Universidad de Cuenca

Facultad de Odontología

Especialidad de Rehabilitación Oral y Prótesis Implanto Asistida

ESTRATEGIAS PARA LA REMINERALIZACIÓN DEL ESMALTE: UNA DESCRIPCIÓN GENERAL DE LAS REVISIONES SISTEMÁTICAS

Trabajo de titulación previo a la obtención del título Especialista en Rehabilitación Oral y Prótesis Implanto Asistida.

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Resumen

Introducción: Los agentes remineralizantes son alternativas al tratamiento bucal que inducen ganancias de minerales; por lo cual, la efectividad en el tratamiento es un campo de necesidad científica.

Objetivo: Evaluar la calidad metodológica de revisiones sistemáticas sobre efectividad en la remineralización de lesiones incipientes en el esmalte a través de diferentes métodos terapéuticos utilizando AMSTAR 2, realizando una descripción general de las revisiones sistemáticas (RS) de ensayos controlados aleatorios (ECA) y estudios in vitro.

Métodos: La búsqueda utilizó cuatro bases de datos y literatura gris. Se incluyeron RS sobre remineralización de lesiones de manchas blancas (WSL) a través de diferentes alternativas terapéuticas.

Resultados: Los resultados evaluados fueron cambios en la estructura del esmalte, incluyendo once RS. Dos estudios informaron que el fosfato de calcio amorfo de fosfopéptido de caseína (CPP-ACP) tenía un mayor potencial de remineralización que otros compuestos. Dos estudios no encontraron diferencias significativas entre CPP-ACP y agentes fluorados. Cuatro estudios informaron sobre eficacia de los agentes fluorados. Un estudio no encontró diferencias entre CPP-ACP y CPP-fosfato de fluoruro de calcio amorfo (CPP-ACFP). Tres estudios no determinaron resultados concluyentes.

Conclusiones: La calidad metodológica se clasificó como alto-riesgo de sesgo para siete RS, y moderado-riesgo de sesgo para cuatro RS. Con un nivel de confianza que va de moderado a bajo, los compuestos fluorados, los compuestos no fluorados y los compuestos combinados en ensayos controlados aleatorios muestran un potencial para remineralizar las WSL. Los compuestos no fluorados en estudios in vitro (CPP-ACP) muestran cambios significativos en la estructura del esmalte.

Palabras clave: caries del esmalte, mancha blanca, remineralización, CPP-ACP, fluoruro

Abstract

Introduction: Remineralizing agents are alternative to oral treatment that induce mineral profits; Therefore, the treatment effectiveness is of scientific necessity.

Objective: The aim of this systematic review is to evaluate the methodological quality of systematic reviews on the effectiveness in the remineralization of incipient lesions in enamel through different therapeutic methods using AMSTAR 2. An overview of systematic reviews (SRs) of randomized controlled trials (RCTs) and in vitro studies was performed.

Methods: The search was performed using four digital databases and the grey literature. SRs on the remineralization of white spot lesions (WSLs) through different therapeutic alternatives were included.

Results: The results evaluated were changes in the enamel structure. Eleven SRs were included. Two studies reported that casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) had greater remineralization potential than other compounds. Two studies found no significant difference between CPP-ACP and fluoridated agents. Four studies reported on the efficacy of fluoridated agents. One study found no difference between CPP-ACP and CPP–amorphous calcium fluoride phosphate (CPP-ACFP). Three studies did not yield conclusive results.

Conclusions: Methodological quality was classified as high risk of bias for seven SRs and moderate risk of bias for four SRs. With a confidence level ranging from moderate to low, fluoridated compounds, nonfluoridated compounds, and combined compounds in randomized controlled trials show a potential to remineralize WSLs. Nonfluoridated compounds in in vitro studies (CPP-ACP) show statistically significant changes in enamel structure, but these results should be interpreted with caution.

Keywords: enamel caries, white spot, remineralization, CPP-ACP, fluoride

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Introduction

Dental caries is a prevalent, multifactorial disease of bacterial origin,[1-3] generated by an imbalance in demineralization and remineralization processes of enamel,[4] an acellular substance that is made up of more than 95% minerals and approximately 1% organic material.[5] Enamel does not regenerate after the posteruptive process, allowing carious lesions to develop throughout life.[6]

At first, carious lesions manifest as white spot lesions (WSLs) on the enamel surface, which are a type of non-cavitated lesion with an opaque and whitish appearance.[7,8] These are located in fissures, pits, or smooth surfaces of the teeth. As demineralization progresses, the tooth surface cavitates, resulting in esthetic and functional problems.[9.10] WSLs are common in patients with orthodontic appliances, where the accumulation of bacterial plaque is evident.[11-13] Early treatment of WSLs is critical to maintaining the integrity of the tooth.[14] Therefore, as the carious lesion progresses, invasive treatments are required, involving an excessive loss of healthy dental structure, which leads to recurrent restorative cycles and considerable costs to patients, in addition to raising public health expenditures. [3]

Currently, the focus of dentistry should be the protection and preservation of dental hard tissues.[6] Remineralization alternatives have been developed, which consist of providing minerals from the surrounding environment to structures that are partially demineralized.[15]Remineralization can occur naturally or be induced by therapies that are based on supplying calcium, phosphate, and fluoride. These remineralization systems have been classified into fluoridated and nonfluoridated agents.[16] Although fluoride remains the gold standard to stop carious lesions, backed by ample scientific evidence, it does not induce the formation of organized apatite crystals, cannot penetrate the lesion, and therefore does not eliminate its opaque white appearance.[9, 15, 17]

For this reason, materials have been developed that contain active compounds such as casein phosphate phosphopeptide, amorphous calcium phosphate (CPP-ACP), and peptide 11-4, among others. Their commercial presentation is in the form of toothpaste, varnish, or mouthwash. These products are used mostly for the treatment of enamel demineralization and plaque-induced WSLs in orthodontic treatments, demonstrating great potential to regenerate the enamel microstructure.[15, 17-19]

