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Systematic review and meta-analysis on the effect of self-assembling peptide P_{11}-4 on arrest, cavitation, and progression of initial caries lesions

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ABSTRACT

Background. Simple noninvasive evidence-based interventions for caries are needed to overcome limitations in the restorative paradigm. The self-assembling peptide P_{11}-4 is a noninvasive intervention that regenerates enamel in initial caries lesions.

Studies Reviewed. The authors conducted a systematic review and meta-analysis on the effectiveness of the P_{11}-4 products Curodont Repair (Credentis; now manufactured by vVARDIS) (CR) and Curodont Repair Fluoride Plus (Credentis; now manufactured by vVARDIS) on initial caries lesions. Primary outcomes were lesion progression after 24 months, caries arrest, and cavitation. Secondary outcomes were changes in merged International Caries Detection and Assessment System score categories, quantitative light-induced fluorescence (QLF; Inspektor Research System), esthetic appearance, and lesion size.

Results. Six clinical trials met the inclusion criteria. Results of this review represent 2 primary and 2 secondary outcomes. When compared with parallel groups, use of CR likely results in a large increase in caries arrest (relative risk [RR], 1.82 [95% CI, 1.32 to 2.50]; 45% attributable risk [95% CI, 24% to 60%]; number needed to treat [NNT], 2.8) and likely decreases lesion size by a mean (SD) of 32% (28%). The evidence also suggests that use of CR results in a large reduction in cavitation (RR, 0.32 [95% CI, 0.10 to 1.06]; NNT, 6.9) and is uncertain about lowering merged International Caries Detection and Assessment System score (RR, 3.68 [95% CI, 0.42 to 32.3]; NNT, 19). No studies used Curodont Repair Fluoride Plus. No studies reported adverse esthetic changes.

Practical Implications. CR likely has clinically important effects on caries arrest and decreased lesion size. Two trials had nonmasked assessors, and all trials had elevated risks of bias. The authors recommend conducting longer trials. CR is a promising treatment for initial caries lesions. The protocol for this systematic review was registered a priori with PROSPERO (304794).

Key Words. Meta-analysis; evidence-based dentistry; dental public health; dental caries; self-assembling peptide P_{11}-4; guided enamel regeneration.

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Globally, untreated cavitated caries lesions are the most common condition in the Global Burden of Disease studies.[1-3] Untreated caries causes disproportionate suffering in underserved populations.[4-6] The reliance of traditional oral health care on invasive, technique-sensitive treatments requiring extensive training results in a system in which fear and expense are barriers to adequate oral health care.[3,7,8] Effective and simple noninvasive interventions are needed to improve efficiency and access to care.[3,9,10]

Tooth enamel cannot regenerate once a cavitated caries lesion has formed. Caries lesions form when tooth minerals are dissolved out due to dental plaque bacteria fermenting dietary sugars into acids. Demineralization results in weakened and porous tooth structure. The first stage often is described misleadingly in the United States as a cavity, although it is not cavitated; international and American Dental Association (ADA) terminologies use the term initial caries lesion.[11-14] A tooth can have initial lesions without cavitation because of the phasic nature of demineralization and remineralization[15] combined with the hierarchical microstructure of enamel; prismatic enamel rod hydroxyapatite is more resilient to demineralization than interprismatic enamel. As a result, the area is affected but the overall structure remains. Saliva protects and heals initial lesions through cleansing, pH buffering, and remineralization. The caries lesion progresses when there is not enough protection to offset sugary diets and caries-mediating bacteria.

As demineralization progresses, the outer surface collapses, resulting in a cavitation that allows bacteria into the dentin. Without intervention, this usually leads to pain and infection. Traditional treatment involves expensive and technique-sensitive dental operative procedures to restore the damaged tooth structure; for example, a dental restoration or crown. With continued consumption of sugars and imperfect dental materials, the margin where the restoration material meets the tooth breaks down through the same caries process, and the area is retreated with a larger restoration or crown. This process is cyclic and progressive, leading to more invasive dental or surgical treatment, expense, and suffering.[3,16,17]

Interventions are available to arrest the caries process. Improved nutrition is paramount.[9] Nearly all treatments recommended by the ADA to arrest initial caries lesions work through the effects of fluoride or by physically sealing the area with dental sealants and resin infiltration.[18,19] The ADA also recommends arresting cavitated lesions with silver diamine fluoride (SDF).[18] Because cavitated lesions are more difficult to arrest owing to being infected and less cleansable, it is expected that initial lesions will be arrested with SDF. There is some evidence to support this; a case series[20] and a randomized split-mouth study[21] document lower rates of caries progression than expected. These approaches have limitations. Patient experience is a barrier, as SDF and traditional fluorides have aversive taste and SDF stains lesions black.[22-25] Dental sealants are an option but usually only for pits and fissures. Additional noninvasive therapies without these limitations are sought to complement the existing options.

Relatively new to this field is P_{11}-4, a self-assembling peptide in a brush-on liquid applied after cleaning and chemical preparation. It works via guiding and catalyzing the regeneration of lost enamel in an initial lesion. The P_{11}-4 peptide, also called Curodont Repair (Credentis; now manufactured by vVARDIS) (CR), has the amino acid sequence QQRFEWEFEQQ. It is kept separate as a lyophilized powder and rehydrated before application. The mechanism is as follows. Peptides absorb into initial lesions, wherein they self-assemble into long structures, like rungs of a ladder. This scaffold attracts and integrates calcium, phosphate, and hydroxide into hydroxyapatite. This guided remineralization process for regenerating damaged enamel shows strong results in 2 weeks in laboratory settings,[26] and studies show this process promotes bone formation via the same mechanism.[27] Research provides evidence that CR is clinically safe.[28] CR Fluoride Plus (CRFP) (Credentis; now manufactured by vVARDIS) also includes 500 ppm sodium fluoride and is registered with the US Food and Drug Administration (NDC 72247-101) as an anticaries drug under the fluoride monograph (21CFR355). CRFP has been available in the United States since 2019, and CR has been available in various European, Middle Eastern, and North African countries since 2016. There is no stain or taste.

Since its introduction, there have been numerous clinical studies of CR, and the outcomes seem supportive of an effect on arresting and shrinking initial caries lesions as measured by means of various criteria such as visual-tactile assessment, digital fluorescence measures, digital photography and radiography, and impression questionnaires. However, the reported primary outcomes are heterogenous and not always validated or of sufficient duration, and the magnitude of observed effects vary, so the efficacy of CR for the treatment of initial caries lesions has not been established thoroughly. Therefore, we conducted this systematic review to assess whether patients with initial caries lesions in permanent teeth treated with CR or CRFP compared with a randomized parallel group experience more caries arrest or less cavitation at any end point or less lesion progression after at least 24 months.

ABBREVIATION KEY

ADA:	American Dental Association.
CR:	Curodont Repair.
CRFP:	Curodont Repair Fluoride Plus.
FV:	Fluoride varnish.
ICDAS:	International Caries Detection and Assessment System.
NA:	Not applicable.
NNT:	Number needed to treat.
NR:	Not reported.
RCT:	Randomized controlled trial.
ROB:	Risk of bias.
SDF:	Silver diamine fluoride.
Tx:	Treatment.
VAS:	Visual analog scale.

METHODS

Inclusion criteria

This systematic review includes randomized controlled clinical trials and follows the methodology from the Cochrane Review Manual[29] with minor modifications described below. Certainty

assessment was performed with Grading of Recommendations, Assessment, Development and Evaluations.[30] GRADEPro software was used to summarize and integrate key information for all outcomes. We evaluated full-text reports identified from screening on the basis of the inclusion and exclusion criteria developed by the ADA Center for Evidence-Based Dentistry in the systematic review[31] for the ADA clinical practice guideline on nonrestorative treatment for caries lesions.[18] For inclusion in this review, studies had to meet the following criteria:

- Participants: patient of any age with active initial (noncavitated) caries lesions in at least 1 permanent tooth
- Intervention: application of topical CR or CRFP
- Comparisons: placebo, fluoride varnish, or no intervention
- Outcomes: Primary outcomes were caries arrest assessed via visual-tactile methods, cavitation (including restoration), and caries progression after at least 24 months (due to low reliability). Secondary outcomes were decrease in International Caries Detection and Assessment System[12,13] (ICDAS) score, with scores 1 and 2, 3 and 4, and 5 and 6 merged as in the ADA caries classification system[11] (merged ICDAS); quantitative light fluorescence[32] (excluding other quantitative methods using light, fluorescence, or thermography; for example, DIAGNOdent or the Canary System); lesion size by radiography or digital photography (continuous measures); and esthetic appearance including discoloration or stain (including report as an adverse outcome). We accepted assessment of primary and secondary outcomes at any time point except for caries lesion progression, for which we required at least 24 months.

Exclusion criteria

Exclusion criteria were adapted from the ADA guideline: not reporting outcomes on lesions existing at baseline (incidence), not a peer-reviewed article, randomization method not described, not reporting caries activity by numbers of lesions, not reporting baseline caries status, not reporting product description by brand or concentration, and articles not published in English.

