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Is there an optimal level of calcium intake for caries prevention?

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Abstract:

Objective: The aim of this study was to examine the evidence available to determine if using calcium in children and adults with incipient caries or increased caries risk will reduce or reverse caries.

Methods: Literature search in various databases was conducted. Also, relevant textbooks were searched and experts were consulted. Our review was limited to articles published in English and clinical trials.

Results: The search in Pub Med yielded 223 relevant articles, Cochrane 78 and 1 from Google scholars. After reading title, abstract and full text, 11 articles were selected for critical appraisal. A final review was conducted on a total of 6, which met our cut off criteria using the checklist. All the articles were RCT'S. **Conclusion:** Based on the evidence of this literature review, there is strong evidence to suggest that calcium intake either topically or systemically will prevent caries or promote remineralization. There is firm evidence suggesting CPP-ACP is useful for the purpose of remineralization and prevention, while for other calcium compounds there have not been enough studies to prove and compare their efficacy. There is not enough information to decide what the optimal concentration of calcium to prevent caries is. We recommend that clinicians should review the literature constantly to expand their treatment options and to be able to give their patients the most appropriate treatment choices.

Introduction:

Calcium is important chemical element in human body, among other functions it contributes to the strength and other physical properties of dental tissues. A high concentration of calcium is present in saliva which remineralizes teeth constantly. A reduction in remineralization due to vast number of reasons can lead to the development and progression of caries. Methods of caries prevention have focused mainly on ways to reduce acid production by oral microorganisms, and ways to prevent solubilization of calcium phosphate minerals in teeth⁸. Therefore, knowing the optimal level of calcium to prevent dental caries and also its role in remineralization of early carious lesions is crucial.

Studies to make the tooth mineral more resistant to dissolution by acid have been numerous. From these, fluoride has proven to be the most effective agent^{1, 12}. Although effective, fluoride reduces caries only partially when applied topically or systemically, and its effects may be limited when pit and fissure caries are considered⁷. Thus there is need for other caries preventive agents. The focus in caries research has recently shifted to the development of methodologies for the detection of early carious lesions and the non invasive treatment of these lesions. However, calcium, when compared to fluoride, is still not widely used by dental practitioners as a part of preventive dentistry.

In this review, Casein Phosphopeptide- Amorphous Calcium Phosphate (CPP-ACP), Alpha Tri Calcium Phosphate, Calcium Lactate and “Cavistat” (Ortek Therapeutics) in the form of chewing gums, remineralizing creams, dentifrices and calcium supplements are reviewed. Solutions containing calcium and phosphate ions have had limited effect on remineralization, due to the low solubility of calcium and phosphate salts. CPP-ACP stabilizes the calcium and phosphate ions preventing transformation into crystalline phases and maintaining a highly supersaturated solution. CPP and ACP have shown to have synergistic effect when given with fluoride¹⁰. “Cavistat” containing arginine bicarbonate/ calcium carbonate enables simultaneous inhibition of both acid production and demineralization, and in addition calcium provides a means of suppressing solubilization of enamel and favoring remineralization⁴. Alpha- tri calcium phosphate increases significantly the tooth mineral saturation of plaque fluid and saliva¹⁴.

The aim of this systematic review is to examine the evidence available regarding topical or systemic calcium compounds that prevent dental caries or reverse incipient caries and the various concentrations of calcium needed to do so. So, our Population, Intervention, Comparison and Outcome (PICO) statement is:

In children and adults with incipient caries or at increased caries risk, does systemic intake or topical application of calcium reverse or reduce caries when compared to non calcium containing treatments or no treatment? If so, is there an optimal level of calcium?

Materials and Methods:

A systematic review of literature was carried out to identify, appreciate and critically appraise the most relevant research to our topic of interest.

Stage 1: Selection of keywords to search Pub Med, Google scholar and Cochrane databases:

We employed the following key words to execute our research,” calcium, dental caries, tooth remineralization, cariostatic agents, and preventive dentistry”. Experts from the departments of Preventive and Pediatric Dentistry at the Faculty of Dentistry, University of Toronto were also consulted.

Stage 2: Setting inclusion and exclusion criteria

Inclusion criteria:

- Human studies in children and adults

- Articles published in English only
- Articles available in Pub Med, Cochrane, Google scholar and available at the university of Toronto library only.

Exclusion criteria:

- In vitro studies
- Bovine enamel in humans
- Root Caries
- Dentine hypersensitivity
- Fluoride as the main intervention
- Articles not available at the University of Toronto Library
- Articles that have been used in an existing systematic review and/or Meta analysis.