In recent years, several systematic reviews (SRs) have evaluated the effectiveness of different treatments to remineralize the enamel of incipient lesions, with promising results

compared to fluoride. However, there are great discrepancies in the results between the individual studies, and no synthesis and general assessment of these reviews has been performed. It is important to synthesize this knowledge, an approach that can be defined as “the contextualization and integration of the research outcomes of individual studies within the broader body of knowledge on the subject”. This allows us to combine and summarize the results of multiple studies to gain accuracy in the conclusions and clarify the discrepancies between the primary studies.[20,21]

The purpose of this study was to evaluate the methodological quality of SRs about the effectiveness in remineralizing incipient lesions of enamel through different therapeutic approaches using the critical evaluation tool for SRs AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews). This paper is a synthesis of knowledge that will facilitate the delivery of relevant information, accessible to the clinician as a single document, facilitating the understanding of the topic and the interpretation of the studies within a global context.

Material and Methods

Protocol and registration

The protocol was registered in INPLASY (The International Platform of Registered Systematic Reviews and Meta-analysis Protocols), available under the number INPLASY2021100001 (doi:10.37766/inplasy2021.10.0001). This paper is based on PRIO-harms (preferred reporting items for overviews of systematic reviews including the PRISMA harms checklist).[22] Ethical approval was not required for this research.

Eligibility criteria and results of interest

The included studies were SRs of clinical and in vitro studies, with or without meta-analysis, that evaluated the effectiveness of treatments to remineralize incipient enamel lesions. The studies had to compare fluoridated and nonfluoridated compounds with different concentrations, presentations, and follow-up times. In addition, the therapeutic strategy was evaluated against a placebo were also included. At present, published results diverge about what type of treatment is the ideal for cases of incipient enamel lesions, since there are numerous materials on the market.

The studies on this topic have a high risk of bias, which hindered the selection process. We considered only SRs that reported on the efficacy of different therapeutic strategies to remineralize enamel. All included SRs had to meet the minimum criteria proposed by the Cochrane Manual for SRs [23]:

1. Clearly established objectives with predefined eligibility criteria for the studies.
2. A systematic search that attempts to identify all studies that meet the eligibility criteria.
3. An explicit and reproducible method.
4. An evaluation of the validity of the findings of the included studies, for example, through risk-of-bias assessment.
5. A systematic presentation and synthesis of the characteristics and findings of the included studies.

There were no time or language restrictions. The exclusion criteria were as follows:

1. Studies with that were not SRs (narrative reviews, rapid reviews, intervention studies, observational studies, preclinical and basic research, summaries, comments, case reports, protocols, personal opinions, letters, and posters).
2. Studies evaluating the remineralization of enamel defects such as hypomineralization and fluorosis.
3. Studies evaluating the prevention of non-established carious lesions.
4. Studies evaluating restorative techniques on incipient lesions.
5. Studies that did not meet the minimum criteria proposed by the Cochrane Manual for SRs.

Sources of information, search strategy, and additional search for primary studies

A digital search was performed on December 5, 2020, in four digital databases (PubMed, Scopus, Web of Science, Google Scholar). The grey literature was consulted through Google Scholar, in addition this database was used to obtain full texts. The reference lists of the included studies were examined for more papers. The articles found were exported to reference management software (Mendeley), and duplicate articles were eliminated. A search update was performed on August, 2022, to identify eligible studies, but this yielded no new articles that met the inclusion criteria. In addition, we contacted the author of one study but did not get a response. [24]

Selection process and data management

The identified articles were tabulated in Microsoft Excel. The studies to include were selected in two phases. In phase 1, the studies were independently screened by two reviewers (B-M A and B-C C) by reading the title and abstract. The data were verified, and disagreements were resolved by a third reviewer (D-G B).

Phase 2 consisted of reading the full text, performed independently by the two reviewers. A third reviewer (D-G B) was consulted in case of disagreements.

Data collection process

The data of the studies were collected independently in duplicate through a table previously created by two reviewers (B-M A and B-C C). The data were cross-checked, and disagreements were resolved by the third reviewer (D-G B).

Evaluation of methodological quality and quality of evidence

Two reviewers (B-M A and B-C C) independently evaluated the methodological quality of the SRs included by using the AMSTAR 2 checklist.[25] The AMSTAR 2 evaluates the methodological quality of SRs through 16 questions that can be answered by three possible answers: “yes,” “no,” or “partially yes.” The overall confidence (high, moderate, low, and critically low) rating on studies was evaluated as suggested by Shea et al.[25]: high: no or one non-critical weakness; moderate: more than one non-critical weakness; low: one critical flaw with or without non-critical weaknesses; and critically low: more than one critical flaw with or without non-critical weaknesses.[26]

Results

Data synthesis

The main data of the SRs included were summarized: author, population, intervention, primary studies, reported limitations, objectives, databases, follow-up, and conclusions (Tables 1 and 2).

Table 1. Summary of the overall descriptive characteristics of the systematic reviews included.