Analysis

Methods for the literature search, data extraction and synthesis,[33] risk of bias assessment,[34] subgroup, and sensitivity assessment are found in the Appendix and eBox, available online at the end of this article.

RESULTS

The review was carried out according to protocol, with addition of risk difference to assess the effect of CR on decreasing merged ICDAS as an exploratory analysis, number needed to treat (NNT) as absolute to complement relative risk, and Grading of Recommendations, Assessment, Development and Evaluation certainty of evidence analysis.

Search results

We identified 193 articles from the PubMed (123) and Embase (70) searches and identified 3 articles through other sources; 55 were duplicative, resulting in 141 articles. We screened 18 articles for full-text review. We included 6 studies in the systematic review (Figure 1). Two of the included studies randomized at the patient level,[35,36] 3 randomized by side or quadrant (split-mouth),[37-39] and 1 randomized various numbers of teeth by pairs within each patient (Table 1).[40] One study[40] was not included in the meta-analyses because it did not report any outcome with control and intervention groups matched to other studies. No included studies assessed CRFP. Four clinical caries trials were excluded because they did not report baseline caries status or randomization method, and the remaining studies either did not study caries or were not clinical (eTable 1, available online at the end of this article).

Five studies were combined in meta-analyses.[35-39] The follow-up length ranged from 6 through 12 months (mean [SD], 8 [3] months). Studies included participants enrolled into groups of 9 through 70 participants (mean [SD], 38 [24]; sum [Σ]: 227). Studies involved 40 through 70 active caries lesions (mean [SD], 53 [10]; Σ: 319), of which 18 through 35 were treated with CR (mean [SD], 25 [6]; Σ: 151) and compared with a parallel group. In total, we assessed end points for 132 lesions active at baseline treated with CR (87% retention) and compared them with a parallel group. All 6 included trials reported the number of lesions that

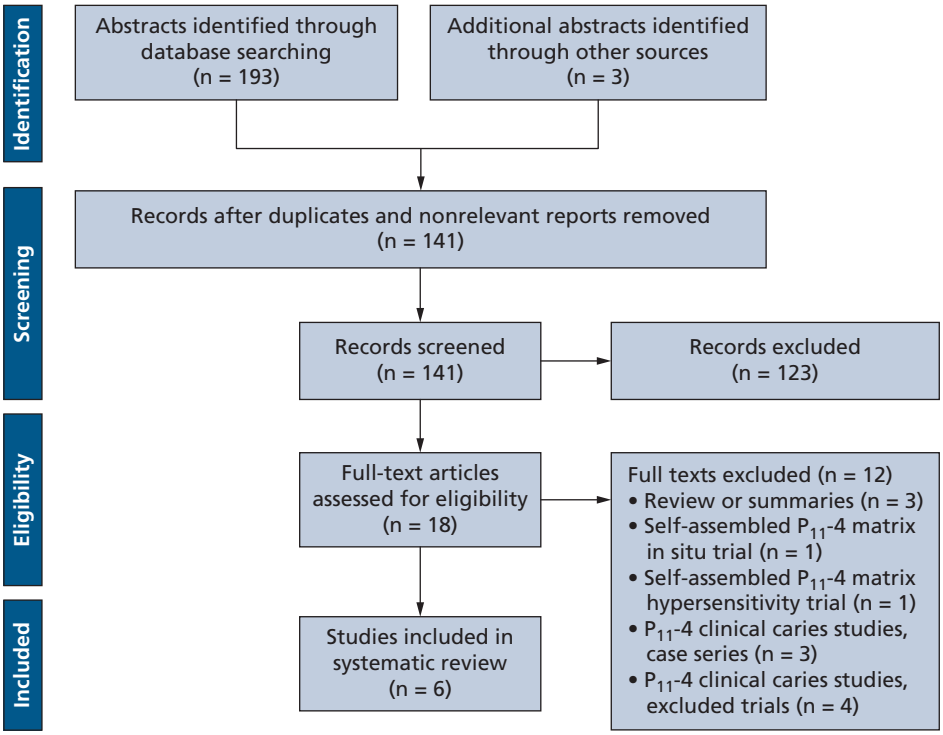

Figure 1. Flow diagram showing the process of identifying, screening, assessing for eligibility, excluding, and including articles.

progressed to cavitation (including restoration) (eTable 2, available online at the end of this article).

Bias

We assessed the overall risk of bias as moderate to high for all studies (Figure 2; eTable 4, available online at the end of this article). The risk of bias increased because of (1) lack of masking clinical and statistical personnel, (2) lack of placebo experiences or masking patients, (3) lack of prospective public trial registration or not following the registered plan, (4) missing data, and (5) differences in baseline caries levels between groups. The manufacturer coauthored and sponsored 2 trials[35,38] and sponsored another that properly handled risk of bias.[36] The remainder declared no specific funding for the trials.[37,39,40] Further details can be found in eTable 4, available online at the end of this article. Meta-analysis could not be subgrouped by risk of bias, as there were not combinable study outcomes in multiple risk categories.

Primary outcome 1: effect of CR on caries arrest

Four trials reported caries arrest; 3[35,36,38] used the Nyvad criteria,[41] and 1[37] used Lesion Activity Assessment-ICDAS.[42] Meta-analysis of caries arrest by CR compared with no treatment parallel control found a risk ratio (RR) of 1.82 (95% CI, 1.32 to 2.50) (Figure 3) across 192 lesions, meeting the clinical importance criteria. This finding translates by 1-1/RR to an attributable risk[43] of 45% (95% CI, 24% to 60%), as in the proportion of all arrested lesions treated with CR estimated to arrest due to CR. This corresponds to an NNT of 2.8 teeth to result in caries arrest of 1 lesion that would not have happened without the treatment.

Two trials showing the largest effect had nonmasked assessment of outcomes,[35,36] which poses a risk of bias. These 2 studies are also the only patient-randomized (non–split-mouth) studies and the only ones to combine fluoride varnish with CR during the intervention (Table 1) (the study[38] with fluoride varnish application in all participants 90 days after the intervention was seen as not combining fluoride varnish with CR). They are also the only 2 trials to assess treatment of occlusal surfaces, whereas all 4 other included trials studied smooth surfaces (nonapproximal). Subgroup analysis found an RR of 2.30 (95% CI, 1.62 to 3.26) for the fluoride varnish—nonmasked—patient-randomized trials, whereas the other group had an RR of 1.30 (95% CI, 0.84 to 2.02), suggesting there may be a difference in treatment effect between these groups ($P = .05$; Figure 3).

Table 1. Characteristics, enrollment, and retention of CR* clinical trial reports included in this systematic review

STUDY	YEAR	CONTROL GROUP	FV† IN ALL (DAYS FROM BASELINE)	SURFACE	STUDY DESIGN	FOLLOW-UP, MO	PATIENTS ENROLLED, NO.		LESIONS ENROLLED, NO.			
							Enrolled‡	Assessed at End	Lesions	CR*	FV	Control
Alkilzy and Colleagues[36]	2018	No Tx§	0, 90	Occlusal	Randomized controlled trial	6	70	62	70	35	NA¶	35
Gözetici and Colleagues[37]	2019	No Tx, FV	No	Facial	Split mouth with 4 teeth per patient, each tooth in 1 group	6	21	20	63	21	21	21
Doberdoli and Colleagues[35]	2020	No Tx	0, 180	Occlusal	Randomized controlled trial	12	60	52	60	30	NA	30
Kobeissi and Colleagues[40]	2020	FV	No	Facial	Split mouth with variable pairs of teeth in each patient allocated to 2 groups	6	9	9	40	20	20	NA
Kondelova and Colleagues[38]	2020	Placebo	90	Facial	Split mouth with 2 teeth per patient, each tooth in 1 group	9	44	40	88	44	NA	44
Welk and Colleagues[39]	2020	No Tx	No	Facial	Split mouth with 2 teeth per patient, each tooth in 1 group	6	23	21	46	23	NA	23

* CR: Curodont Repair (Credentis; now manufactured by vVARDIS). † FV: Fluoride varnish. ‡ Enrollment excludes treatments not considered in this review. § Tx: Treatment. ¶ NA: Not applicable.

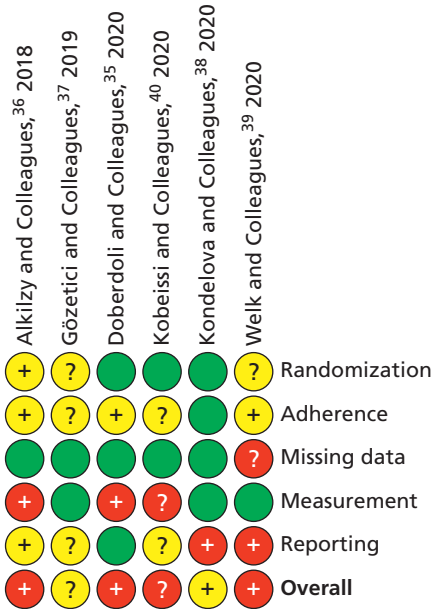

Figure 2. Summary of bias risk across included clinical trials. Colors indicate the level of risk (red is high, yellow is moderate, green is low), and symbols indicate perceived direction of bias toward (+), unclear (?), or against (−) the intervention (this is different from traditional representation). Details are available in eTable 3.