After using the following combination of Keywords and limits, total of 223 articles were retrieved:

Table 2: Search Strategy Table for Pub Med:

Keywords	Number of Articles
"Calcium"[Mesh] OR "Calcium Compounds"[Mesh]	257385 articles.
("Calcium"[Mesh] OR "Calcium Compounds"[Mesh]) AND ("Dental Caries"[Mesh] OR "Dental Caries Susceptibility"[Mesh] OR "Preventive Dentistry"[Mesh] OR "Tooth Remineralization"[Mesh] OR "Cariostatic gents"[Mesh])	2479 articles
Limits: Clinical trials, English, human studies, children ,adults	223 articles

Table 3: Cochrane search strategy:

Keywords	Number of Articles
Calcium caries prevention	78 articles
Title scan	9 relevant

Stage 3: Article selection

We applied the title, abstract and full text screening stages to obtain relevant articles. Each article was reviewed by at least 3 group members. In case of disagreement, the consensus was established. Of 223 articles obtained, 200 articles were rejected at the title stage. The abstracts of the remaining 23 articles were screened and 12 articles were rejected and 11 accepted. Full text screening resulted in 5 articles

For Cochrane data base, the search resulted in 78 articles from the “Cochrane central register of controlled trials”. All articles were screened by title, abstract and if the abstract was not available, the full text was reviewed. This resulted in the selection of 6 articles and full text screening resulted in 4

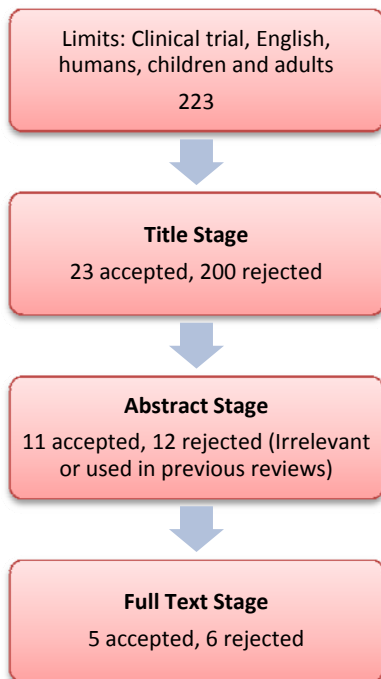
articles that met the criteria. One article from Google scholars also met the inclusion criteria.

Stage 4: Quality appraisal

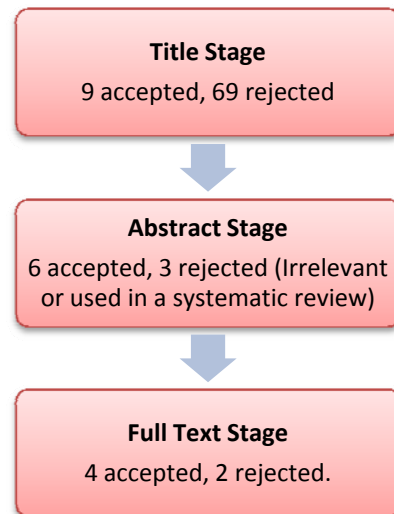
The 10 articles approved at the full text stage were critically appraised using the “Checklist to Assess Evidence of Efficacy of Therapy or Prevention”³ by at least 3 members of the team. 4 articles were rejected on the basis that they were already used in a Meta analysis¹⁵ or did not meet the cut off score. The 6 remaining articles met all the necessary criteria, scoring a minimum of 12 out of 17 on the **Checklist to Assess Evidence of Efficacy of Therapy or Prevention (Appendix 1)** and were subsequently analyzed with their findings reported in Table 4.

The following chart shows the number of articles approved and rejected in the 3 different screening stages based on our pre-defined inclusion and exclusion criteria:

Pub Med



Cochrane



Stage 5: Creating an evidence table

We abstracted evidence from the selected papers onto abstraction sheets and finally transferred the data into the evidence table. The table also includes the strength of the evidence and the grade of recommendation in each article based on Canadian Task Force of Preventive Health Care (CTFPHC) Grades of Recommendation and Quality of Published Evidence (**APPENDIX 2, 3**)

Table 4: Table for Critical Appraisal based on Checklist to Assess Evidence of Efficacy of Therapy or Prevention:

