



# Adding calcium phosphate agents alongside fluorides may enhance caries prevention and remineralization, although evidence is limited

DOI:

[10.1016/j.jebdp.2024.102024](https://doi.org/10.1016/j.jebdp.2024.102024)

## Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

## Citation for published version (APA):

Lu, W., Zhang, H., & Hua, F. (2024). Adding calcium phosphate agents alongside fluorides may enhance caries prevention and remineralization, although evidence is limited. *Journal of Evidence-Based Dental Practice*, 24(3), Article 102024. <https://doi.org/10.1016/j.jebdp.2024.102024>

## Published in:

Journal of Evidence-Based Dental Practice

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## Review Analysis and Evaluation Template

**DECLARATIVE TITLE:** Adding calcium phosphate agents alongside fluorides may enhance caries prevention and remineralization, although evidence is limited

**PURPOSE/QUESTION:** Do calcium phosphate agents have additional caries-preventive and tooth-remineralizing effects compared to no intervention / placebo / fluorides alone?

**ARTICLE TITLE AND BIBLIOGRAPHIC INFORMATION:** Effectiveness of Calcium Phosphate derivative agents on the prevention and remineralization of caries among children- A systematic review & meta-analysis of randomized controlled trials. *Singal K, Sharda S, Gupta A, Malik VS, Singh M, Chauhan A, Agarwal A, Pradhan P, Singh M.* J Evid Based Dent Pract. 2022 Sep; 22(3):101746.

### Strength of Recommendation Taxonomy (SORT) Grading

**STRENGTH OF RECOMMENDATION GRADE:** B

**LEVEL OF EVIDENCE:** Level 2

**SOURCE OF FUNDING:** Indian Council of Medical Research

**TYPE OF STUDY/DESIGN:** Systematic review with meta-analysis

**KEY WORDS:** Childhood caries, Tooth remineralization, Streptococcus mutans, Laser fluorescence, Casein phosphopeptide-amorphous calcium phosphate

## Summary

### Subjects or Study Selection:

The literature search included Embase, Ovid, PubMed, Scopus, Web of Science, Cochrane central register of controlled trials (CENTRAL), and the grey literature for related research up to April 2021. The search strategy employed a combination of terms including “white spot lesion (WSL)”, “dental caries”, “streptococcus mutans (S. mutans)”, “DIAGNOdent”, “laser fluorescence”, “amorphous calcium phosphate (ACP)”, “tricalcium phosphate (TCP)”, “functionalized  $\beta$ -tricalcium phosphate (fTCP)”, “casein phosphopeptide-amorphous calcium phosphate (CPP-ACP)”, and “casein phosphopeptide-amorphous calcium fluoride phosphate (CPP-ACFP)”.

A total of 2,161 records were finally identified. Two researchers independently screened the titles and abstracts of these records. Subsequently, the full-texts of 65 documents were assessed for eligibility and 26 of them were included in this review.

**Key Study Factor:**

This systematic review and meta-analysis evaluated the cariostatic and tooth-remineralizing effect of various calcium phosphate (CaP) derivatives compared to fluoride with or without placebo in children. Among the included trials, fTCP, CPP, ACP varnish and ACP sealant were studied in 1 trial each, while 3 trials studied TCP. The remaining 19 trials evaluated the performance of CPP-ACP, while none of the included trials reported the potential effect of calcium sodium phosphosilicate agent. These CaP agents were provided in several forms, namely cream, toothpaste, and varnish. The follow-up period of included studies varied between 48 hours and 24 months.

**Main Outcome Measure:**

Changes in the number of active and reversed WSLs, fluorescence lesion (area) value, DIAGNOdent values, and salivary *S. mutans* count were the main outcomes of this review. The proportion of children with high post-intervention *S. mutans* count was compared to analyze the cariostatic performance of CaP derivatives (2 trials). The remineralization effect was explored via synthesizing the post-intervention changes in fluorescence ( $\Delta F$  values) (3 trials), number of active white spot lesions (WSLs) (3 trials), lesion area (3 trials), WSLs complete regression (2 trials), and DIAGNOdent values (2 trials).