Subgroup analysis suggests there may be no difference in treatment effect of study duration on caries arrest ($P = .87$) (eFigure 1, available online at the end of the article).

Heterogeneity was low for this and all assessments.

Primary outcome 2: effect of CR on cavitation

All studies reported on cavitation, but only 3 observed any occurrence; these studies were 6, 6, and 12 months in duration.[35,36,39] Meta-analysis of reducing cavitation with CR compared with control

Table 1. (Continued)

BASELINE-ACTIVE LESIONS ENROLLED, NO.				LESIONS ASSESSED, NO.				BASELINE-ACTIVE LESIONS ASSESSED, NO.			
Lesions	CR	FV	Control	Lesions	CR	FV	Control	Lesions	CR	FV	Control
70	35	NA	35	62	30	NA	32	62	30	NA	32
52	18	17	17	60	20	20	20	49	17	16	16
55	29	NA	26	52	27	NA	25	47	26	NA	21
40	20	20		40	40	20	NA	40	20	20	NA
56	26	NA	30	80	40	NA	40	50	22	NA	28
46	23	NA	23	34	17	NA	17	34	17	NA	17

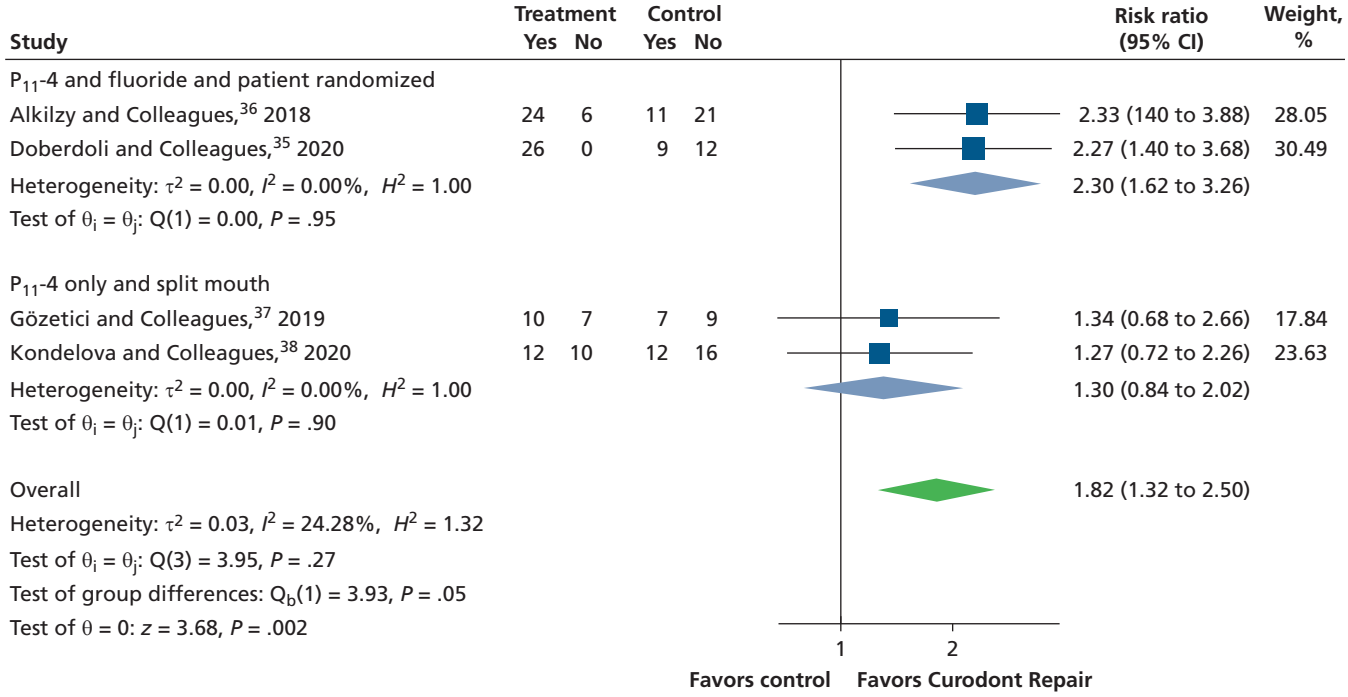

Figure 3. Meta-analysis of caries arrest in randomized controlled trials of Curodont Repair (Credentis; now manufactured by vVARDIS) vs parallel no treatment control from 6 through 12 months. Subgroups show (1) the effect of fluoride varnish in both Curodont Repair and control groups at the baseline intervention and (2) patient randomization (P_{11}-4 and fluoride) vs split mouth (P_{11}-4 only) on caries arrest. These 2 factors result in the same delineation between studies. These studies also group identically by having unmasked assessors and being performed in occlusal surfaces (P_{11}-4 and fluoride), and masking assessors and being performed in smooth surfaces (P_{11}-4 only).

found an RR of 0.32 (95% CI, 0.10 to 1.06) (Figure 4) across 143 lesions. This corresponds to an NNT of 6.9 teeth to prevent 1 cavitation. Lack of cavitation in the other 3 studies likely represents underestimation of effect, owing to outcomes that would be captured accurately in longer studies.[37,38,40]

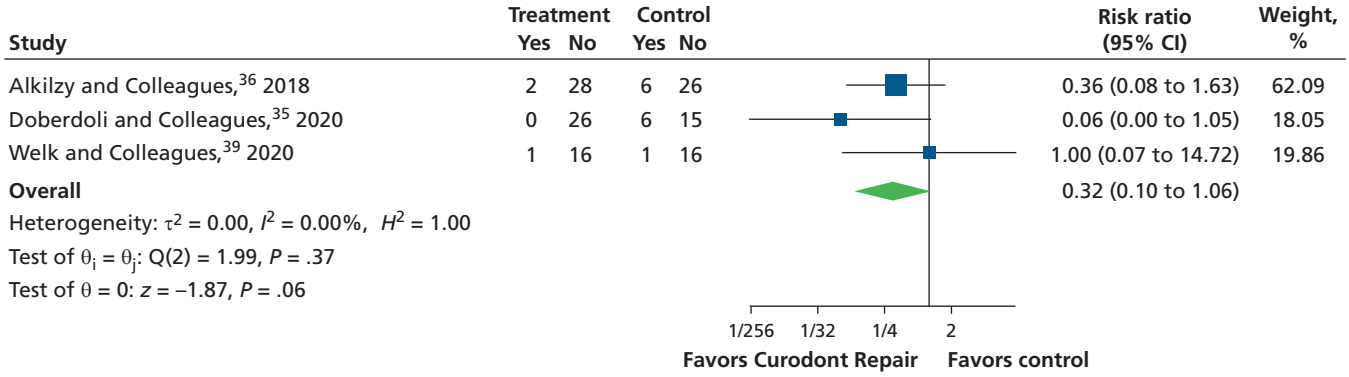

Figure 4. Meta-analysis of preventing cavitation in randomized controlled trials of Curodont Repair (Credentis; now manufactured by vVARDIS) vs parallel no treatment control from 6 through 12 months.

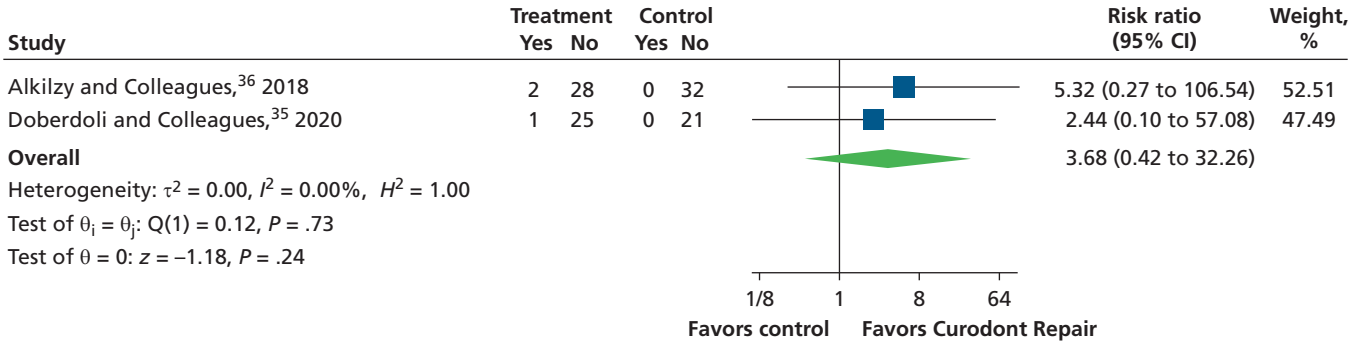

Figure 5. Meta-analysis of decrease in merged International Caries Detection and Assessment System score in randomized controlled trials of Curodont Repair (Credentis; now manufactured by vVARDIS) vs parallel no treatment control from 6 through 12 months.