Author Year	Study Design	Population	Intervention	Control	Outcome	Critical appraisal, comments and score	Conclusion	Strength of evidence, grade of recommendation For prevention
Cai Fan et al, 2009,	RCT	Adults aged 25-55 wore palatal appliance containing human enamel slab(n=10)	(1) Gum containing CPP-ACP 2) Gum containing Calcium Carbonate/Citrate.	2 types of Sugar-Free gums	CPP-ACP gum increased re-mineralization of enamel subsurface lesions when compared to sugar-free gum or gum containing Calcium Carbonate/ Citrate	Checklist score: 14/17	As fluoride was used by both groups, there is a possible effect of synergism of F with ACP No accurate measurement methods.	Level of Evidence: Level I Recommendation Grade : A
S.Teotia M. Teotia 1994	RCT	23,273 Children Residing In non-Endemic And Endemic Fluoride areas with Calcium deficiency, (less than 0.5gm/day)	Calcium supplements 1gm/supplement once a day for 5 years	The control group received placebo	Incidence of dental Fluorosis and caries increased with increased Fluoride intake and dietary Calcium deficiency.	Checklist Score: 14/17	There is Significant evidence of difference in caries levels between the test group that received calcium supplement and the control group who received placebo	Level of evidence: Level I Recommendation Grade: A
Acevedo, Kleinberg, Riviera, 2005	RCT	11-12 year old Venezuelan children (601 total)	(CaviStat) containing dentifrice in 304 test group	297 used a commercially available 1100 ppm Fluoride toothpaste	Statistical Difference Between the two groups was highly Significant	Checklist Score: 13/17	Statistical difference in the degree of re-mineralization.	Level of evidence Level I Recommendation: Grade A

Vogel G.L. et al., 1998,	RCT crossover in situ	Adults 25 to 53 years old with no denture or unfilled cavities(n=14)	Sugarless Gum with 2.5% α -Tri-Calcium Phosphate	Sugarless Gum	Increase in PH, Free Ca and phosphate concentrations in plaque fluid and saliva in experimental group .Significant increase in re - mineralization potential.	Checklist Score: 12/17	Study shows a possible indirect effect on remineralization. Small number of population with diverse oral conditions at baseline, based on this result we cannot conclude regression or prevention in caries.	Level of Evidence: I, Recommendation Grade B
Suda, Suzuki, Egawa Sano, Hasega-wa, 2002	RCT crossover in situ	22-27 Years old (Enamel Slabs in 10 volunteers.)	Calcium lactate to chewing gum containing Xylitol	Chewing gum containing Xylitol only	The degree of remineralization with Xylitol-ca chewing gum tripled as compared to control and test group of only Xylitol chewing gum which doubled compared to control group	Check list Score: 12/17	There is no statistical difference between control and test specimens or between treatment Phases. But the study shows the synergistic effect between Xylitol and calcium lactate.	Level of evidence: Level 1 Recommendation Grade: A
Bailey D.L., 2009,	RCT	White spot lesions 12 - 18 year olds, right after orthodontic bracket removal (n=45 with 408 white spot lesions)	Topical Re-mineralizing Cream containing CPP-ACP	Placebo Cream N=22	Significant regression of white-spot lesions with severity 2-3 after 3 months compared to placebo.	Checklist score: 14/17	As fluoride was used by both groups, there is a possible effect of synergism of F with ACP No accurate measurement method.	Level of Evidence: I Recommendation Grade: A

Table 5: Exclusion Table:

Author	Article	Score	Reason for Exclusion
M.V. Morgan, G.G. Adams, and colleagues (2007)	The Anti cariogenic Effect of sugar-free gum containing CPP-ACP Nanocomplexes on Approximal Caries Determined using digital bitewing	15/17	Part of systematic review.
Graham G Craig	The use of a calcium Orthophosphate complex as a cariostatic agent	4/17	The Australian dental association does not endorse calcium sucrose phosphate as anti-caries as a public health measure, and it is not an economical preventive measure.
M.N. Naylor, R.L. Glass	A 3 year clinical trial of Calcium carbonate dentifrice containing calcium Glycerophosphate and sodium Monofluorophosphate	7/17	Bias of examiner, lack of a strong RCT design, intervention was not validly and reliably measured, and the duration was not enough. The groups were not treated equally.
E.C. Reynolds and colleagues	Fluoride Casein Phosphopeptide-Amorphous Calcium phosphate	13/17	The current study shows mostly that CPP increases the fluoride anti cariogenic effects rather than the anti cariogenic and preventive effect of Calcium.

Results:

The 6 articles in the review used CCP-ACP, Calcium Lactate, Cavistat and Alpha Tri calcium phosphate as interventions in the form of chewing gum, tooth paste and remineralizing cream. CPP-ACP and Calcium Lactate showed significant reduction in caries development as well as increased remineralisation^{4, 5, 6, 11, 14}. Alpha -Tri calcium phosphate increased the levels of calcium in plaque and saliva as a secondary effect, even though it did not show to directly reduce caries or increase remineralisation¹⁴. In one study calcium was administered systemically in the form of supplements and showed significant reduction in caries¹³.

