disease.

This systematic review sought to critically evaluate the evidence for CPP-ACP supplements in terms of its ability to remineralize enamel subsurface lesions.

## Material and Methods

- The methodology followed recommended guidelines provided by the Evidence based Medicine group of the McMaster University, Canada<sup>1,2</sup>.
- The review objective was to appraise whether there is evidence for a caries reversal effect of CPP-ACP supplements for early white spot (carious) lesions.
- Nine anglo- and two lusophone databases were searched using English and Portuguese key words (2 June 2005). Relevant articles in English, German, Portuguese and Spanish were included for further review.

### Search Keywords

English	Portuguese
CPP-ACP AND (remineralization OR remineralisation)	CPP/ACP (no key words translated)
CPP/ACP AND (caries OR tooth decay)	

### Inclusion criteria

Two reviewers assessed articles (Trials and Reviews) independently. Articles were included according to the criteria:

- Listing in above databases;
- Relevant to review objective of the particular MI topic;
- Language of publication comprehensible by reviewers:



English



German



Spanish



Portuguese

### Exclusion criteria

Included articles were reviewed in-depth and **excluded** according to the criteria:

#### a. for Trials:

- They were not truly random;
- No control group was included;
- Drop out rate >33%;
- Patients and clinicians not 'blinded' where possible and appropriate;
- No baseline data provided for control and study group;
- Baseline differences not statistically adjusted;
- Clinically important outcomes for patients were not assessed.

#### b. for Reviews

- Focus on population or intervention not clearly stated in title and abstract;
- No clear inclusion and exclusion criteria;
- No clear search strategy, key words and used databases;
- No study-by-study critique table or discussion of

- In-vitro* laboratory studies or with animal tissues were excluded on basis of uncertainty of extrapolating *in-vitro* results to physiological effects in humans<sup>3,4</sup>.
- In-situ* studies were included if they followed a randomised-controlled design.

Articles, which passed exclusion criteria, were rated according to following scoring system:

### Scoring system for evidence

Quality aspect	Criteria	Points
Study setting	In situ	1
	In vivo	2
Article provides information on:	How Samples were collected	1
	How examiners/patients were blinded	1
	How operators were trained or calibrated	1
	Examiner reliability	1
Sample drop out rate	30-20%	0
	10-19%	2
	<10%	3
Follow up period	<1 year	0
	1 year	1
	>1 year	2

Strong evidence = 10-11

Good evidence = 6-9

Reasonable evidence = 0-5

Systematic reviews were rated as **Strong** evidence.

## Results

A hundred and twenty six (126) articles were identified of which only 7 were judged to be relevant. Subsequently, 1 review and two trials were excluded (Table 1). Reasons for Review exclusion was that the article had: (1) no clear exclusion and/or inclusion criteria stated; (2) A lack of information on clear search strategy, key words and databases used; and (3) a study-by-study critique table was missing. Two trials were excluded because of an unacceptable study design (*neither in vivo nor in situ*

Table 1. Number of Reviewed articles

Found	Included for review	Excluded	Accepted as evidence
126	7	3	4

The 4 accepted articles described in total 7 separate *in situ* studies (Table 2) which were scored according to criteria described in the methodology.

Table 2: Included Studies and Quality Rating for Strength of Evidence

Author	Trial #	Strength of evidence		
		Strong	Good	Reasonable
Shen P, et al (2001)	(1)		1	
	(2)		1	
	(3)		1	
Reynolds EC, et al (2003)	(4)		1	
	(5)		1	
Cai F, et al (2003)	(6)			1
Iijima Y, et al (2004)	(7)			1

The included articles with authors, journals and bibliography are presented in Table 3.

All of the study participants were adults. Regardless of the method of delivery, lesions in patients in the intervention groups (CPP-ACP) showed significant improvement in the percentage increase in remineralization compared to control lesions (Tables 4a and 4b)

Table 3: Included Studies

Author	Journal	Year
Shen P, et al	J Dent Res	2001 80:2066-2070
Reynolds EC, et al	J Dent Res	2003 82:206-211
Cai F, et al	Aus Dent J	2003 48:240-243
Iijima Y, et al	Caries Res	2004 38:551-556

### Place of origin of trials



All of the study participants were adults. Regardless of the method of delivery, lesions in patients in the intervention groups (CPP-ACP) showed significant improvement in the percentage increase in remineralization compared to control lesions. (Tables 4a and 4b)

