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CARIES REMINERALIZATION, REGENERATION, AND REPAIR OF NATURAL TOOTH STRUCTURE: SYSTEMATIC REVIEW AND META-ANALYSIS.

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ABSTRACT

Background: A white spot (opacity) is the result of acid dissolution (demineralization) of the existing hydroxyapatite crystal structure, which produces porosity in the enamel's base.

Aim: To assess the effect of 5 % NaF (Sodium fluoride) and 38 % SDF (Silver diamine fluoride) on remineralization of early enamel caries**.**

Methods: This systematic review encompassed 6 studies, with 3482 patients. The primary search across five databases yielded 450 studies. Upon the removal of duplicate studies, 178 unique articles remained for further assessment. Screening involved scrutinizing the titles and abstracts, as a consequence, sixty-six research with potential relevance were identified & subjected to full text assessment. Fifty of this research were excluded in accordance with predetermined criteria.

Results: Remineralization using 5 % NaF (Sodium fluoride) was evaluated in three research totaling 264 patients with statistically significant higher remineralization of early enamel caries in the 5 % NaF (Sodium fluoride) group than the control group. RR and corresponding 95%CI= 1.89[1.46, 2.45],p-value<0.00001. Heterogeneity was observed among our pooled studies with chi-p=0.12, and I2=54%. Meta-analysis of the five-research using 38 % SDF (Silver diamine fluoride) to arrest dentine caries.

Conclusion: Remineralization of early enamel caries is demonstrated when five percent sodium fluoride or silver diamine fluoride solution at thirty-eight percent varnish is applied professionally. Further clinical trials should be conducted to examine the arresting impact of dental caries, as the number of such trials is limited.

Keywords: Caries Remineralization, NaF, SDF

INTRODUCTION

Early caries is characterized by a white spot (opacity) that results from acid dissolution (demineralization) of the existing hydroxyapatite crystal structure, which creates porosity inside the underlying enamel. To facilitate remineralization or regeneration of this subsurface lesion, a scaffold is required to serve as a template for hydroxyapatite formation & assist in crystal alignment, similar

to the function of matrix proteins throughout enamel formation. It is necessary that this scaffold has the capability to penetrate the demineralized tissue. Therefore, it is optimal for the scaffold to develop organically within the lesion body **(1).**

Present restoration agents, including casein phosphopeptide−amorphous calcium phosphate (ACP) paste & fluoride dentifrice, exhibit an inability to regenerate enamel. Instead, they promote the development of irregular crystals on the enamel layer that has been eroded. This characteristic represents a significant limitation. Thus, in order to advance regenerative or restorative strategies, much remains to be learned regarding the specific processes by which enamel matrix proteins direct the building of enamel with an orderly structure **(2).**

Multiple techniques have been utilized in the process of remineralizing dentin that has become demineralized. For example, researchers have employed fluoride, adhesives based on resins that release amorphous calcium phosphate (ACP), or adhesives containing bioactive glass in order to enhance the resistance of bonded restorations against secondary caries **(3).** The majority of these investigations, on the other hand, concentrated on remineralizing carious dentin that had become partially demineralized. This was accomplished by deposition of phosphate & calcium ions epitaxially on pre-existing apatite seed crystallites **(4).**

In the absence of seed crystallites, remineralization does not take place using conventional ion-based techniques. Therefore, in order to remineralize fully demineralized dentin present in hybrid layers formed by etch-&-rinse adhesive systems or the superficial portion of a caries-affected dentin lesion remaining after minimally invasive caries elimination, the traditional ion-based crystallization concept may not be applicable. This is because seed crystallites are not present in those areas, which hinders the achievement of homogeneous nucleation of apatite crystallites **(5).**

An alternative strategy for dealing with this issue is biomimetic remineralization, which utilizes biomimetic analogs of noncollagenous proteins to stabilize liquid-like ACP nanoprecursor particles into the demineralized dentin collagen **(6).**

The objective of this study was to assess the impact of 5 % NaF & 38 % SDF on remineralization of early enamel caries.

METHODS

This article examined the evolving theories surrounding the calcium phosphate mineralization of fibrillar collagen & the hydroxyapatite crystal structure of enamel. It covered various topics such as the formation of polymer-induced liquid precursors (PILP), experimental collagen models for mineralization, the non-classical particle-based crystallization concept that was recently identified, the necessity of employing phosphate-containing biomimetic analogs for biomimetic collagen mineralization, & PILP formation. Then, published research by different research teams were reviewed regarding the precise mechanisms by which enamel matrix proteins direct the formation of enamel with an ordered structure, the remineralization of resin-dentin bonds, & the creation of artificial caries-like lesions. In conclusion, this paper examines the challenges & advancements that arise during the process of translating a scientifically validated concept into a clinically relevant approach.