Author (year)	Population	Intervention	Primary studies	Mention of the following elements 1. PRISMA 2. PROSPERO 3. GRADE 4. META-ANALYSIS	Reported limitations
Asokan *et al.* (2019)	White spot lesions	CPP-ACP 10% (Tooth Mousse) CPP-ACP cream CPP-ACP 2%	RCT	1. No 2. No 3. No 4. No	Lack of reliable evidence to support the clinical effectiveness of other commercially available nonfluorinated agents
Chen *et al.* (2013)	Post-orthodontic white spots	Fluoride 50 ppm 5% fluoride 0.5% fluoride CPP-ACP CPP-ACPF	RCT	1. No 2. No 3. No 4. No	Additional high-quality studies are required, with strict eligibility criteria, a combination of specific and sensitive detection methods, and

					reliable statistical analysis.
Fernández-Ferrer *et al.* (2018)	Post-orthodontic white spots	CPP-ACP Fluoride rinses CPP-ACFP (MI Paste Plus and Tooth Mousse Plus, GC)	RCT In vivo studies	1. No 2. Yes 3. No 4. No	The evidence for a therapy of choice is scarce.
Hu *et al.* (2020)	White spots during orthodontic treatment	Sodium fluoride (NaF) Amine fluoride Regular fluoride toothpaste Acidulated phosphate fluoride (APF) Difluorosilane varnish (Dfs) High fluoride toothpaste (HFT) CPP-ACP cream	RCT	1. No 2. Yes 3. No 4. Yes	There is no consensus about the best remineralizing agents.
Imani *et al.* (2019)	White spots in	CPP-ACP CPP-ACPF	RCT	1. Yes 2. No	There is no protocol for using

	orthodontic patients during or after treatment			3. No 4. No	CPP-ACP and CPP-ACPF. Different visual impact for each observer, lack of blinding of patients and provider, small sample, and heterogeneous results.
Indrapriyadharshini *et al.* (2018)	Post-orthodontic white spots of natural origin	CPP-ACP	RCT	1. No 2. No 3. No 4. No	Well-designed RCTs are required to improve the level of evidence in this area.
Li *et al.* (2014)	In vivo white spot lesions	CPP-ACP (in any presentation)	RCT	1. No 2. No 3. No 4. No	High-quality and well-designed clinical studies are required before making definitive recommendations.
Ma *et al.* (2019)	Patients with early enamel caries Human teeth with WSLs	CPP-ACP	RCT In vitro studies	1. Yes 2. No 3. No 4. Yes	N//A

Sardana *et al.* (2019)	White spots during or after orthodontic treatment	Topical fluoride (fluoride dentifrices, mouthwashes or self-applied gels)	RCT	1. Yes 2. Yes 3. No 4. No	The inclusion of only English-language papers and the inability to perform quantitative synthesis due to the small number of studies
Sardana *et al.* (2019)	Patients undergoing fixed orthodontic treatment	Fluoride in the form of gels, foams or varnishes or applied professionally	Randomized, quasi-randomized controlled clinical trials	1. Yes 2. Yes 3. No 4. Yes	Limited number of clinical trials, more research required
Wang *et al.* (2017)	Patients at risk of caries (both sexes and all ages)	CPP-ACP gel	RCT	1. No 2. No 3. No 4. No	The small number of articles, follow-up time, design, and small sample size; longer follow-ups are required.

Table 2. Summary of the general descriptive characteristics of the systematic reviews included.

Author (year)	Objectives	Databases	Follow-up	Main conclusions
Asokan *et al.* (2019)	Evaluate the clinical effectiveness of	PubMed, Medline, IndMed,	1 year	There was a significant reduction in the quantitative light-induced

	nonfluoridated remineralizing agents in early enamel caries lesions	Cochrane, Embase and Google Scholar		fluorescence scores of WSLs after a minimal application of CPP-ACP for 4 weeks. The use of CPP-ACP over 4 months and 1 year decreased the size of WSLs and the mean score of decayed, missing, and filled surface. The use of CPP-ACP for 2 years showed the lowest increase in caries compared to fluoridated toothpaste.
Chen *et al.* (2013)	Investigate which remineralizing agents are effective for the treatment of WSLs after orthodontic treatment	PubMed, Ovid Medline, Web of Science and Cochrane Library	2 weeks-12 months	There is a lack of reliable evidence to support the effectiveness of remineralizing agents for the treatment of post-orthodontic white spot lesions.
Fernández-Ferrer *et al.* (2018)	Investigate the effectiveness of remineralization therapies for WSLs resulting from orthodontic treatment	PubMed, Embase, Scopus, Cochrane Library and Web of Science	2 weeks-6 months	Among the remineralization therapies, the only effective active agent for the remineralization of WSLs was 5% fluoride varnish professionally applied once a month for 6 months. The effect of fluoride varnish on dental

				aesthetics remains unclear.
Hu *et al.* (2020)	Compare the clinical effectiveness of different remineralizing agents in the prevention and reversal of orthodontic WSLs, providing guidance for making relevant clinical decisions.	Medline, Embase, Cochrane Central Register of Controlled Trials, Web of Science, Scopus, China National Knowledge Infrastructure (CNKI), Chongqing VIP Information, Wanfang and the Chinese biomedical literature database	0-36 months	NaF varnish was the best agent against orthodontically induced WSLs. APF foam was the best agent against orthodontic-induced WSLs, followed by the Dfs and HFT varnish. No explicit conclusions could be drawn regarding the reversal of orthodontic-induced WSLs.
Imani *et al.* (2019)	Evaluate the efficacy of CPP-ACP and CPP-ACPF for the prevention and remineralization of WSLs in orthodontic patients	Web of Science, Scopus, PubMed and Cochrane Library	1-36 months	The review revealed that both CPP-ACP and CPP-ACPF can have a positive impact on remineralization of or decrease the prevalence of WSLs during and after orthodontic treatment. Due to the small number

				of homogeneous studies, future studies are required to draw a more precise conclusion.
Indrapriyadharshini *et al.* (2018)	Evaluate the long-term remineralizing potential of CPP-ACP in comparison with fluoride varnish or placebo in WSLs of natural and post-orthodontic origin, in vivo	PubMed and Google Scholar	1-12 months	Evidence of the high remineralizing level of CPP-ACP was found in natural WSLs and post-orthodontic WSLs compared to the placebo/fluoride toothpaste and fluoride varnish; however, there was no significant difference.
Li *et al.* (2014)	Evaluate the long-term remineralizing effect (> 3 months) of CPP-ACP compared to placebo and fluorides on early caries lesions in vivo	PubMed, Web of Science, Embase, Cochrane-Central, Science Direct, CBM (Chinese Biological Medical), CNKI (Chinese National Knowledge Infrastructure)	3 months-2 years	CPP-ACP had a long-term remineralization effect in early caries lesions compared to placebo, although this effect was not significantly different from that of fluorinated agents. The clinical benefits of using CPP-ACP supplements over fluoride are still unclear.