Secondary outcome 1: effect of CR on decrease in merged ICDAS

Three trials reported change in ICDAS score[35,36,40] and were assessed via the merged criteria, with a change from 3 through 0, 1, or 2; 1 through 0; or 2 through 0 qualifying as a decrease. In the published article for 1 study,[40] the ICDAS outcomes were duplicated errantly across both groups, which are incorporated accurately and available in our review (eFigure 2, available online at the end of this article). Meta-analysis found the RR for decreasing merged ICDAS by CR compared with no treatment parallel control as 3.68 (95% CI, 0.42 to 32.26) (Figure 5) across 109 lesions. This corresponds to an NNT of 19 teeth to result in decreased merged ICDAS. The large CI occurs because of 0 events in the control group. Accordingly, we calculated the risk difference (0.05; 95% CI, −0.01 to 0.11) (eFigure 3, available online at the end of this article).

The included study[40] that does not have groups matching other studies (not represented in meta-analyses) had an RR of 1.15 for CR compared with fluoride varnish for a decrease in merged ICDAS (95% CI, 0.77 to 1.74).

Secondary outcome 2: effect of CR on lesion size

Two trials reported change in lesion size measured via automated software from digital photography.[38,39] Meta-analysis revealed a standardized mean difference in favor of CR treatment compared with no treatment parallel control, reducing caries lesion surface size by a mean (SD) of 32% (28%) with respect to baseline, with an effect size compared with control of −0.59 (Hedges *g*; 95% CI, −1.03 to −0.15; Figure 6) across 81 lesions, meeting the clinical importance criteria.

Other outcomes

No trials were long enough to measure caries progression. No trials used quantitative light-induced fluorescence (QLF; Inspektor Research System) as an outcome measure. No included trials reported on esthetic appearance, although 1 excluded trial reported on color change assessed through a spectrophotometer.[44]

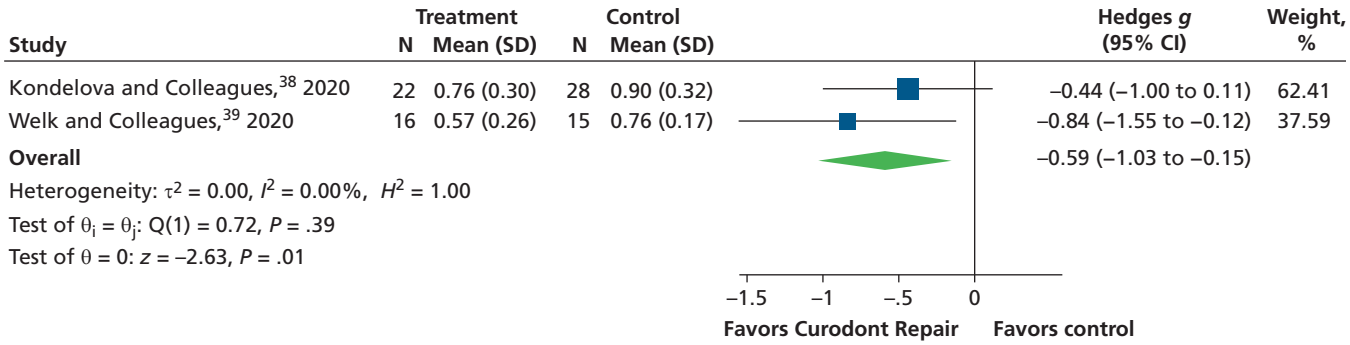

Figure 6. Meta-analysis of decrease in caries lesion surface size (proportion relative to baseline) in randomized controlled trials of Curodont Repair (Credentis; now manufactured by vVARDIS) shows an effect vs parallel no treatment control from 6 through 12 months.

Adverse outcomes

Four included trials reported no adverse outcomes,[35,36,38,40] 2 of which explicitly measured them.[36,38] One excluded case series involving 15 healthy adults reported 1 patient with dentin hypersensitivity and 1 with new sensitivity from a chlorhexidine mouthrinse.[28] No studies reported adverse esthetic changes.

Certainty of evidence

We summarized the effects of CR vs control and the certainty of the evidence for all outcomes in Table 2 (elaborated in eTable 4 available online at the end of this article).

DISCUSSION

This systematic review and meta-analysis found that CR likely has clinically important effects on initial caries lesions. CR likely results in a large increase in the primary outcome of caries arrest. Overall, 73% of all CR-treated caries lesions were anticipated to arrest (Table 2). For 45% of these arrested caries lesions, the arrest could be attributed to the effect of CR (55% due to other factors). In other words, considering all CR-treated teeth, 33% of caries lesions were anticipated to arrest that would not have arrested without CR. The evidence suggests that CR results in a large reduction in the primary outcome of cavitation. The evidence is very uncertain about the effect of CR on the secondary outcome of lowering merged ICDAS. Longer studies could show stronger results for prevention of cavitation and regression in merged ICDAS, as we expect these outcomes to take longer than the duration of these trials. For the secondary outcome of effect on lesion size, this work found that CR likely shrinks caries lesions, with all masked assessors.

The clinical implications of these results are uncertain because of moderate to high risk of bias and imprecision. The 2 studies that were masked and had moderate risk of bias showed effects with CIs overlapping an outcome of no clinical importance, whereas the 2 studies with high risk of bias and lack of masking supported a clinically important caries arrest outcome. It is possible to mask assessors as well as all providers, patients, and statisticians in trials of CR. The 2 studies contributing the decreased lesion size result had masked assessment.[38,39] Researchers can and should conduct masked CR trials that are longer and larger and in populations with higher caries activity. Nonetheless, nonmasked studies have led to important progress in oral health care, such as SDF affecting the patient-centered outcome of avoiding general anesthesia.[45-47]

These limitations are similar to those for the studies included in the systematic review and network meta-analysis underlying the ADA clinical practice guidelines for nonrestorative caries treatment.[18,31]

There are few therapeutic agents for caries; however, 10 clinical trials show an anticaries effect via CR.[35-40,44,48-50] Some of these studies did not meet the selection criteria, and the ones that did were at a moderate to high risk of bias. Other evidence-based brush-on therapies include traditional fluorides, sealants (including resin infiltration), and SDF (including silver nitrate and fluoride varnish).[18,51]

Limitations

We were not able to contact the authors of the excluded CR caries trials, but they could have the missing data necessary for inclusion in this review.

Table 2. Summary of findings for comparison of CR* with control for treating initial caries lesions.

OUTCOMES	FOLLOW-UP, RANGE, MO	ANTICIPATED ABSOLUTE EFFECTS†		RELATIVE EFFECT (95% CI)	PARTICIPANTS, NO. (STUDIES, NO.)	CERTAINTY OF THE EVIDENCE (GRADING OF RECOMMENDATIONS, ASSESSMENT, DEVELOPMENT AND EVALUATIONS[30])	COMMENTS
		Risk With Control	Risk With CR (95% CI)				
Primary: Caries Arrest, via Visual-Tactile Assessment	6-12	402 per 1,000	732 per 1,000 (531 to 1,000)	RR,‡ 1.82 (1.32 to 2.50)	192 (4 RCTs§)	Moderate¶,#	CR likely results in a large increase in caries arrest.
Subgroup: Caries Arrest With Fluoride Varnish at Same Visit, via Visual-Tactile Assessment	6-12	377 per 1,000	868 per 1,000 (611 to 1,000)	RR, 2.30 (1.62 to 3.26)	109 (2 RCTs)	Moderate¶,#	CR with fluoride varnish during the intervention visit likely results in a large increase in caries arrest.
Subgroup: Caries Arrest With No Fluoride Varnish at Same Visit, via Visual-Tactile Assessment	6-9	422 per 1,000	549 per 1,000 (355 to 853)	RR, 1.30 (0.84 to 2.02)	84 (2 RCTs)	Low¶,#,**	The evidence suggests CR without fluoride varnish increases caries arrest.
Primary: Less Cavitation, (Lower Is Better), via Diagnosis or Restoration	6-12	186 per 1,000	59 per 1,000 (19 to 197)	RR, 0.32 (0.10 to 1.06)	143 (3 RCTs)	Low¶,#,**	The evidence suggests that CR results in a large reduction in cavitation.
Primary: Caries Lesion Progression	No studies reported this outcome			NR††	NR	NR	NR
Secondary: Lesion Size (Lower Is Better) via Photometry	6-9	The mean was 15% shrinking of normalized lesion size	Hedges *g*, –0.59 (–1.03 to –0.15) Mean difference, 17% points more shrinking of normalized lesion size (4%-30% points more shrinking)	NR	84 (2 RCTs)	Moderate#	CR likely shrinks caries lesions.
Secondary: Lowers Merged International Caries Detection and Assessment System Categories by 0, 1-2, 3-4, 5-6 Criteria	6-12	0 per 1,000	54 per 1,000 (–5‡‡ to 167)	RR, 3.68 (0.42 to 32.26)	109 (2 RCTs)	Very low¶,#,§§,¶¶,##	The evidence is very uncertain about the effect of CR on lowering merged International Caries Detection and Assessment System.
Secondary: Quantitative Light-Induced Fluorescence (QLF; Inspektor Research System)	No studies reported this outcome			NR	NR	NR	NR
Secondary: Esthetic Appearance	No studies reported this outcome			NR	NR	NR	NR

* CR: Curodont (Credentis; now manufactured by vVARDIS). † The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). ‡ RR: Risk ratio. § RCT: Randomized controlled trial. ¶ Studies had nonmasked assessors. # No trials had prior registration or analysis plan. Some industry sponsorship. Some unconventional published analysis, but sufficient data reporting to enable standard by group comparison here. ** 95% CI suggests that people undergoing the treatment may experience a large benefit and a negligible harm. †† NR: Not reported. ‡‡ Unrealistic estimation due to 0 control events. §§ Surrogate outcome. ¶¶ Studies not powered to detect difference. ## 95% CI suggests that people undergoing the treatment may experience a large benefit and a large harm.

