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Review article

The effect of bioactive glasses on enamel remineralization: A systematic review

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ABSTRACT

Introduction/Objectives: To evaluate the effectiveness of bioactive glasses in promoting enamel remineralization.
Data: An electronic search with a complementary gray literature search for in vivo and in vitro research. No language restrictions were applied.
Sources: MEDLINE and EMBASE via OVID, the Cochrane Oral Health Group's Trials Register, CENTRAL and LILACS
Study selection: One hundred and sixteen studies were identified, of which, eleven met the inclusion criteria and formed the basis of this systematic review. Methodological quality was assessed independently by two reviewers. Factors investigated in the selected articles included the objective and subjective measures of enamel remineralisation; harms, including evidence of damage to the enamel surface; patient satisfaction; and in vitro evidence of enamel remineralisation, using recognized laboratory techniques.
Results: A total of 11 laboratory-based studies were included in this review. The methodological quality was deemed to be high in four, and medium in the remaining studies. Based on the in vitro studies, enamel remineralization improved with bioactive glasses, irrespective of the method of application. Ex vivo signs of remineralization such as increase in enamel hardness, the formation of an enamel-protective layer and reduced intensity of light backscattering were less evident with alternatives including fluoride, and casein phosphopeptide-amorphous calcium phosphate (CPP-ACP).
Conclusions: Based on in vitro findings only, bioactive glasses may be capable of enhancing enamel remineralization in various formulations, compared with other topical remineralizing materials including fluoride, and CPP-ACP. However, clinical research to confirm their effectiveness is now overdue.
Clinical significance: Bioactive glasses have potential utility in promoting enamel remineralization; however, clinical research exploring their clinical effectiveness is required.

1. Introduction

Enamel demineralization is a reversible precursor of overt dental caries and is highly prevalent both among orthodontic and non-orthodontic populations. White spot lesions (WSLs), for example, are a common complication associated with fixed orthodontic treatment, particularly in the presence of poor oral hygiene [1]. Fixed appliances offer retentive areas for accumulation of bacterial plaque. The acidic by-products of cariogenic bacteria are responsible for the subsequent enamel demineralisation and formation of WSLs, which are reported in up to 96% of orthodontic patients [2]. This is further aggravated by the fact that most orthodontic patients are adolescents, who are at increased risk due to the susceptibility of newly- erupting teeth to acid attack [3].

A number of topical remineralizing agents have been used to inhibit and remineralize enamel and WSLs, in particular [4]. Fluoride has formed the mainstay of enamel remineralization for many decades. It is known to control caries predominantly through its topical effect inhibiting demineralization by forming fluorapatite on the enamel surface. Fluorapatite is less soluble, therefore increasing the resistance of enamel to dissolution relative to hydroxyapatite during acid attack [5]. Various modes and formulations have been used to deliver fluoride such as varnishes, toothpastes, mouth-rinses, solutions, gels and orthodontic adhesives incorporating a source of fluoride.

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Convincing evidence of the effectiveness of agents in prevention and reversal of enamel WSLs is limited. Notwithstanding this, a recent Cochrane systematic review reported that the application of fluoride varnish on a 6-weekly basis was effective in preventing WSL formation [6]. This approach, however, is onerous, requires professional input and may be costly. The use of CPP-ACP has been advanced in recent years as an alternative to fluoride to promote remineralisation [4]. The CCP-ACP complex may be applied by means of chewing gum, tooth-paste, lozengens, mouth-rinses, or sprays. These complexes adhere to dental biofilm, preventing colonization of bacteria and providing a supersaturated environment of calcium and phosphate [7]. However, clinical research has given disappointing results with little difference in outcome relative to the use of fluoride [8,9]. Recently, a preventative treatment regimen involving the daily use of CPP-ACP (MI Paste Plus) for 3 minutes daily in a fluoride tray throughout orthodontic treatment has been recommended [10].

More recently, a bioactive glass (45S5) has been developed for dental use and applied in a plethora of studies to remineralize WSLs [12–17]. This glass has shown promise in inducing apatite formation when brought into contact with saliva or any physiological fluid. These apatites constitute either hydroxyapatites [18], or fluorapatites [19], if fluoride was incorporated into the chemical composition of the glass structure. Fluoride-containing glasses have 'smart' properties, with increased remineralization activity in low pH environments [20]. Consequently, it has variously been added to tooth-paste, prophylactic gels and dental materials to treat enamel demineralization. Nevertheless, there is limited research in relation to the effectiveness of bioactive glasses in inducing remineralization. The current systematic review therefore aims to evaluate the effectiveness of bioactive glasses in inducing enamel remineralization compared to competing topical treatment including fluoride and CPP-ACP.