Ma *et al.* (2019)	Perform a meta-analysis that includes clinical research and in vitro studies to determine if CPP-ACP provides more remineralizing benefit than no intervention or placebo	PubMed, Embase, and Ovid	1 day, 30 days (in vitro); 1 month, 1 year (clinical)	According to this study that analysed in vitro and clinical data, CPP-ACP exhibited an excellent remineralization of WSLs compared to the other groups, with higher WSL regression rates, lower roughness of the enamel surface, and greater recovery of surface microhardness. This indicates that CPP-ACP can effectively restore form, aesthetics, and function. Therefore, CPP-ACP seems effective for the remediation of WSLs.
Sardana *et al.* (2019)	Systematically evaluate the current literature on the effectiveness of self-applied topical fluorides in the prevention and reversal of WSLs on enamel that occur during fixed orthodontic treatment with multiple brackets	Cochrane Library, Embase, Medline, and Scopus	26-40 weeks	Although the review did not confirm the effectiveness of self-applied fluorides in the reversal of WSLs after fixed orthodontic treatment, it did partially show the positive role of self-applied fluorides in the prevention of WSLs.

Sardana *et al.* (2019)	Systematically review the effectiveness of professionally applied topical fluorides in the prevention and reversal of WSLs that occur during fixed orthodontic treatment	Medline, Embase, Cochrane library, Scopus	1-8 months	Due to the difficulties in evaluating the reversal of WSLs and mineral content, it is not clear whether professional topical fluorides effectively reverse WSL after orthodontic treatment. According to the present systematic review and the combination of data from the interpretation of the DIAGNOdent scores, it seems that professional topical fluoride reduces the mean scores of DIAGNOdent compared to the control.
Wang *et al.* (2017)	Systematic review of RCTs on enamel demineralization treatment with CPP-ACP gel to evaluate its therapeutic effect	CNKI, VIP, Wanfang, PubMed, Embase and Cochrane Library	1-18	There is no solid evidence that CPP-ACP is superior to conventional preparations containing fluoride.

Overlap

A total of 51 primary studies were covered by the SRs, approximately 39.21% of which were included in more than one SR. One study was included seven times, one study was included six times, three studies were included five times, two studies were included four times, seven studies

were included three times, six studies were included twice, and thirty-one studies were included only once. From the SRs, we extracted the data from the primary articles that had a lower risk of bias than the others.

Table 3. Overlapping of primary studies in systematic reviews.

Primary Studies	Systematic Reviews that included the primary studies	Times that primary studies were included
Andersson et al. (2007)	Asokan et al., 2019; Chen et al., 2013; Fernández-Ferrer et al., 2018; Hu et al., 2020; Indrapriyadharshini et al., 2018; Li et al., 2014.	6
Bailey et al. (2009)	Asokan et al., 2019; Chen et al 2013; Fernández-Ferrer et al, 2018; Hu et al, 2020; Imani et al., 2019; Indrapriyadharshini et al., 2018; Li et al, 2014; Wang et al., 2017.	8
Rao et al. (2009)	Asokan et al., 2019; Indrapriyadharshini et al., 2018; Li et al., 2014.	3
Brochner et al. (2011)	Asokan et al., 2019; Chen et al, 2013; Fernández-Ferrer et al, 2018; Hu et al, 2020; Imani et al, 2019; Indrapriyadharshini et al., 2018; Wang et al., 2017.	7
Sitthisettapong et al. (2012)	Asokan et al., 2019; Indrapriyadharshini et al., 2018; Li et al., 2014.	3
Memarpour et al. (2014)	Asokan et al., 2019; Indrapriyadharshini et al., 2018; Ma et al, 2019.	3
Willmot et al. (2004)	Chen et al, 2013; Fernández-Ferrer et al, 2018; Hu et al, 2020; Sardana et al., 2019.	4
Beerens et al. (2010)	Chen et al, 2013; Fernández-Ferrer et al, 2018; Hu et al, 2020; Imani et al, 2019; Indrapriyadharshini et al., 2018; Li et al., 2014.	6

Huang et al. (2013)	Fernández-Ferrer et al, 2018; Indrapriyadharshini et al., 2018; Imani et al., 2019; Sardana et al, 2019; Wang et al., 2017	5
He et al. (2016)	Fernández-Ferrer et al., 2018; Hu et al, 2020; Li et al., 2014; Sardana et al., 2019.	4
Singh et al. (2016)	Fernández-Ferrer et al., 2018; Hu et al., 2020; Imani et al., 2019; Sardana et al., 2019; Wang et al., 2017.	5
Ebrahimi et al. (2017)	Hu et al., 2020; Sardana et al., 2019.	2
Robertson et al. (2011)	Imani et al., 2019; Indrapriyadharshini et al., 2018; Li et al., 2014.	3