**Main Results:**

Three included trials were assessed to have an overall low risk of bias while the rest presented high risk of bias. Based on three trials and low-certainty evidence, active WSLs were reduced after the application of the CPP-ACP + fluoride therapy compared to fluoride alone (RR = 0.80; 95% CI, 0.70 to 0.90;  $P = .0004$ ,  $I^2 = 0\%$ ). The meta-analysis of two studies with very low-certainty evidence depicted that the combined therapy had a higher possibility of complete WSL regression than fluoride alone (RR = 1.56; 95% CI, 1.27 to 1.91;  $P < .0001$ ,  $I^2 = 0\%$ ). Additionally, the meta-analysis on *S. mutans* count, based on 2 trials and low-certainty evidence, indicated that CPP-ACP alongside fluoride had significantly better antibacterial effect when compared to fluoride alone (RR= 0.69; 95% CI, 0.48 to 0.99;  $P = 0.47$ ,  $I^2=0\%$ ). However, no significant difference in lesion area,  $\Delta F$  values, and DIAGNOdent values were observed between the 2 groups.

**Conclusions:**

The authors concluded that the combined use of CPP-ACP and fluoride may have greater remineralizing and antibacterial effect on early caries among children, when compared to using

fluoride alone. Apart from CPP-ACP, there was insufficient evidence supporting the additional effects of other CaP derivatives.

## Commentary and Analysis

Dental caries remains a common and serious oral condition which affects all age groups, impacting oral health-related quality of life<sup>1</sup>. In order to treat caries while preserve tooth structure, early caries detection and non-invasive approaches have become the focus of caries research in the last decade, as part of the paradigm shift in dental caries management<sup>2</sup>. In the realm of non-invasive remineralizing agents, fluoride and CaP are widely recognized as two of the most prominent products.

The therapeutic effect of fluoride on early-stage caries has been well-established in previous research.<sup>3</sup> However, the current trends of fluoride intake from multiple sources are incurring increased public concerns on the potential fluoride toxicity<sup>4</sup>. Moreover, its remineralizing effect relies heavily on calcium and phosphate from saliva and proved limited in cavity caries<sup>5</sup>.

Therefore, CaP and its derivatives have been explored as substitutes for fluoride therapy. These complexes, which are tasteless and biocompatible, can stabilize free calcium and phosphate ions and serve as calcium and phosphate reservoir<sup>6</sup>. Furthermore, they can maintain a state of supersaturation, thus inhibiting demineralization and promoting remineralization<sup>6</sup>. Some researchers reported that CaP and its derivatives have an additional advantage on potentiating the remineralization process of enamel<sup>7, 8</sup>. However, according to previous evidence, whether CaP agents could surpass fluoride and serve as a replacement remains unclear<sup>9</sup>. Consequently, numerous studies have begun investigating the remineralizing effect of CaP + fluoride therapy.

This systematic review focused on the effects of CaP agents combined with fluoride in children's caries management compared to fluoride alone. According to the findings, CaP derivatives plus fluoride may outperform fluoride alone in reducing WSLs, activating remineralization, and controlling *S. mutans*. However, the presence of limitations necessitates interpretations with caution.

Firstly, all the confidence intervals of significant effects were close to the null line, indicating a limited degree of advantage. Besides, when the outcome was measured by quantitative light-induced fluorescence ( $\Delta F$  values and lesion area value), the performance of combined therapy did not differ from that of fluoride alone. Secondly, due to substantial heterogeneity and a small

sample size, the body of evidence was assessed to be of very low to low certainty.

Moreover, another potential limitation is the relatively short follow-up period of the studies included in the meta-analysis (ranging from 4 to 12 weeks). A previous *in vitro* study by Thierens et al demonstrated that a 12-week application of CPP-ACP yielded better results than a 6-week application. This phenomenon was also confirmed by several studies included in this systematic review. As a result, a synthesis of studies on extended applications of CaP and its derivatives may provide a more reliable estimation of the cariostatic performance and be of more clinical significance.

In summary, according to the results, CaP may have additional caries prevention and remineralization effects than using fluoride alone. However, the long-term prognosis of this combined therapy remained unclear. Nevertheless, based on the evidence from this SR/MA, general dentists could consider the combined therapy of CPP-ACP plus fluoride for the prevention and treatment of early-stage childhood caries in a short term.

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