Table 4a: Methodology of included trials

Author	Trial #	Design	Subjects	Method	Added CPP ACP (18.8 mg)	Application
Shen P, et al	(1)	In situ	10, age 33±7 yrs	Randomized, double blind, cross over design	Dental chewing gum (Pellet based)	4x/day 20 min
	(2)	In situ	10, age 33± 7 yrs	Randomized, double blind, cross over design	Dental chewing gum (Slab based)	4x/day 20 min
	(3)	In situ	10, age 34±6 yrs	Randomized, double blind, cross over design	Dental chewing gum (Pellet based)	4x/day 20 min
Reynold EC, et al	(4)	In situ	30, age 22-44 yrs	Randomized, double blind, cross over design	Dental chewing gum (Pellet based)	4x/day 20 min
	(5)	In situ	30, age 22-44 yrs	Randomized, double blind, cross over design	Dental chewing gum (Slab based)	3x/day 20 min
Cai F, et al	(6)	In situ	10, age 34±6.6 yrs	Randomized, double blind, cross over design	Lozenge	Dissolve in mouth no chewing
Iijima Y, et al	(7)	In situ + acid challenge	10, age 21-45 yrs	Randomized, double blind, cross over design	Dental chewing gum (Slab based)	4x/day 20 min

Table 4b: Interventions and summary results of included trials

Author	Trial #	Control (without CPP-ACP)	Percentage Enamel subsurface lesion remineralization (%R)		Significance of difference	Location of trial
			CPP-ACP	Control		
Shen P, et al	(1)	Dental chewing gum (Pellet based)	18.4 ± 3.0	9.1 ± 1.2	P <0.001	Melbourne - Australia
	(2)	No gum	17.1 ± 2.5	4.3 ± 1.6	P <0.001	Melbourne - Australia
	(3)	Dental chewing gum (Pellet based)	19.1 ± 1.6	8.9 ± 1.1	P <0.001	Melbourne - Australia
Reynolds EC, et al	(4)	Dental chewing gum (Pellet based)	19.0 ± 2.5	8.9 ± 1.4	P <0.01	Melbourne - Australia
	(5)	Dental chewing gum (Slab based)	19.4 ± 1.6	6.3 ± 1.2	P <0.01	Melbourne - Australia
Cai F, et al	(6)	Lozenge	12.5 ± 1.48	7.03 ± 0.65	P <0.01	Melbourne - Australia
Iijima Y, et al	(7)	Dental chewing gum (Slab based)	10.4 ± 1.19	1.08 ± 1.02	P < 0.05	Melbourne - Australia

## Discussion and Conclusion

The quality of the studies ranged from good (5) to reasonable (Table 2). Although some trials compared different amounts of CPP-ACP by weight (e.g. Cai et al randomized 4 treatments consisting of sugar free lozenges containing either 18.8 mg CPP-ACP, 56.4mg CPP-ACP, 0mg CPP-ACP or no lozenge at all), the reviewers in this study could only compare 18.8mg CPP-ACP versus control across trials. In all four trials there was a significant improvement in remineralization rates when CPP-ACP was used. The use of lozenges as a vehicle as delivery for CPP-ACP was as effective as sugar free gum and could be used as an alternative to gum. In summary, the evidence suggests that CPP-ACP supplements of 18.8 mg can remineralize enamel subsurface lesions or white spot lesions. However, the results need to be confirmed *in vivo*.

## References

- Susan E. Sutherland. Evidence-based Dentistry: Part IV. Research Design and Levels of Evidence. J Can Dent Assoc 2001; 67:5-8.
- Susan E. Sutherland. Evidence-based Dentistry: Part V. Critical Appraisal of the Dental Literature: Papers about Therapy. J Can Dent Assoc 2001; 67: 442-5.
- Pitts NB. Clinical diagnosis of dental caries: a European perspective. J Dent Educ 2001; 65:972-978.
- Theodosopoulou JN, Niederman R. A systematic review of *in vitro* retrograde obturation materials. J Endod 2005; 31:341-349.
- US Food and Drug Administration. Guidance for industry- significant scientific agreement in the review of health claims for conventional food and dietary supplements. December 22, 1999. <http://www.cfsan.fda.gov/~dms/ssaguide.html>
- US Food and Drug Administration. Interpretation of significant scientific agreement in the review of health claims. June 24-25, 1999. <http://www.cfsan.fda.gov/~dms/facssa.html>
- Minimum Intervention (MI): A New Approach In Dentistry - Evidence-Based Compendium. S Mickenautsch, V Yengopal, M Bönecker, SC Leal, ACB Bezerra, LB Oliveira. 1<sup>st</sup> Edition, Midentistry cc Johannesburg, 2006. ISBN: 0-620-34080-0. <http://www.midentistry.com/academia.html>

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