Review and selection of primary studies

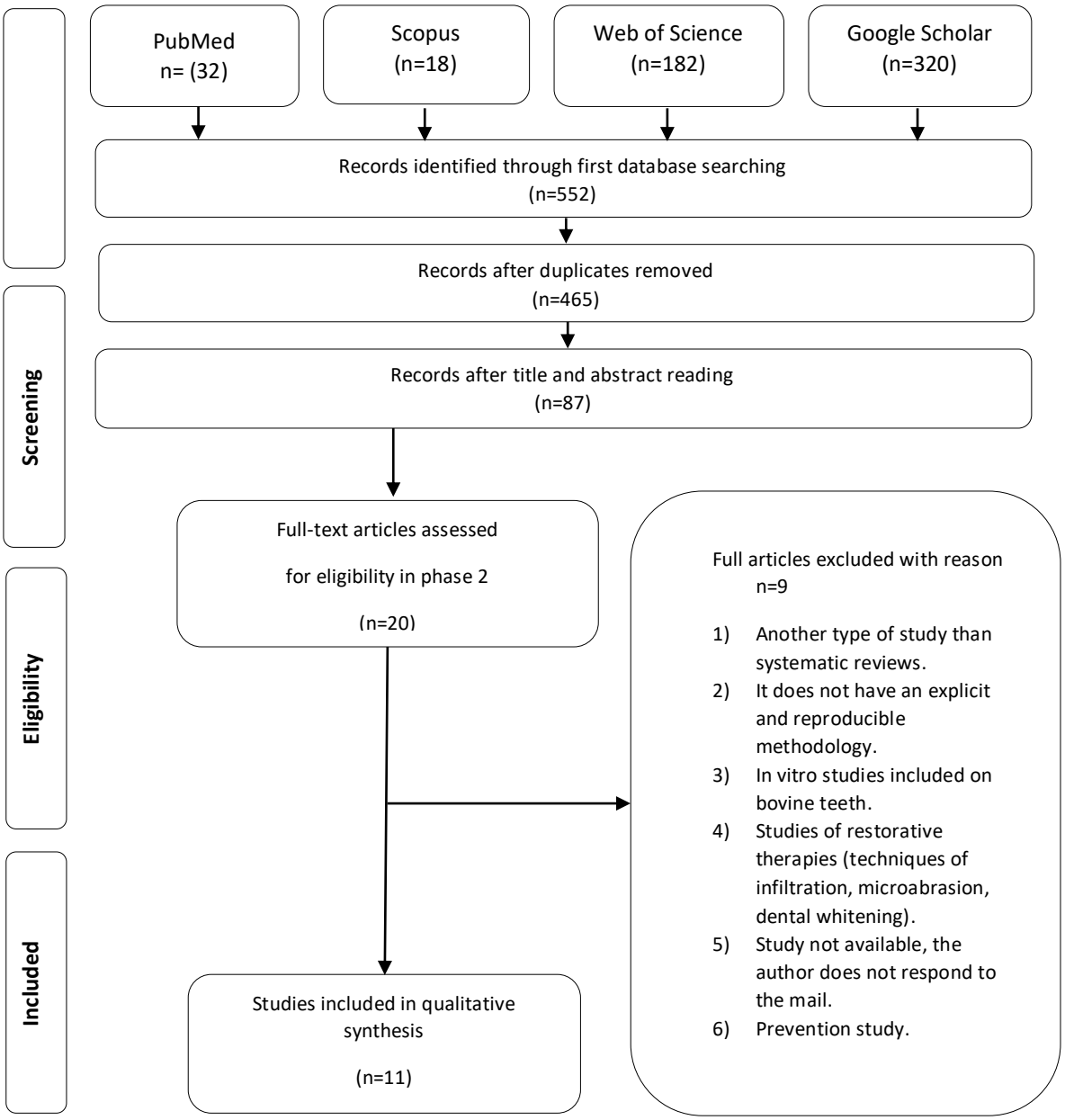
The digital database search retrieved 552 articles, including grey literature. After eliminating duplicates, 465 articles were left. In phase 1, through title and abstract screening, 20 articles were included for full-text review. In phase 2, a full-text reading was performed, and 11 articles were included for data extraction. No additional articles were found in the search update. The reasons for the exclusion of studies are:

A. Studies with methodological designs other than systematic reviews (narrative reviews, rapid reviews, intervention studies, observational studies, preclinical and basic research, abstracts, comments, case reports, protocols, personal opinions, letters and posters).
B. Studies that evaluate restoration or prevention techniques on incipient injuries.

C. The requested data is not available after 3 attempts to contact the author by email, within 30 days.

The process of the identification and selection of studies is shown in Figure 1.

Figure 1. Flow diagram of the literature search and selection criteria.



Evaluation of methodological quality and quality of evidence

Seven SRs were judged to have a high risk of bias, while the other four SRs were judged to have a moderate risk of bias. The domains considered most critical were related to whether the study included an explicit statement that the protocol was established before conducting the review (domain 2), an adequate literature search strategy (domain 4), justification of the exclusion of individual studies (domain 7), assessment of the risk of study bias (domain 9), appropriate methods for meta-analysis (domain 11), an accounting of the risk of bias when interpreting the results of the review (domain 13), and adequate investigation of the presence and likely impact of publication bias (domain 15). More information on methodological quality can be found in Figure 2.

Figure 2. AMSTAR 2.

Authors	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	Overall
Asokan et al. (2019)	-	-	+	+	+	x	X	+	+	x	NM	NM	x	x	NM	+	High risk
Chen et al. (2013)	x	-	+	-	+	x	+	+	+	x	NM	NM	x	x	x	+	High risk
Fernández-Ferrer et al. (2018)	+	-	-	+	+	x	+	+	+	x	NM	NM	x	x	NM	x	Moderate risk
Hu et al. (2020)	+	+	x	-	+	+	X	x	+	x	X	x	x	x	x	+	High risk
Imani et al. (2019)	+	-	x	-	x	+	X	-	+	x	NM	NM	x	x	NM	+	High risk
Indrapriyadharshini et al. (2018)	+	-	x	+	+	+	X	-	+	x	NM	NM	x	x	NM	+	High risk
Li et al. (2014)	x	-	+	+	+	+	X	+	+	x	NM	NM	x	x	NM	+	High risk
Ma et al. (2019)	+	+	+	-	-	+	-	+	+	x	+	x	x	+	+	+	Moderate risk
Sardana et al. (2019)	+	-	x	+	+	+	X	+	+	x	NM	NM	x	+	NM	+	Moderate risk
Sardana et al. (2019)	+	+	x	+	+	+	X	+	+	x	+	+	x	+	+	+	Moderate risk
Wang et al. (2017)	+	-	x	-	x	x	X	+	+	x	NM	NM	x	x	NM	x	High risk