Literature search

An extensive investigation was undertaken encompassing numerous databases., involving Web of Science, PubMed, Scopus, Cochrane, gray literature including google scholar, to collect relevant literature. The search encompassed literature from inception of these databases up until February 2024. Additionally, we conducted a manual examination of reference lists from eligible articles & previously performed meta-analyses to ensure the identification of any relevant citations. The search terms: ((fluoride) & (remineralization or arresting or remineralization) & (caries OR early childhood caries)).

Eligibility criteria

To be considered for our systematic review, an individual had to satisfy the subsequent criteria: 1) In RCTs involving minors, the outcome of the research should be an assessment of the efficacy of fluoride therapy in preventing caries remineralization.

Numerous studies were omitted from our analysis due to specific exclusion criteria: 1) basic science studies, 2) research not published in English, 3) no full-text availability, and 4) incorporation of unpublished data.

Data gathering

The data extraction procedure comprised the utilization of an offline data extraction method to collect relevant data from every research study. Aspects like the first author's name & the year of publication were included in the extracted data, study geographic distribution, sample size, gender distribution, patient's ages, inclusion criteria, conclusions, and outcomes.

Risk of bias assessment

The evaluation of the involved trials' quality was performed using the Cochrane Risk of Bias evaluation Tool 1 (ROB1), this tool encompassed various parameters involving allocation bias, concealment bias, performance bias, detection bias and selection bias.

Data synthesis

In our meta-analysis, we utilized the inverse difference approach specifically for continuous outcomes pooled MD with 95% CI however for categorical data we used R.R with 95% CI, For the purpose of determining the total proportion of remineralized early enamel caries, a meta-analysis was conducted utilizing the random-effects model. Utilizing the I2 statistics chi2 test, we investigated the statistical heterogeneity among studies. The results indicated that the studies were considered heterogeneous if the chi2-p value was greater than 0.1. Furthermore, the I2 values that were greater than or equal to fifty percent indicated a significant degree of heterogeneity. RevMan, which stands for Review Manager Software, version 5.4. Served as the basis for our meta-analysis.