A study with a population of 10 adults showed chewing CPP-ACP containing gum resulted in significantly greater enamel remineralization, when compared to three other gum products⁶. Study with a group of 45 adolescents with 408 white spot lesions found difference in reversion of lesions between the treatment group using CPP-ACP and the one using placebo was not statistically significant at 12 weeks (OR=1.67, P=0.16). When the analysis was restricted to those lesions with severity codes 2 or 3 at baseline, the odds ratio was statistically significant⁵. In a study involving 14 adults, 25 to 53 year old, compared the anti-caries potential of α -Tri Calcium Phosphate fortified gum with a gum without this additive. They found significant increases in PH and in free Calcium and phosphate concentrations compared to the control gum¹⁴. One study reported in a group of 601

out of 726 children who completed their study, the children in a control group continued to use regular fluoridated toothpaste and a test group used toothpaste containing CaviStat. In this 2 years study, caries development overall was significantly less in subjects who used CaviStat with most of the lesions involving the pits and fissures of posterior teeth⁴. In an in situ randomized crossover study on 10 Volunteers aged 22 to 27 years, the researchers tested gum containing 2.5 gram Xylitol and 94 mg calcium lactate against a control gum with no calcium. They concluded that chewing gum containing calcium lactate as well as Xylitol enhances remineralization of sub surface enamel lesions more than Xylitol only gum. They also suggested that the effect of remineralization is greater in subjects with high caries activity¹¹. In a group of 23,273 (10 year old) children living in non-endemic and endemic fluoride areas, the test group received 1gm of elemental calcium supplement/day for 5 years and the other group received a placebo with no calcium. The researchers concluded that adequate dietary calcium intake greater than 800 mg/day provides an effective control in prevention of dental caries and dental flourosis¹³.

Discussion:

The primary objective of this systematic review was to determine the caries preventive effect of topical or systemic use of calcium. No attempt was made to search for articles other than in English and this is a shortcoming of this review.

For the articles related to the use of CPP-ACP, a previous systematic review referenced articles published up to 31 august 2008¹⁵. We used existing reviews as well as articles published after this review to produce the evidence for our review. This previous systematic review provided evidence for use of CPP-ACP for caries prevention. Initial carious lesions exposed to CPP-ACP were found to have a more significant improvement in remineralization than control lesions that were not exposed to CPP-ACP.

Study using CPP-ACP in the form of gum highlights the importance of calcium ion bioavailability in the remineralization of enamel subsurface lesions⁶. However, one of the limitations of this study was the relatively short exposure time of 15 days and it was an In- situ study. Study using remineralizing cream containing CPP-ACP⁵ was conducted by group of investigators who patented the CPP-ACP complex which may have biased how they presented their findings, but their results have been supported by the independent research of other groups. Another possible confounding factor in this study was, all 45 participants were also using fluoride toothpaste (1000ppm) and were receiving

supervised fluoride mouth rinses (900ppm). As indicated by Reynolds (2008) the combination of calcium and fluoride could have synergistic effects and there could have been an overestimation of the results obtained when fluoride was used along with CPP-ACP. In the study conducted using chewing gum containing calcium lactate and Xylitol enhanced remineralization¹¹. However, this study was crossover in situ study done for a very short duration of 14 days with only 10 volunteers participating in the study. In addition, chewing gum alone might have influenced remineralization due to increased salivary flow rate and there may have been a synergistic effect between Xylitol and calcium lactate. One study tested CaviStat and concluded that it resulted in less caries when compared with non-CaviStat controls by increasing the arginolytic bacterial component of the oral microflora and that also the calcium carbonate increased remineralization⁴. This study was supported by Ortek Therapeutics Inc, the company licensed to develop Cavistat, and this could be a potential source of bias. Also, all the test subjects had to undergo supervised brushing once a day and two unsupervised brushings, it is not clear to what extent tooth brushing itself, exclusive of therapeutic dentifrices, alters the caries attack level. Andlaw (1978) and Bellini et al (1981) showed that children with good oral hygiene had a lower caries incident than those with poor oral hygiene, but the difference was very small. So, even though use of Cavistat showed significant remineralization the results might have been due more to the action of Arginine than calcium carbonate itself and possibly from improved oral hygiene due to supervised brushing.