Yes (+)
Partial yes (-)
No (x)
No meta-analysis (NM)

D1. Did the research questions and inclusion criteria for the review include the components of PICO?
D2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
D3. Did the review authors explain their selection of the study designs for inclusion in the review?
D4. Did the review authors use a comprehensive literature search strategy?
D5. Did the review authors perform study selection in duplicate? D6. Did the review authors perform data extraction in duplicate?
D7. Did the review authors provide a list of excluded studies and justify the exclusions? D8. Did the review authors describe the included studies in adequate detail?
D9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
D10. Did the review authors report on the sources of funding for the studies included in the review?
D11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?
D12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
D13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?
D14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
D15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
D16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Summary of results

From the SRs included in this study, the results of primary studies with low and moderate risk of bias were extracted. The results were classified into three groups: those of nonfluoridated agents, fluoridated agents, and combinations of compounds.

Nonfluoridated agents (CPP-ACP, CPP-ACFP)

Within the results table, it is indicated a positive impact on the remineralization of WSLs compared to placebo, paste without fluoride, and controls. Bailey et al. reported a significant reduction in

WSL regression with the use of CPP-ACP during a follow-up time of 12 weeks, using the ICDAS II system for evaluation. Imani et al. indicated a positive impact on the remineralization of WSLs during orthodontic treatment with the use of nonfluoridated agents (CPP-ACP, CPP-ACFP) compared to fluoride agents (fluoride varnish, fluoride rinse) and the control, with a follow-up time of 36 months. The following diagnostic methods were used: clinical examination, quantitative light-induced fluorescence (QLF), DIAGNOdent pen, photographs, and scanning electron microscopy.

Robertson et al. found a decrease in the decalcification index of the enamel with the use of CPP-ACFP compared to the placebo by means of photographs.

Bröchner et al. demonstrated through in vitro experiments that the surface roughness and surface microhardness of WSLs improved with the use of CPP-ACP over the control. However, when it was analysed by QLF, there was a reduction of 58% in the area of the WSLs on the permanent teeth after the application of the paste with 10% CPP-ACP for 4 weeks.

Sitthisettapong et al. used QLF to compare 10% CPP-ACP plus fluoride toothpaste brushing with a placebo control and reported that there were no significant results after a follow-up time of 1 year.

Rao et al. using visual indices (oral hygienic index, decayed surface index), did not find a statistically significant difference in the reduction of WSLs with the use of 2% CPP-ACP vs. sodium monofluorophosphate over a follow-up time of 24 months.

Memarpour et al. used the decayed, missing, and filled surface index and indicated that there was no significant difference in caries reduction or lesion size (measured by a probe) between CPP-ACP and fluoride varnish over a follow-up time of 1 year.

Beerens et al. used QLF to estimate lesion depth. Follow-up was performed at 12 weeks, and there was no significant difference between CPP-ACFP (MI Paste Plus) and paste without fluoride with calcium.

Andersson et al. used laser fluorescence to compare the effects of CPP-ACP and fluoride mouthwashes for 1 year. They found no significant difference between the two groups.

Li et al. found that CPP-ACP had a long-term remineralization effect on WSLs, although this effect was not significantly different from that of fluoridated agents.

Brochner et al. by QLF, showed no significant differences between the use of toothpaste with CPP-ACP and placebo toothpaste during a follow-up of 4 weeks.

Huang et al. took photographs of teeth over an 8-week follow-up, finding no significant difference in the effectiveness of CPP-ACP (MI Paste Plus) or fluoride varnish compared with the regular hygiene regimen with toothpaste in the improvement of WSLs.

Fluoridated agents

Willmot in their study, indicated that there was no significant difference in the reduction of the size of the WSL when using sodium fluoride rinse compared to a control rinse at a follow-up time of 26 weeks. The results were analysed by photography.

He et al. analysed fluoride agents using QLFs, such as fluoride varnish and 5% sodium fluoride (Duraphat), compared to a placebo control during a follow-up period of 6 months and showed that fluoridated agents were more effective in remineralization than the placebo control.

Ebrahimi et al. through photographic analysis, indicated that there is no significant difference in the use of 2% neutral sodium fluoride gel (NaF), fluoridated hydroxyapatite (Remin Pro) and CPP-ACFP.

Some studies investigated the combination of fluoridated and nonfluoridated compounds. Singh et al. through clinical examination, observed a decrease in WSLs with the use of CPP-ACP combined with fluoride varnish, finding that this combination and fluoride varnish alone are effective at remineralization compared to a non-fluoride paste.

Hu et al. compared various combinations of fluoridated and nonfluoridated compounds. There was no significant difference in remineralization. These results are summarized in Table 4.

A colour-coded visual chart was generated, where green represents no differences between the groups compared and yellow when there is a difference between the compared therapies. These results are summarized in Table 4.

Table 4: Synthesis of the results.