2. Materials and methods

2.1. Search methodology

This systematic review was conducted in accordance with the PRISMA guidelines [21] based on a pre-defined, unpublished protocol. The research question was: How effective are bioactive glasses in inducing enamel remineralization in comparison to placebo or other topical treatments. The following selection criteria were applied:

Participants: Prospective clinical studies including randomized and non-randomized designs. In vitro studies involving assessment of enamel demineralization utilizing human teeth were also to be included.

Interventions: Use of bioactive glasses in any formulation

Comparators: Untreated control or alternative intervention to address enamel demineralization including fluoride and CPP-ACP

Outcomes: Clinical and in vitro measures of enamel remineralization

A comprehensive literature search was performed without language or date restrictions. The following databases were screened: PubMed/Medline (PubMed, www.ncbi.nlm.nih.gov), EMBASE via OVID, the Cochrane Oral Health Group's Trials Register (February 2017), the Cochrane Central Register of Controlled Trials (CENTRAL The Cochrane Library Issue 1, 2017), Literature in the Health Sciences in Latin America and the Caribbean (LILACS, February 2017). Unpublished literatures were searched using ClinicalTrials.gov (www.clinicaltrials.gov) and the National Research Register (www.controlled-trials.com) using the terms 'dental' and 'dentistry'. After identifying the potential eligible studies in the above databases, these studies were imported into Endnote ×7 software (Thompson Reuters, Philadelphia, PA, USA) to remove duplicates. In addition, the reference lists of included studies were assessed to identify further potentially eligible studies.

2.2. Study selection

The titles and abstracts of all articles identified by the electronic search were read and assessed by two authors (AT, PSF). The full text article was retrieved if the title and abstract were deemed ambiguous or when no abstract was available. All studies, which unrelated to bioactive glasses or enamel remineralization, were excluded initially on the basis of the titles and abstracts of these studies.

2.3. Data extraction

One author (AT) extracted the data using a pre-piloted data collection form, and a second author (PSF) verified data extraction independently for completeness and accuracy. Data obtained included number of teeth used, tooth type, demineralization protocol, remineralization procedures and control conditions; and approach to outcome analysis. Any potential conflict was resolved by joint discussion between the two authors.

2.4. Study quality assessment

The methodological quality of each included study was assessed independently by two authors (AT, PSF). If randomized studies were identified, the risk of bias was to be assessed using the Cochrane risk of bias tool with ROBINS-I used for non-randomized interventional designs. The methodological quality of the in vitro studies was to be evaluated using an accepted quality assessment tool for dental in vitro studies [22,23]. Specifically, studies were evaluated according to the description of randomization of teeth, presence of caries, blinding of the examiner, statistical analysis, the presence of a control group, sample preparation, outcome measures used and sample size calculation. Where the parameter was reported clearly the domain was scored as "Yes". If it was not possible to find the information, it was graded as "No". Studies that reported one to three items were classified as having a low methodological quality, four or five items as medium methodological quality and six to eight items as having high methodological quality.

Meta-analysis was to be considered if sufficient studies of high or moderate methodological quality with clinical homogeneity existed. Statistical heterogeneity was to be assessed using a chi-squared test and quantified on the basis of an I-squared statistic. The existence of publication bias was to be assessed if sufficient (> 10) clinical studies were included within a *meta*-analysis.

3. Results

3.1. Study selection and characteristics

A total of 116 potentially relevant records were identified from the database search (Fig. 1). After the removal of duplicates, 86 records were examined; 72 studies were excluded because they did not meet the eligibility criteria and 14 full-texts were assessed. Of the 14 studies retained for detailed full-text review, 3 were excluded- one review article and two in vitro studies involved bovine tooth samples. A total of 11 studies were included in this review. No clinical studies were identified; therefore, all included studies were laboratory-based. The characteristics of the included studies are summarized in Table 1.

3.2. Study quality assessment

Of the 11 in vitro studies included, four were deemed to have high and seven medium methodological quality (Table 2). In particular, blinding of the examiner was rarely reported potentially introducing a level of bias within these. In view of the lack of overlapping clinical studies, *meta*-analysis was not considered appropriate.