Absolute size from 1 trial[39] was normalized with respect to baseline size to match the scale of the other and thereby enable combination through meta-analysis. The measurement technique in the other study[38] did not enable conversion to the absolute size needed to assess the contrast effect, but focus on normalized change brings limitations.[52]

Comparison to other reviews

The caries arrest outcome (RR, 1.82; 95% CI, 1.32 to 2.50) is in the range of significant effects for nonrestorative treatments on specific surface noncavitated lesions in the ADA clinical practice guidelines, such as fluoride varnish (RR, 2.05; 95% CI, 1.63 to 2.60), acidulated phosphate fluoride (RR, 2.13; 95% CI, 1.79 to 2.54), sealants (RR, 1.84; 95% CI, 1.35 to 2.52), and resin infiltration (RR, 1.82; 95% CI, 0.90 to 3.68) vs no treatment.[18]

The systematic review found in our review similarly reported positive effect estimates.[53] It represents only 1 trial for caries arrest and not the 3 others reported here. Data for 1 study were overrepresented by an order of magnitude for lesion size. A conflict of interest was not disclosed: the department head of all authors is the primary patent holder for Icon (DMG) infiltration resin (patent US8686063B2), a directly competitive product.

Implications for research

This meta-analysis suggests that longer or larger trials may show clinically important effects across cavitation and decrease in merged ICDAS. We expect clinical trials of caries progression to last at least 24 months.[54-57] However, caries arrest trials can show an effect after just 2 weeks.[58] The trials here ranged from 6 to 12 months. Trials should also assess whether reapplication is beneficial or necessary to maintain or build effect over time, as it is with SDF.[59]

The combined effect of CR and simultaneous fluoride might be synergistic beyond that of P_{11}-4 alone or fluoride varnish alone. Two trials comparing fluoride varnish with CR[35,36] to fluoride varnish only had a larger CR caries arrest risk ratio than those with no fluoride in either group. The group treated with CR only had lower risk ratios for caries arrest than fluoride varnish only, whereas groups treated with both CR and fluoride varnish had higher risk ratios than fluoride varnish only. Therefore, we may expect enamel regeneration incorporating fluoride to be more successful than not. Trials to determine whether CR acts synergistically with fluoride should be done, perhaps by comparing CR with CRFP or CR with CR without fluoride varnish. The effect of other potentially mechanistically complimentary materials such as antimicrobial agents should be assessed in clinical trials as well. The studies on occlusal lesions showed a strong effect on caries arrest. The studies showing an effect on lesion size were on facial lesions (anterior, posterior). We recommend conducting studies to determine the respective effects on the converse surfaces and on approximal surfaces.

Implications for practice

The effects on promoting caries arrest and decreasing lesion size suggest that CR is a viable treatment option for initial caries lesions alongside other evidence-based interventions for initial caries lesions. This finding is a clinically meaningful addition beyond the effect of behavior change and other preventive interventions.

International guidance for caries management has been building. The International Caries Classification and Management System Guide[60] distills best evidence into recommendations supported by an FDI World Dental Federation policy statement and packaged by CariesCare International[61] into a practice-friendly format that engages patients as long-term health partners and uses a 4D cycle: Determine risk, Detect disease, Decide on a personalized care plan, and Do the tooth-preserving care. Caries management via CR fits well within this overall care framework.

Expanding noninvasive treatment options for initial lesions has the promise of improving outcomes. For example, a school program of dental hygienists applying SDF, sealants, fluoride varnish, 10% povidone-iodine, and glass ionomer without excavation decreased general anesthesia use by 69%.[46] Considering that over 90% of dentists report routinely restoring initial caries lesions,[62,63] despite international guidelines concluding that this does more harm than good,[64] having another noninvasive alternative would benefit patients. Reorienting oral health services toward noninvasive care has economic benefits.[65] Reimbursement at a lower rate than restorations and performed by nondentist dental team members would benefit payers, dental teams, and patients.

CRFP, the product available in the United States, is identical to the international product except it contains 500 ppm sodium fluoride. Therefore, the generalizability of these results within the United States is unknown.

CONCLUSIONS

This systematic review and meta-analysis provides evidence that CR is likely effective for arresting initial (noncavitated) caries lesions across 4 studies and for reducing lesion size across 2 studies. Further research is needed to clarify the effects on preventing cavitation and merged ICDAS. All 6 included trials have moderate to high risk of bias. Longer trials with low risk of bias and study of potential synergistic effects with CR and fluoride or antimicrobial agents are recommended. CR is an addition to the pharmacopeia for the most common disease in humans, caries.[1] ■

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at: https://doi.org/10.1016/j.adaj.2023.03.014.

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CareQuest Innovation Partners in collaboration with CareQuest Institute for Oral Health led the development and authorship of this systematic review and meta-analysis in collaboration with an expert panel. The expert panel informed and reviewed all aspects of the study protocol before registration. All coauthors voted on each of 23 aspects of the study plan. They discussed items with less than 80% agreement until this level of consensus was reached. They shared and reviewed all included studies, extracted data, and bias interpretations regularly with all coauthors. All coauthors contributed to and reviewed the final manuscript.

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APPENDIX. DESCRIPTION OF METHODS FOR LITERATURE SEARCH, DATA EXTRACTION AND SYNTHESIS, RISK OF BIAS ASSESSMENT, SUBGROUP, AND SENSITIVITY ASSESSMENT.

METHODS

Literature search

A medical librarian (K.V.) developed a search strategy for English language articles. We performed the search strategy in PubMed with the following query: (self-assembling peptide OR Curodont OR "P(11)-4" OR "P11-4" OR CH3CO-QQRFEWEFEQQ-CONH2 OR 72247-101-12 OR "P11-4 peptide"[nm]) AND ((Dental Caries[MeSH Terms]) OR (dental decay OR carious lesion* OR dental white spot* OR white spot lesion* OR WSL OR cavit* OR initial cari* lesion* OR non-cavitated caries OR incipient OR early carious lesion* OR early caries lesion* OR enamel lesion* OR enamel caries lesion* OR incipient carious lesion* OR caries lesion* OR cari*). We performed an identical search in Embase. We ran searches for all articles published from database inception through November 19, 2021.

The team assessed citations within all identified clinical trial articles and reviewed additional studies. We also contacted the manufacturer of Curodont Repair (CR) (vVARDIS) to request knowledge of any additional trials. Two contributors (L.J.S., J.H.K.) independently screened titles and abstracts of studies identified from the search in duplicate based on the inclusion and exclusion criteria. These contributors also conducted a full-text review independently and in duplicate. For both the title and abstract review and the full-text review, contributors resolved disagreements via discussion and development of consensus.

Data extraction

Two contributors (L.J.S., J.H.K.) independently extracted data in duplicate from included studies using specially developed data extraction forms (Table 1; eTable 2). They collected data regarding primary and secondary outcomes, baseline caries activity status, diagnostic criteria and methodology, randomization and allocation process, adherence to allocation, missing data, measurement methodology, blinding of assessors, reporting for risks of bias, intervention details for all groups, background exposure (for example, fluoride), and adverse outcomes.

For 3 trials, we contacted study authors who provided separated outcome data for lesions reported as active by visual-tactile criteria at baseline.[35,37,38] For another, we contacted authors who provided raw lesion size data[39] to make them combinable with the other study reporting this outcome.[38] We extracted and compared data. The team resolved disagreements via discussion and consensus.

Risk of bias

After calibration, 2 contributors (L.J.S., J.H.K.) independently and in duplicate assessed the risk of bias of each included study against key criteria using the Cochrane Risk of Bias tool 2.0[34]: randomization, effect of assignment, missing outcome data, measurement, and selective reporting. The 2 authors resolved disagreements via consensus and consulted a third author (J.F.H.) as necessary.