Authors	Primary studies	Diagnostic methods	Interventions and Comparated	Conclusions
Asokan et al. (2019) [27]	Rao et al. (2009) [28]	DS//OHI index	CPP-ACP 2% vs sodium monofluorophosphate (SMFP)	No significant difference in caries reduction.
	Bailey et al. (2009) [29]	ICDAS II	CPP-ACP vs placebo	Significant reduction in the regression of WSLs with the use of CPP-ACP.
	Memarpour et al. (2015) [30]	Lesion size in mm	CCP-ACP vs fluoride varnish	No significant difference in caries reduction.
Chen et al. (2013) [31]	Willmot et al. (2004) [32]	Photographs	Sodium fluoride (rinse) vs control rinse	No significant difference in lesion size reduction.
Fernandez-Ferrer et al. (2018) [33]	Beerens et al. (2010) [34]	QLF	CPP-ACFP (My paste plus) vs Paste without fluoride with calcium	No significant difference in the mineralization of white enamel spots.
	He et al. (2016) [35]	QLF	Fluoride varnish or 5% sodium fluoride vs Control (Duraphat)	No significant difference in readings (DIAGNOdent) between the 5% sodium fluoride

				or fluoride varnish vs control group
	Singh et al. (2016) [36]	Clinical examination	CPP-ACP +fluoride varnish vs paste with fluoride	WSLs decreased further when fluoride varnish and CPP-ACP cream were in addition to daily use of fluoride toothpaste, but the differences were not statistically significant
Hu et al. (2020) [9]			CPP-ACP cream + RFT vs RFT	No significant difference
			CPP-ACP cream + RFT vs CPP-ACFP+ RFT	No significant difference
			NaF + RFT vs NaF varnish + RFT	No significant difference
			CPP-ACFP cream + RFT vs RFT	No significant difference
			NaF + RFT vs RFT	No significant difference
			NaF + RFT vs CPP-ACFP cream+ RFT	No significant difference
			NaF + RFT vs CPP-ACP	No significant difference
Indrapriyadharshini et al et al. (2018) [37]	Sitthisettapong et al.(2012) (38)	QLF	CPP-ACP 10% with addition of regular	No significant difference

			toothbrushing with fluoridate toothpaste vs control placebo.	
	Andersson et al. (2007) [39]	Laser fluorescence	CPP-ACP vs Fluoride mouthwashes	No significant difference
	Robertson et al. (2011) [40]	Photographs	CPP-ACFP (My paste plus) vs placebo paste	Enamel decalcification index scores the MI Paste Plus group reduced by 53.5% vs placebo group.
Imani et al. (2019) [41]		Clinical examination, QLF, DIAGNOdent pen, photographs, SEM	CPP-ACP or CPP-ACFP vs control	CPP-ACP and CPP-ACPF have a positive impact on enhancing remineralization of WSL vs control.
Li et al. (2014) [42]		QLF, clinical assessment with DIAGNOdent, bitewing radiographic or visual examination	CPP-ACP vs Fluoride agents	CPP-ACP had a long-term remineralization effect on early caries lesions, although not significantly more than a fluoride agent
Ma et al. (2019) [43]	Bröchner et al. (2011) [44]	QLF	CPP-ACP vs Placebo paste without CPP-ACP	No significant difference between toothpaste with

				CPP-ACP and placebo
		Surface roughness	CPP-ACP vs Control	Significant reduction in the regression of WSLs with the use of CPP-ACP.
		Surface microhardness	CPP-ACP vs control	Significant reduction in the regression of WSLs with the use of CPP-ACP.
Sardana et al. (2019) [45]	Ebrahimi et al [46]	Photographs	2% neutral sodium fluoride gel (NaF) vs CPP-ACFP or fluoridate hydroxyapatite (Remin Pro)	No significant difference between Remin Pro, CPP-ACP, F and neutral sodium fluoride
	Huang et al. (2013) [47]	Photographs	CPP-ACP or fluoride varnish vs control	No difference in effectiveness of CPP-ACP(MI Paste Plus) or fluoride varnish vs. hygiene

QLF: Quantitative light induced fluorescence, OHI: Oral Hygenic Index, DS: decayed surface, EDI: enamel descalcification index, DMFS: decayed missing and filled surface, SEM: scanning electron microscopy, RFT: Regular Fluoride Toothpaste

Discussion

The evaluation of remineralization of incipient enamel lesions has been a topic of interest within the field of minimal intervention dentistry. For this reason, materials and strategies have been developed that promote the remineralization of white spots. Several randomized controlled trials (RCTs) and SRs have compared different therapeutic alternatives, offering evidence that supports their use. In addition, there are in vitro studies that support the use of Bioglass (BG-45S5) for the remineralization of WSL with promising results, this is an inorganic amorphous material of sodium and calcium phosphosilicate, which induces the formation of apatite on contact with the saliva. However, these are in vitro studies where artificial enamel demineralization is generated, it is not known whether this approach can be applied in the clinic. [48-50] On the other hand, there is no consensus on the effectiveness of the materials used. We performed this study to evaluate the methodological quality of SRs of the effectiveness of different therapeutic alternatives in the remineralization of incipient lesions of enamel.

Some studies on the effects of fluoridated and nonfluoridated materials have had contradictory results due to multiple factors, such as the concentrations and application protocols of remineralizing agents, different diagnostic methods, combinations of agents, and follow-up times.[45] This generates high heterogeneity, which makes it difficult to evaluate the outcomes. For this reason, this study synthesizes the information described and assesses the methodological quality.

A literature search was conducted to determine the methodological quality, since the risk of bias is unknown, which makes it difficult to draw explicit conclusions for clinical decision-making on the remineralization of WSLs. For the final analysis, 11 articles that met the inclusion criteria were considered. Of the articles included, none was considered to have a low risk of bias, since none complied with all the domains of the AMSTAR 2 tool, showing the need to perform SRs with greater methodological rigor on the subject. In the present knowledge synthesis, the methodological quality of the SRs was evaluated using the AMSTAR 2 tool to identify the quality of the primary studies they cited. No selected article addressed the sources of funding of the primary studies (domain 10), nor was risk of bias taken into account in the individual studies when interpreting/discussing the results of the review (domain 13). The inclusion of these domains in the development of future SRs is recommended.

Many SRs have studied enamel remineralization, and 39.21% of the articles included were evaluated in more than one study. It will be necessary to conduct new high-quality primary studies to overcome the methodological limitations of current SRs.

Of the remineralizing agents, we can distinguish three groups: fluoridated, nonfluoridated, and combined compounds.