RESULTS

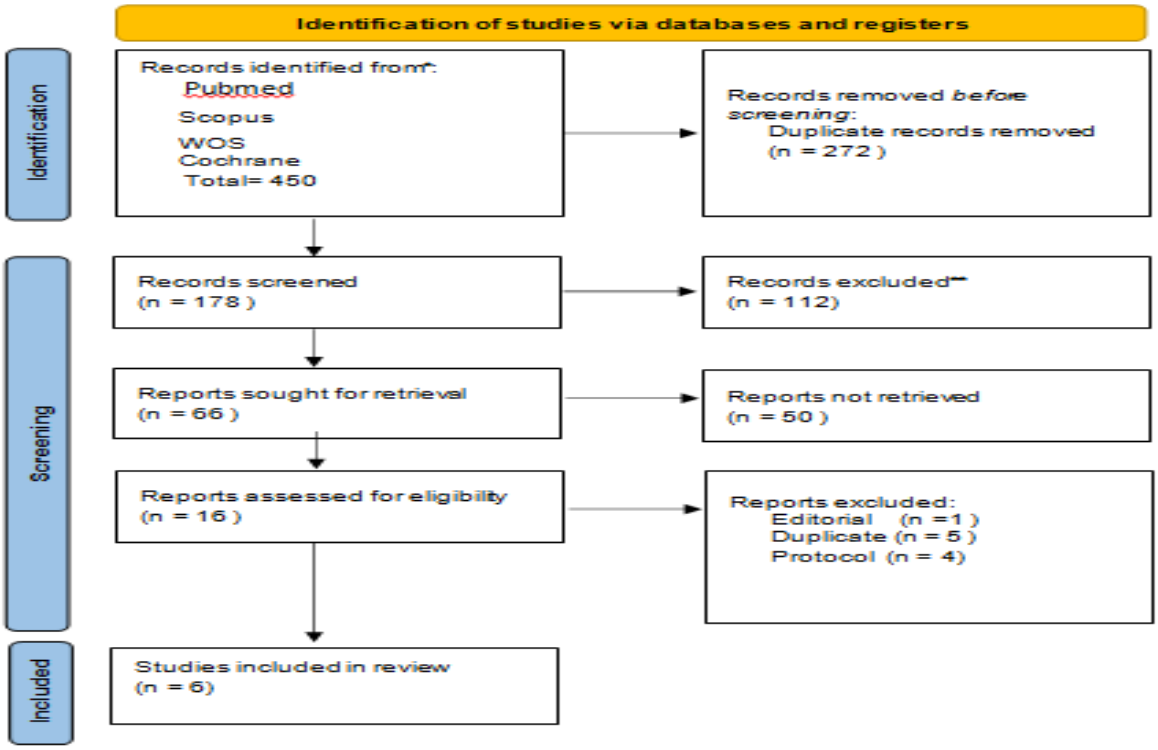
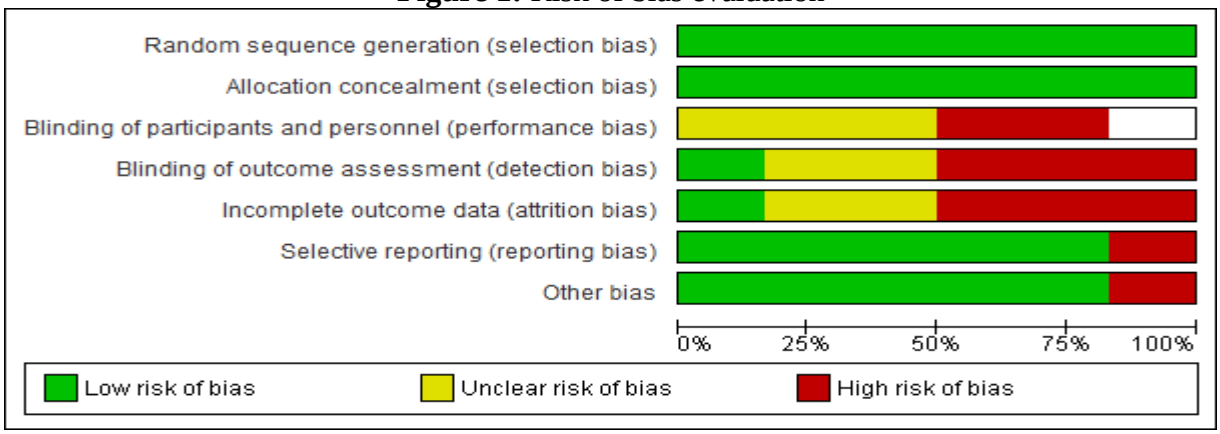


Figure (1): The PRISMA flow diagram of the included studies

Our comprehensive systematic review encompassed 6 research, with 3482 cases. The primary search across five databases yielded 450 studies. Upon the removal of duplicate studies, 178 unique articles remained for further assessment. Screening involved scrutinizing the titles and abstracts, As a consequence, sixty-six studies with potential relevance were identified & subjected to extensive text assessment. Fifty of these studies were omitted in accordance with predetermined criteria. In the end, six studies that satisfied the inclusion criteria for our systematic review & meta-analysis were considered eligible.

Figure 1: Risk of bias evaluation



Each of the six trials in our analysis had a low risk regarding selection bias, according to ROB1. ROB1 summary is provided in Supplementary. (Figure 2)