Data synthesis

We conducted a meta-analysis of studies with combinable results, using Stata version 17 (StataCorp; eBox). We calculated risk ratios and 95% CIs from raw numbers for dichotomous outcomes. We also calculated pooled risk ratio estimates using a random effects model that uses inverse variance methods to assign more weight to larger rather than smaller studies and accounts for both within- and between-study variability.[33] Number needed to treat was calculated with the outcomes of the control groups used for the baseline risks. For continuous outcomes, we calculated summary effect size using the Hedge's g statistic for standardized mean differences. We estimated heterogeneity using the I^2 statistic (> 50% was considered substantial) and the Cochrane Q test. Change in lesion size relative to baseline was assessed to standardize across relative and absolute data. The clinical importance threshold from the American Dental Association guideline was used: greater than 10% from null.

No adjustments were made for split-mouth data. Data were combined across parallel no treatment or placebo groups in which treatment with Curodont Repair (Credentis; now manufactured by vVARDIS) or Curodont Repair Fluoride Plus (Credentis; now manufactured by vVARDIS) was the only difference but not with other interventions such as fluoride varnish. When fluoride varnish was applied to both intervention (Curodont Repair or Curodont Repair Fluoride Plus) and control groups, this was considered a no treatment parallel control group.

SUBGROUP AND SENSITIVITY ANALYSES

We planned subgroup analyses a priori as follows: study design (split mouth vs parallel arm); effect of study duration on outcome; immediate treatment with fluoride in experimental and control groups or not; and baseline lesion size by depth, merged International Caries Detection and Assessment System, physical size by photograph or radiograph, or quantitative light-induced fluorescence (QLF; Inspektor Research System) scores. Sensitivity analyses were to be done if there were outliers, to determine the effect on summary estimates.

eBox. Statistical analysis programming script written for STATA.

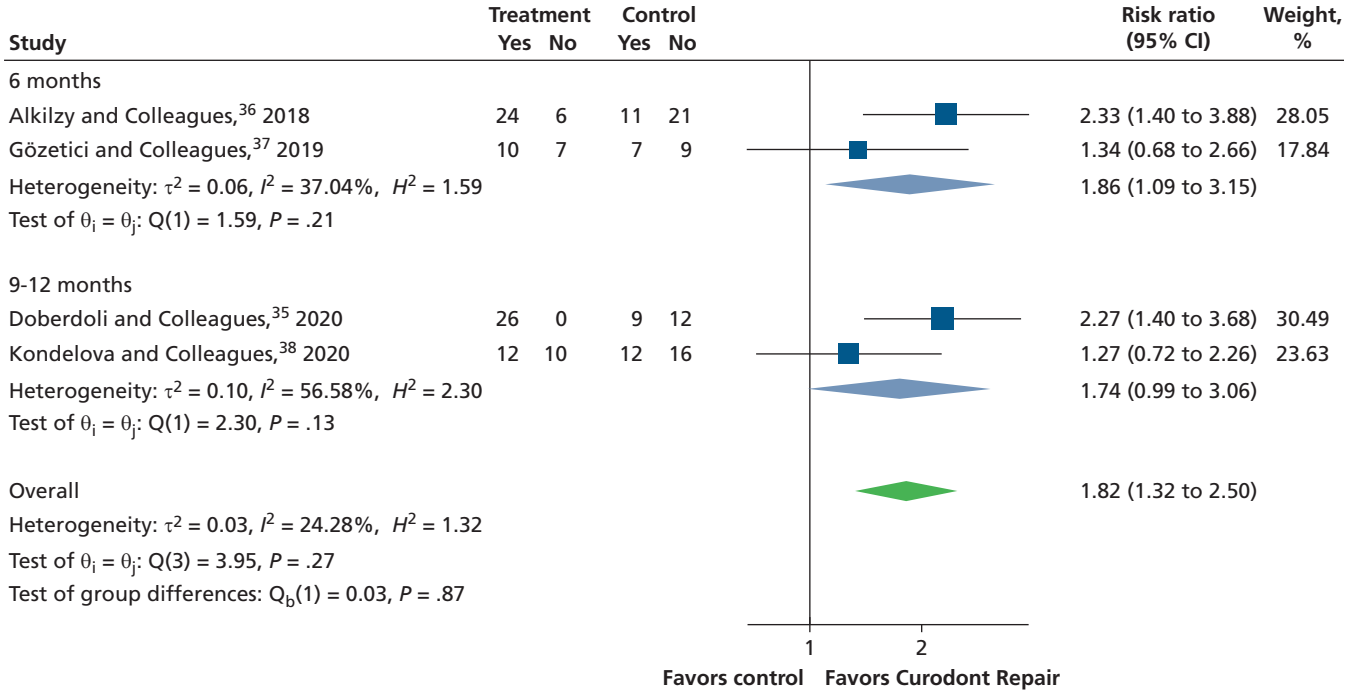
```
**********************************CARIES ARREST**********************************

import excel "CurodontTrials\Meta analysis.xlsx", sheet("Caries Arrest") firstrow

meta esize nst nft nsc nfc, esize(lnrratio)
replace _meta_studylabel= Author
replace _meta_studylabel = "Alkilzy, 2018" in 1
replace _meta_studylabel = "Gözetici, 2019" in 2
replace _meta_studylabel = "Doberdoli, 2020" in 3
replace _meta_studylabel = "Kondelova, 2020" in 4

meta summarize, rr
meta forestplot, rr

meta esize Yes_t No_t Yes_c No_c, esize(lnrratio)
replace _meta_studylabel= Author
replace _meta_studylabel = "Alkilzy, 2018" in 1
replace _meta_studylabel = "Gözetici, 2019" in 2
replace _meta_studylabel = "Doberdoli, 2020" in 3
replace _meta_studylabel = "Kondelova, 2020" in 4

meta summarize, rr
meta forestplot, rr

/*Define subgroups*/
generate str subgroup1a = "P11-4 + fluoride" in 1
replace subgroup1a = "P11-4 + fluoride" in 3
replace subgroup1a = "P11-4 only" in 2
replace subgroup1a = "P11-4 only" in 4

generate str subgroup1b = "Parallel arm" in 1
replace subgroup1b = "Parallel arm" in 3
replace subgroup1b = "Split mouth" in 2
replace subgroup1b = "Split mouth" in 4

generate str subgroup1c = "Non-blinded" in 1
replace subgroup1c = "Non-blinded" in 3
replace subgroup1c = "Blinded" in 2
replace subgroup1c = "Blinded" in 4

generate str subgroup2 = "6 months" in 1
replace subgroup2 = "6 months" in 2
replace subgroup2 = "9-12 months" in 3
replace subgroup2 = "9-12 months" in 4

meta summarize, subgroup(subgroup1a) rr
meta forestplot, subgroup(subgroup1a) rr
graph export "CurodontTrials\Subgroup1A.png", as(png) name("Graph")

meta summarize, subgroup(subgroup1b) rr
meta forestplot, subgroup(subgroup1b) rr
graph export "CurodontTrials\Subgroup1B.png", as(png) name("Graph")
```