With respect to the nonfluoridated agents, Bailey (2009)[29] that the use of a paste containing CPP-ACP significantly improved the regression of WSLs compared to a similar paste that did not contain CPP-ACP. The compound stabilizes calcium and phosphate ions on the tooth surface, in addition to remaining in a bioavailable form to promote the remineralization of lesions of the enamel subsurface, restoring the former appearance.[29] On the other hand, agents with concentrated fluoride should not be immediately used in post-orthodontic lesions because they make fluoride precipitate on the superficial part of the enamel, which affects its natural appearance.[41] Brochner et al. found a shrinkage of small WSLs (0.19 mm^2), but no significant difference was found between CPP-ACP and the placebo paste, which could be because the intervention period was short, and additional changes in WSLs over time cannot be ruled out.[44] In the study of Sitthisettapong et al.,[38] the percentage of reduction of the lesion area when applying CPP-ACP was lower than that reported by Bröchner et al. [44] In contrast, in the Rao (2019) study, [28] despite having a follow-up time of 24 months, no significant difference was found between 2% CPP-ACP incorporated in a toothpaste and sodium monofluorophosphate in the reversal of WSLs in children. It must be taken into consideration that the paediatric population studied could not adhere adequately to the treatment. Andersson et al. compared the effect between CPP-ACP and fluoride mouthwashes for 1 year and found no significant difference between the groups. [39]

Memarpour et al. indicated that oral hygiene along with the application of fluoride varnish or CPP-ACP during a follow-up period of 12 months reduced the size of WSLs on primary teeth and resulted in a slight increase in the values of the decayed, missing, and filled surface index, both to similar degrees. In children, the use of CPP-ACP is attractive because it helps to reduce the risk of caries.[30] Li et al. mentioned that CPP-ACP had a long-term (> 3 months) remineralizing effect in early carious lesions compared to placebo, but when comparing CPP-ACP with fluoride, there was no significant difference.[42] Similarly, Huang et al. found no significant difference between CPP-ACP (MI Paste Plus) and fluoride varnish (PreviDent). [39] Ma et al. in their SR that included in vitro studies, showed significant differences in the quantitative light-induced fluorescence, lower average surface roughness, higher Vickers microhardness and Knoop microhardness between the CPP-ACP and control groups. [43] These results indicate that CPP-ACP can effectively restore the form, esthetics, and function and ultimately remineralize WSL. It is important to mention that the included in vitro studies had uncertain risks of sequence generation and allocation masking. Therefore, the authors recommend that the results should be considered with caution.

Another compound is CPP-ACFP, which has the same potential as CPP-ACP but contains the additional benefits of fluoride. Robertson et al. revealed a decrease in the enamel decalcification index with the use of CPP-ACFP compared to placebo, [40] unlike Beerens et al., who found no significant difference in the effects of CPP-ACFP vs. paste without fluoride but with calcium. [51]

Regarding fluoridated compounds, Willmot used a combination of mouthwash-toothpaste with low fluoride content compared to a nonactive control. This study showed no significant difference in the therapeutic effect. They believed that noncompliance with the treatment regimen may explain these results. [32] He et al. demonstrated that fluoride varnish (5% Duraphat sodium fluoride) and fluoride film (5% sheer acidified sodium fluoride) were effective at remineralizing enamel around braces after orthodontics; however, there was no significant difference between the two groups. In addition, it seems that high doses of fluoride are useful for inhibiting the formation of WSLs, low doses are effective in controlling lesion progression. [35] Ebrahimi et al. used three types of compounds, MI Paste Plus, Remin Pro, and NaF, three times for 10 days to reduce the area of WSLs and increase its mineral content in children from 7 to 12 years of age. No significant difference was found between MI Paste Plus, Remin Pro, and NaF in the reversal of WSLs in children. [46]

Regarding the combined compounds, Hu et al. analysed 16 types of interventions with eight active ingredients. The evidence showed that NaF varnish combined with regular fluoride toothpaste may be better at reversing WSLs than the rest of the interventions; however, these results were not statistically significant. [9]

Implications for clinical practice

Fluoridated compounds, nonfluoridated compounds, and combined agents show potential in remineralization and represent minimally invasive treatment options against incipient carious lesions. It is important to emphasize that the opaque white appearance of WSLs improves only with nonfluoridated compounds, which is relevant in esthetic areas.

Implications for research

Through this overview, we found many SRs, but there is a need to improve their methodological quality. As a suggestion for future SRs, the use of quality assessment tools to guide their development is advised, as is the improvement of the selection criteria to obtain homogeneous results that facilitate meta-analysis. Primary studies (RCTs) with high

methodological rigor should be carried out following the Consolidated Standards of Reporting Trials guidelines, i.e., [50] improving the selection criteria, combining specific and sensitive detection methods, and providing reliable statistical analysis to obtain greater homogeneity of primary studies with similar clinical characteristics, all this we considered a limitation of evidence. Clear differentiation between the terms of prevention and reversal is recommended because these generate confusion.

In in vitro studies, there is a clear improvement of WSLs in terms of reversal; this can be because it is possible to control the study variables in vitro. RCTs have had variable results without statistically significant differences, so it is recommended to improve the methodological quality of RCTs for their clinical application.

Conclusions

Fluoridated, nonfluoridated, and combined compounds in RCTs show the potential to remineralize WSLs, but there are no significant conclusive outcomes. Nonfluoridated compounds in in vitro studies (CPP-ACP) show changes in quantitative light-induced fluorescence, lower average surface roughness, higher Vickers microhardness, and higher Knoop microhardness, with statistically significant results, but these results should be interpreted with caution. The location of the WSL, the age of the patient, and the size of the lesion should be analysed to make a clinical decision about which procedure to follow and which material to use for the remineralization of the lesion. Finally, when evaluating the studies with the AMSTAR 2 tool, a high to moderate risk of bias was evidenced, so the methodological quality and design of the studies should be improved to generate conclusive results that guide daily clinical practice.

Conflict of interest

The authors declare no competing interests.

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