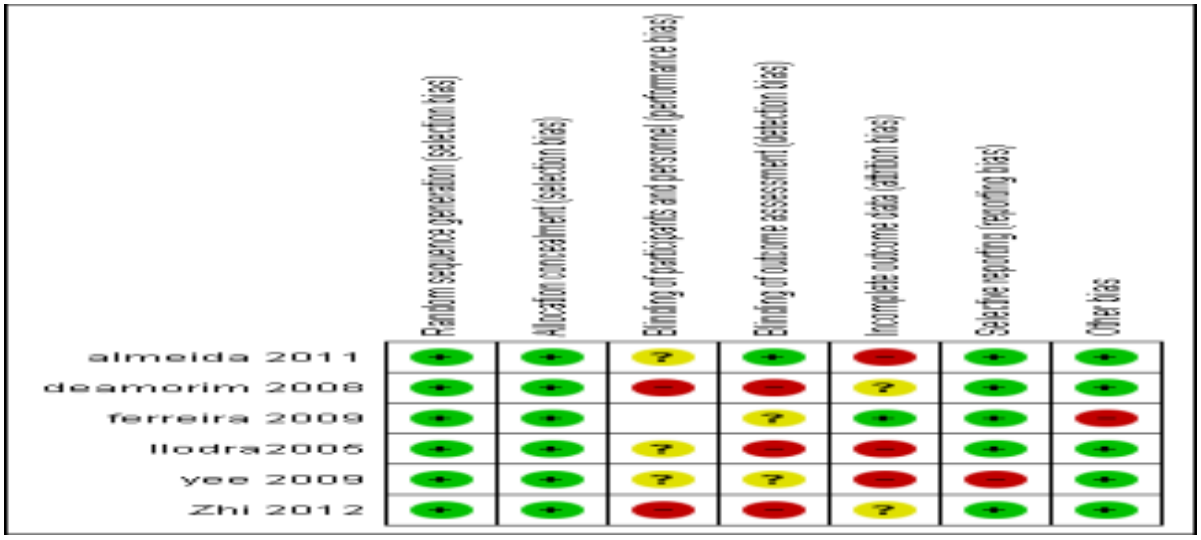


Figure (3): Outcomes of early enamel caries lesion

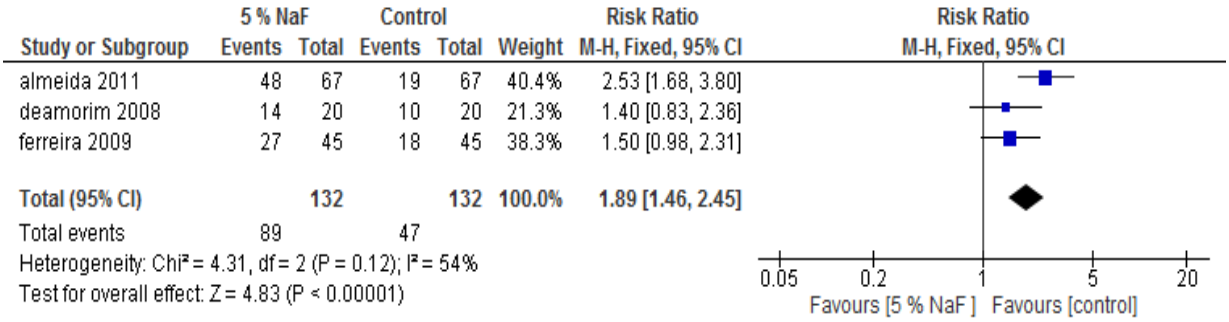


Figure (4): Represents the forest plot for the outcome.

Remineralization using 5 % NaF (Sodium fluoride) was assessed in three studies totaling 264 patients with statistically significant higher remineralization of early enamel caries in the 5 % NaF (Sodium fluoride) group than the control group. RR and corresponding 95%CI= 1.89[1.46, 2.45],p-value<0.00001. Heterogeneity was observed among our pooled studies with chi-p=0.12, and I2=54%. Meta-analysis of the five-research utilizing thirty eight percent silver diamine fluoride to arrest dentine caries. (Figure 4)

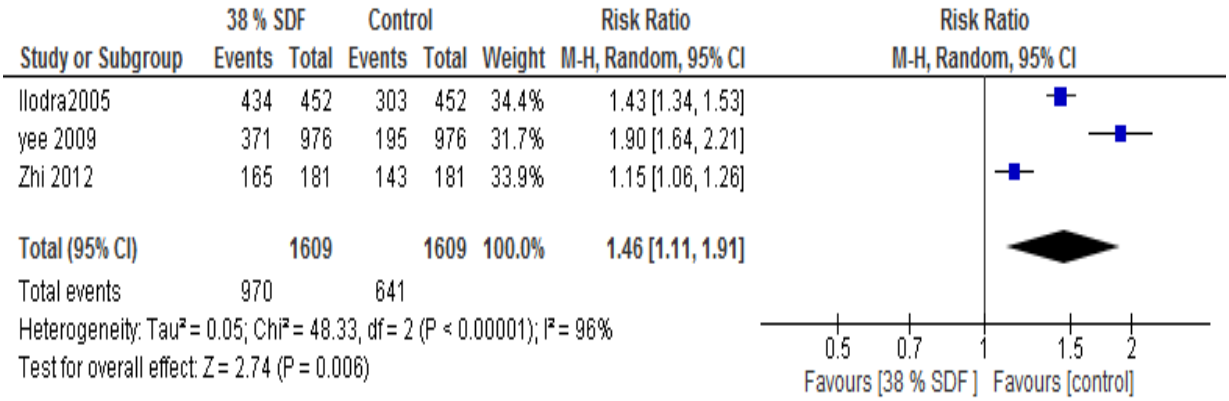


Figure (5): Represents the forest plot for this outcome.