eBox. Continued

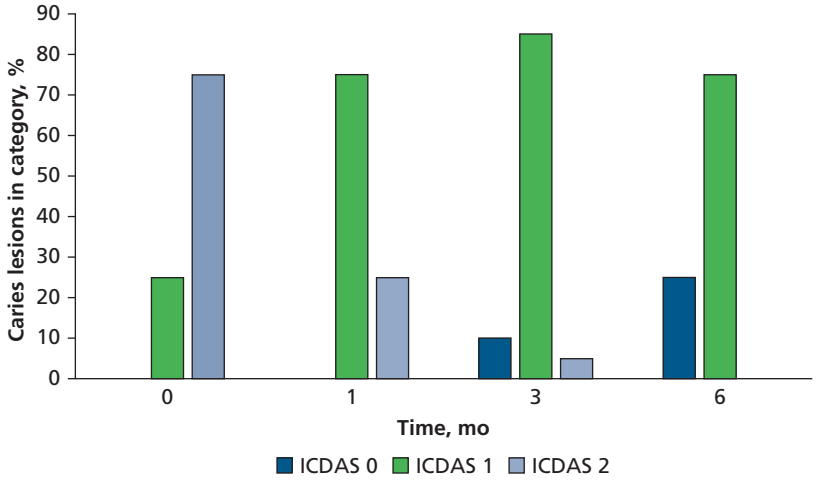
```
meta summarize, subgroup(subgroup1c) rr
meta forestplot, subgroup(subgroup1c) rr
graph export "CurodontTrials\Subgroup1C.png", as(png) name("Graph")

meta summarize, subgroup(subgroup2) rr
meta forestplot, subgroup(subgroup2) rr
graph export "CurodontTrials\Subgroup2.png", as(png) name("Graph")



*****************************RESTORATIONS*****************************************

import excel "CurodontTrials\Meta analysis.xlsx", sheet("Restorations") firstrow
*****************Drop studies with no events in both arms*********
sort nsc
drop in 1/4

meta esize nst nft nsc nfc, esize(lnrratio)
replace _meta_studylabel= Author
replace _meta_studylabel = "Alkilzy, 2018" in 3
replace _meta_studylabel = "Doberdoli, 2020" in 2
replace _meta_studylabel = "Welk, 2020" in 1

meta summarize, rr
meta forestplot, rr

/*Risk Difference*/

*****************Drop studies with no events in both arms*********
sort nsc
drop in 1/4

meta esize nst nft nsc nfc, esize(rdiff)
replace _meta_studylabel= Author
replace _meta_studylabel = "Alkilzy, 2018" in 2
replace _meta_studylabel = "Doberdoli, 2020" in 3
replace _meta_studylabel = "Welk, 2020" in 1

meta summarize
meta forestplot

*********************************ICDAS Small*****************************************
import excel "CurodontTrials\Meta analysis.xlsx", sheet("ICDAS_small") firstrow

meta esize nst nft nsc nfc, esize(lnrratio)
replace _meta_studylabel= Author
replace _meta_studylabel = "Alkilzy, 2018" in 1
replace _meta_studylabel = "Doberdoli, 2020" in 2

meta summarize, rr
meta forestplot, rr

/*Risk Difference*/
meta esize nst nft nsc nfc, esize(rdiff)
replace _meta_studylabel= Author
replace _meta_studylabel = "Alkilzy, 2018" in 1
replace _meta_studylabel = "Doberdoli, 2020" in 2

meta summarize
meta forestplot

*********************************ICDAS Big*****************************************
import excel "CurodontTrials\Meta analysis.xlsx", sheet("ICDAS_big") firstrow

meta esize nst nft nsc nfc, esize(lnrratio)
replace _meta_studylabel= Author
replace _meta_studylabel = "Alkilzy, 2018" in 1
replace _meta_studylabel = "Doberdoli, 2020" in 2

meta summarize, rr
meta forestplot, rr

/*Risk Difference*/
```

eBox. Continued

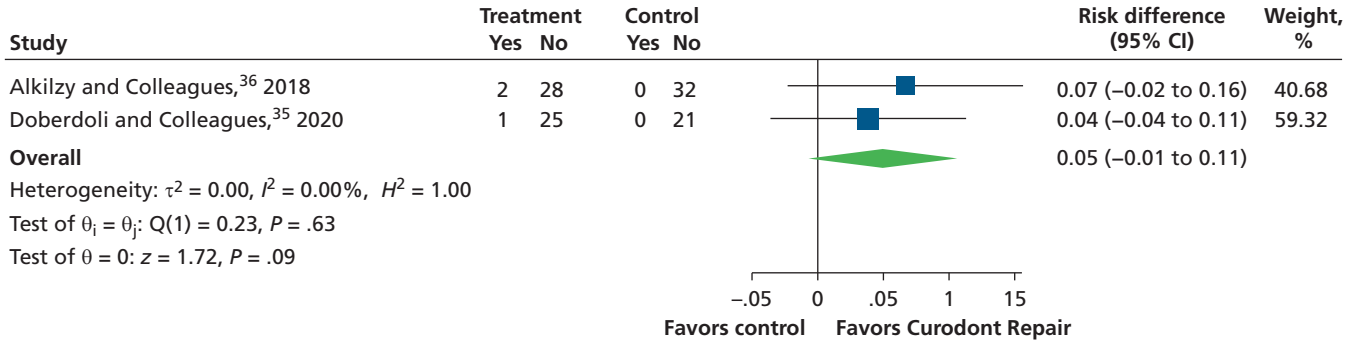
```
meta esize nst nft nsc nfc, esize(rdiff)
replace _meta_studylabel= Author
replace _meta_studylabel = "Alkilzy, 2018" in 1
replace _meta_studylabel = "Doberdoli, 2020" in 2

meta summarize
meta forestplot

**********************************Lesions****************************************
import excel "CurodontTrials\Meta analysis.xlsx", sheet("Lesion") firstrow

/*Hedges's g standardized mean differences*/
meta esize nt meant sdt nc meanc sdc
replace _meta_studylabel= Author
replace _meta_studylabel = "Kondelova, 2020" in 1
replace _meta_studylabel = "Welk, 2020" in 2

meta summarize
meta forestplot

import excel "CurodontTrials\Meta analysis.xlsx", sheet("Lesion_nomissing") firstrow

/*Hedges's g standardized mean differences*/
meta esize nt meant sdt nc meanc sdc
replace _meta_studylabel= Author
replace _meta_studylabel = "Kondelova, 2020" in 1
replace _meta_studylabel = "Welk, 2020" in 2

meta summarize
meta forestplot
```



eFigure 1. Subgroup analysis on the effect of study duration (≤ 6 vs > 6 months) on caries arrest. Curodont Repair was manufactured by Credentis and now is manufactured by vVARDIS.



eFigure 2. International Caries Detection and Assessment System outcomes for Curodont Repair (Credentis; now manufactured by vVARDIS) group, from Kobeissi and colleagues.[40] In the article, the respective result for the fluoride varnish group was errantly duplicated for both.



eFigure 3. Meta-analysis of decrease in merged International Caries Detection and Assessment System (ICDAS) score in randomized controlled trials of Curodont Repair (Credentis; now manufactured by vVARDIS) by risk difference.

eTable 1. Clinical studies excluded at full-text review with detail and reasons for exclusion.

ARTICLE DATA	BRÖSELER AND COLLEAGUES,[44] 2020	METWALLY AND COLLEAGUES,[48] 2017	RIAD AND COLLEAGUES,[49] 2020	KAMH AND COLLEAGUES,[50] 2018	SCHLEE AND COLLEAGUES, 2018	JABLONSKI-MOMENI AND COLLEAGUES, 2019
Citation	44	48	49	50	Schlee M, Rathe F, Bommer C, Bröseler F, Kind L. Self-assembling peptide matrix for treatment of dentin hypersensitivity: a randomized controlled clinical trial. *J Periodontol*. 2018;89(6):653-660. PubMed identification no. 29520816. https://doi.org/10.1002/JPER.17-0429	Jablonski-Momeni A, Korbmacher-Steiner H, Heinzel-Gutenbrunner M, Jablonski B, Jaquet W, Bottenberg P. Randomised *in situ* clinical trial investigating self-assembling peptide matrix P11-4 in the prevention of artificial caries lesions. *Sci Rep*. 2019;9(1):269. PubMed identification no. 30670760. https://www.nature.com/articles/s41598-018-36536-4
Inclusion Criteria (Screening)						
Population: patients with initial caries in permanent teeth	Yes	Yes	Yes	Yes	No dentin hypersensitivity	No, bovine teeth in human mouths
Intervention: CR† or Curodont Repair Fluoride Plus (Credentis; now manufactured by vVARDIS)	CR	CR	CR	CR	No, Curodont D'Senz	No, Curodont Protect
Comparison: placebo or no CR	Placebo	FV‡	FV	2 FVs	Control = 8% arginine and calcium carbonate toothpaste	No treatment, FV
Randomized controlled trial?	Yes	Yes	Yes	Yes	Yes	Yes, crossover in situ (in patients)
Primary Outcomes						
Outcome 1: caries arrest	No	No	No	No	No	No
Outcome 2: cavitation (or restoration)	Restorative treatment	No	No	No	NA	No
Outcome 3: no progression ≥ 24 mo	NA	NA	NA	NA	NA	NA
Secondary Outcomes						
ICDAS§	No	Yes	No	Yes	No	No
Quantitative light-induced fluorescence (QLF; Inspektor Research System) (product only)	No	No	No	No	No	No
Appearance	VAS¶; Patient Global Assessment of Change	No	Color change assessed through Vita Easyshade Spectrophotometer	No	VAS	No
Lesion size	Morphometry of clinical photos	Radiodensity (radiographs)	No	Clinical photos	NA	Micro–computed tomography (and laser)
Subgroup						
Follow-up duration, mo	12	6	6	3	3	NA
Fluoride treatment	Both groups at days 1, 90, and 180 from baseline	Only in 2 FV groups, not 2 CR groups	Only in FV group, not CR	No full-mouth FV	NA	No
Baseline ICDAS score	No	Yes	No	No	NA	NA
Baseline lesion size	Morphometry	NA	No	No	NA	Yes, micro–computed tomography
Study design	Split mouth	Split mouth	Split mouth	Split mouth	Parallel arm	Parallel arm (in same 9 volunteers, over time)
Bias assessment	Not performed	Not performed	Not performed	Not performed	NA	NA
Other American Dental Association Evidence-Based Database Criteria						
Full peer reviewed article	Yes	Yes	Yes	Yes	Yes	Yes
Randomization method (some hidden)	"Randomly assigned by computer program"	"Randomly assigned," method not described	"Randomized clinical trial," method not described	"Randomized clinical trial," method not described	NA	NA
Able to make 2 × 2 table for inactive lesions	No	No	No	No	NA	No
Able to make 2 × 2 table for inactive lesions with author contact	No	No	No	No	NA	NA
Reports baseline caries status	No	No	No	No	NA	Yes, artificial caries
Clinical outcome method	Restorations; impressions of activity change; lesion size	ICDAS-II; lesion size	Color change	ICDAS-II	NA	NA
Product description by brand or concentration	CR	CR	CR	CR	CR	NA
Include?	No	No	No	No	No	No
Reason	No baseline caries status	No baseline caries status; randomization method not described	No baseline caries status; randomization method not described	No baseline caries status; randomization method not described	Not caries trial; not CR	Not human study; not CR