One study showed that adequate dietary calcium intake provided effective control and prevention of dental caries. The authors recommended an adequate calcium intake by nutrition or supplementation of 1gm/day¹³. However, this study focused on effect of calcium deficiency in endemically high fluoride areas associated high prevalence of dental fluorosis and dental caries. The study doesn't provide information on whether the same level of calcium intake is necessary in optimally fluoridated areas nor does it indicate if there is any possible remineralization with the use of calcium supplements. One of the articles examined the composition of plaque and saliva in subjects after they rinsed with sucrose and chewed a gum fortified with α -Tri-Calcium Phosphate. The results of this study suggest that this compound when incorporated into chewing gum may have significant remineralization potential¹⁴. However, though the study showed increased calcium levels in saliva and plaque as a secondary effect, it did not present significant evidence in terms of caries prevention itself. Also, the number of participants in the study was small and appropriate criteria were not applied in selection of these participants.

Conclusions/Recommendations:

- There is good evidence (Level of Evidence 1, Grade of Recommendation A) through our review to suggest that calcium taken either topically or systemically will prevent caries and/or promote remineralization.
- There is firm evidence from many studies that CPP-ACP is useful for the purpose of remineralization and caries prevention. None of the included studies tested for the potential formation of calculus resulting from the use of CPP-ACP.
- For other the compounds there have not been enough studies to prove and compare their efficacy, the same applies to the lack of enough systemic calcium studies.
- From the review of the literature there is not enough information to determine the optimal concentration of calcium to prevent caries, but there is good evidence showing that the important factor that determines the caries prevention or remineralization property of calcium is its bioavailability, rather than its absolute concentration.
- There is some evidence of synergism or additive effect when CPP-ACP and fluoride are combined.
- More well designed and conducted double blind randomized clinical trials with adequate sample size, limited or minimal loss to follow up and using carefully standardized methods of measurements and analysis is needed to enable researchers to evaluate the efficacy and cost effectiveness of different calcium compounds in reducing or eliminating dental caries or promoting remineralization.

Appendix 1:

Checklist to Assess Evidence of Efficacy of Therapy or Prevention

Citation: _____

1. Was the study ethical? _____

2. Was a strong design used to assess efficacy? _____

3. Were outcomes (benefits and harms) validly and reliably measured? _____

4. Were interventions validly and reliably measured? _____

5. What were the results?

Was the treatment effect large enough to be clinically important? _____

Was the estimate of the treatment effect beyond chance and relatively precise? _____

If the findings were “no difference” was the power of the study 80% or better _____

6. Are the results of the study valid?

• Was the assignment of patients to treatments randomized? _____

• Were all patients who entered the trial properly accounted for and attributed at its conclusion?

i) was loss to follow-up less than 20% and balanced between test and control _____

ii) Were patients analyzed in the groups to which they were randomized? _____

• Was the study of sufficient duration? _____

• Were patients, health workers, and study personnel “blind” to treatment? _____

• Were the groups similar at the start of the trial? _____

• Aside from the experimental intervention, were the groups treated equally? _____

• Was care received outside the study identified and controlled for _____

7. Will the results help in caring for your patients?

Were all clinically important outcomes considered? _____

Are the likely benefits of treatment worth the potential harms and costs? _____

Adapted from: Fletcher, *Fletcher and Wagner. Clinical epidemiology – the essentials. 3rd ed 1996 and Sackett et al. Evidence-based medicine: how to practice and teach EBM. 1997.*

Appendix 2, 3:

Definitions of levels of evidence and grades of recommendations of the Canadian Task Force on Preventive Health Care

Levels of evidence

Research-design rating

I	Evidence from randomized controlled trial(s)
II-1	Evidence from controlled trial(s) without randomization
II-2	Evidence from cohort or case–control analytic studies, preferably from more than one centre or research group
II-3	Evidence from comparisons between times or places with or without the intervention; dramatic results from uncontrolled studies could be included here
III	Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees

Grades of recommendations for specific clinical preventive actions†

A	There is good evidence to recommend the clinical preventive action
B	There is fair evidence to recommend the clinical preventive action
C	The existing evidence is conflicting and does not allow making a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
D	There is fair evidence to recommend against the clinical preventive action
E	There is good evidence to recommend against the clinical preventive action
I	There is insufficient evidence (in quantity or quality or both) to make a recommendation; however, other factors may influence decision-making

*General design-specific criteria are outlined by Harris and associates.⁴⁵ Inclusion and exclusion criteria are detailed in the Methods section of that article.

†The task force recognizes that, in many cases, patient-specific factors must be considered and

discussed, such as the value the patient places on the clinical preventive action, its possible positive and negative outcomes, and the context or personal circumstances of the patient (medical and other). In certain circumstances where the evidence is complex, conflicting or insufficient, a more detailed discussion may be required.

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