Remineralization using 38 % SDF (Silver diamine fluoride) was evaluated in three research totaling 3218 patients with statistically significant higher remineralization of early enamel caries in the 38 % SDF group than the control group. RR and corresponding 95%CI= 1.46[1.11, 1.91], p-value=0.006. Heterogeneity was observed among our pooled studies with chi-p<0.00001, and I2=96%. (Figure 5)

Discussion

A gradual procedure, demineralization causes the hydroxyapatite crystals in enamel to gradually dissolve, ultimately culminating in the deposition of tooth tissue. The occurrence of demineralization of enamel & dentin seems to be on the rise, despite advancements in oral hygiene technology & awareness programs. Its primary effects include greater sensitivity of the dentin & the onset of dental caries . **(7)**.

Dental caries is the most common disease worldwide. It leads to the destruction of dental hard tissues. The process of caries formation begins by dissolving the minerals from enamel, due to the organic acids produced by bacteria accumulated on the surface of the tooth. Prolonged acid attack creates a subsurface, demineralized lesion, known as white spot lesion (WSL) **(8)**.

Dental enamel is an avascular, hard, hydroxyapatite nanocrystal-based, acellular tissue composed of ninety-six percent inorganic material, three percent water, & one percent organic component **(9).**

Remineralization is the procedure by which minerals are restored into the lattice structure of hydroxyapatite. Oral hygiene can be supplemented with a variety of remineralizing agents, such as fluoride applications (in the form of varnishes, lotions, or gels) at home or in the office. An alternative course of action could involve the utilization of remineralizing agents, such as dental sealants & glass ionomer composites, which are not dependent on cases compliance **(10).**

The current meta-analysis assessed the impact of five percent NaF on remineralization of early enamel caries. The pooled data of three studies **(11-13)** with a total of 264 patients showed statistically significant higher remineralization of early enamel caries in the 5 % NaF (Sodium fluoride) group than the control group with no significant heterogeneity among the pooled studies.

Also, the current meta-analysis assessed the effect of 38 % SDF (Silver diamine fluoride) on remineralization of early enamel caries. The pooled data of three studies **(14-16)** with a total of 3218 patients showed statistically significant higher remineralization of early enamel caries in the 38 % SDF group than the control group (p-value=0.006) with significant heterogeneity among the pooled studies.

Collectively, both 5 % NaF and 38 % SDF resulted in significant effect on remineralization of early enamel caries.

Silver has been utilized for many years due to its antimicrobial effect and in NaF and SDF provided in combination with fluoride. Clinical, in vitro, and in vivo evidence have established that compounds containing silver are effective agents for both primary & permanent dentition caries prevention & arrest.

Gao et al. conducted a systematic review & meta-analysis to evaluate the clinical effectiveness of professional fluoride treatment in remineralizing & stopping cavities in children, which is consistent with the present findings. In four studies employing five percent sodium fluoride varnish to remineralize early enamel caries, a meta-analysis was conducted. The cumulative percentage of enamel caries that underwent remineralization was 63.6 percent (95% CI: 36.0%-91.2%; $p < 0.001$) **(17).** In addition, a meta-analysis was conducted on five publications that employed thirty-eight percent silver diamine fluoride to halt dentine caries progression; the proportion of dentine caries arrested was 64.9 percent (95% CI: 41.2%-90.7%; $p < 0.001$). Early enamel caries can be remineralized with professionally applied five percent sodium fluoride varnish, & dentine caries can be effectively arrested with thirty-eight percent silver diamine fluoride, according to the review.

The effectiveness of NaF varnish in preventing dental caries was also reported in earlier reviews **(18, 19)**.

A literature review explains through various studies that SDF can be a medical modality of managing and preventing dental caries **(20, 21)**.

A recent systematic review by **Zhao et al.,** SDF was discovered to be bactericidal against cariogenic bacteria, specifically Streptococcus mutans. On teeth, it impeded the development of cariogenic biofilms. Mineral loss of demineralized enamel & dentine was observed to be diminished subsequent to SDF treatment. A calcium & phosphate-rich, highly mineralized surface developed on arrested carious lesions. Additionally, it was discovered that SDF exhibited inhibitory effects on collagenases, specifically matrix metalloproteinases & cysteine cathepsins, while protecting dentine collagen against degradation **(20).**

Additionally, **Peng et al.** demonstrated in a separate systematic review that silver compounds are thought to inhibit demineralization & have an antibacterial impact on carious tooth tissues through interference with bacterial cell membranes, cytoplasmic enzymes, & DNA replication. **(21)**.

Conclusion

Remineralization of early enamel caries is demonstrated when five percent sodium fluoride or silver diamine fluoride solution at thirty-eight percent varnish is applied professionally. Further clinical trials should be conducted to examine the arresting effect of dental caries, as the number of such trials is limited.

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