* NA: Not applicable. † CR: Curodont Repair (Credentis; now manufactured by vVARDIS). ‡ FV: Fluoride varnish. § ICDAS: International Caries Detection and Assessment System. ¶ VAS: Visual analog scale.

eTable 1. (Continued)

BRUNTON AND COLLEAGUES,[28] 2013	AZIZ AND COLLEAGUES, 2016	SCHLEE AND COLLEAGUES, 2018	PITTS, 2013	ALKILZY AND COLLEAGUES, 2018	WIERICHS AND COLLEAGUES,[53] 2021
28	Aziz FA, Marei TE, Elmalt MA. Assessment of self-assembling peptide P 11-4 in the treatment of white spot lesions after orthodontic treatment. *Egypt Orthod J*. 2016;50:35-48. https://eos.journals.ekb.eg/article_78670.html	Schlee M, Schad T, Koch JH, Cattin PC, Rathe F. Clinical performance of self-assembling peptide P_{11}-4 in the treatment of initial proximal carious lesions: a practice-based case series. *J Investig Clin Dent*. 2018;9(1). PubMed identification no. 28868637. https://doi.org/10.1111/jicd.12286	Pitts N. Summary of: treatment of early caries lesions using biomimetic self-assembling peptides—a clinical safety trial. *Br Dent J*. 2013;215(4):174-175. PubMed identification no. 23969659. https://www.nature.com/articles/sj.bdj.2013.811	Alkilzy M, Santamaria RM, Schmoeckel J, Splieth CH. Treatment of carious lesions using self-assembling peptides. *Adv Dent Res*. 2018;29(1):42-47. PubMed identification no. 29355413. https://journals.sagepub.com/doi/10.1177/0022034517737025	53
Yes	Yes	Yes	NA*	NA	NA
CR	CR	CR	NA	NA	NA
No control	No control	No control	NA	NA	NA
Noncomparative safety study	No control	No control	Summary article	Review	Systematic review
No	NA	Yes	NA	NA	NA
No	NA	No	NA	NA	NA
NA	NA	NA	NA	NA	NA
			NA	NA	NA
No	NA	No	NA	NA	NA
No	NA	No	NA	NA	NA
VAS and digital intraoral images at days 1, 30, and 180 from baseline and global impression of change	NA	(Radiographs? whitish or blackish, page 3)	NA	NA	NA
VAS	Radiodensity (radiographs)	Visual pairwise evaluation of radiographs by 2 masked assessors	NA	NA	NA
6	NA	12	NA	NA	NA
NA	NA	No FV	NA	NA	NA
NA	NA	NA	NA	NA	NA
VAS	NA	Yes, radiographs	NA	NA	NA
Prospective uncontrolled case series	Prospective uncontrolled case series	Uncontrolled case series	NA	NA	NA
NA	NA	To be determined	NA	NA	NA
Other American Dental Association Evidence-Based Database Criteria					
Yes	NA	Yes	NA	NA	NA
NA	NA	NA	NA	NA	NA
No	NA	No control	NA	NA	NA
NA	NA	NA	NA	NA	NA
Yes, table 1 (VAS)	NA	Yes	NA	NA	NA
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA
No	No	No	No	No	No
Not comparative trial	Not comparative trial	Not comparative trial	Not experiment nor clinical use	Not experiment nor clinical use	Not experiment nor clinical use

eTable 2. Outcome data for treatment of baseline active initial caries lesions (assessed with visual-tactile systems) with CR,* FV,† and no-CR controls for primary and secondary outcomes considered in this review‡

STUDY	YEAR	CARIES ARREST (INACTIVITY)						CAVITATION						DECREASE IN MERGED INTERNATIONAL CARIES DETECTION AND ASSESSMENT SYSTEM						NORMALIZED PHOTOGRAPHIC LESION SIZE		
		CR		FV		Control		CR		FV		Control		CR		FV		Control		CR	FV	Control
		Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Mean (SD)	Mean (SD)	Mean (SD)
Alkilzy and Colleagues[36]	2018	24	6	NR§	NR	11	21	2	28	NR	NR	6	26	2	28	NR	NR	0	32	NR	NR	NR
Gözetici and Colleagues[37]	2019	10	7	13	3	7	9	0	17	0	16	0	16	NR	NR	NR	NR	NR	NR	NR	NR	NR
Doberdoli and Colleagues[35]	2020	26	0	NR	NR	9	12	0	26	NR	NR	6	15	1	25	NR	NR	0	21	NR	NR	NR
Kobeissi and Colleagues[40]	2020	NR	NR	NR	NR	NR	NR	0	20	0	20	NR	NR	5	15	7	13	NR	NR	NR	NR	NR
Kondelova and Colleagues[38]	2020	12	10	NR	NR	12	16	0	22	NR	NR	0	28	NR	NR	NR	NR	NR	NR	0.76 (0.30)	NR	0.90 (0.32)
Welk and Colleagues[39]	2020	NR	NR	NR	NR	NR		1	16	NR	NR	NR	16	NR	NR	NR	NR	NR	NR	0.57 (0.26)	NR	0.76 (0.17)

* CR: Curodont Repair (Credentis; now manufactured by vVARDIS). † FV: Fluoride varnish. ‡ These values represent a subset of published data for the Gözetici, Doberdoli, and Kondelova studies, which included mixed baseline active and arrested lesions. § NR: Not reported.

eTable 3. Details of the risk of bias analysis.

ROB*	ALKILZY AND COLLEAGUES,[36] 2018	GÖZETICI AND COLLEAGUES,[37] 2019	DOBERDOLI AND COLLEAGUES,[35] 2020	KONDELOVA AND COLLEAGUES,[38] 2020	WELK AND COLLEAGUES,[39] 2020	KOBEISSI AND COLLEAGUES,[40] 2020
Study Design and Details	Parallel-arm RCT† Duration = 6 mo 70 patients, 70 lesions Average age = 10.0 y Groups: (1) Curodont (Credentis; now manufactured by vVARDIS), (2) no treatment. Both groups received FV‡ at days 0 and 90 from baseline	4-way split-mouth RCT Duration = 6 mo 21 patients, 84 lesions Average age = 15.4 y Groups: (1) Curodont, (2) Icon (DMG), 3. FV, (4) no treatment	Parallel-arm RCT Duration = 12 mo 90 patients, 90 lesions Average age = 11.8 y Groups: (1) Curodont, (2) Curodont and preassembled Curodont at home, (3) no treatment Groups 1 and 3 had FV at days 0 and 180 from baseline	Split-mouth RCT Duration = 9 mo 44 patients, 88 lesions Average age = 27.1 y Groups: (1) Curodont, (2) placebo Both groups received FV at day 90 from baseline	Split-mouth RCT Duration = 6 mo 23 patients, 46 lesions Average age = 15.4 y	Split-mouth RCT Duration = 6 mo 9 patients, 40 lesions Average age = 11.1 y Groups: (1) Curodont, (2) FV
ROB Arising From the Randomization Process	Some. Third-party comp-generated random allocation sequence. Laser fluorescence and visual analog scale scores showed test group lesions were larger at baseline; but grouped International Caries Detection and Assessment System baseline scores were similar.	Some. Quasi-randomization: Randomization by third party, but if there was more than 1 tooth in the quadrant, investigators selected one. The control group had the lowest DIAGNOdent scores.	Low. Good randomization by third party. No baseline differences identified.	Low. Good randomization by third party. No baseline differences identified.	Some. Randomization was via flipping a coin. Baseline difference of 8.8 mm^2 (test) vs 6.8 mm^2 (control) in morphometric measurement. Baseline impedance values were very similar.	Low. Simple randomization via flipping a coin. Grouped International Caries Detection and Assessment System baseline scores were similar.
Adherence: ROB Due to Assignment to Intervention, Intention to Treat, and Masking	Some. The study was unmasked. No placebo experience.	Some. The treatment investigators were unmasked. The patients had 4 treatments, so likely were masked.	Some. The treatment investigators were unmasked. No placebo experience; single treatment and outcome investigator.	Good. Quadruple masked; placebo experience.	Some. No placebo experience. Unmasked treatment investigator.	Some. The study was unmasked. No placebo experience.
Missing Outcome Data	Low. 8 patients (11%) were lost; 62/70 patients at end point.	Low. 1 patient (5%) was lost; 20/21 patients at end point.	Low. 8 patients (13%) were lost; 52/60 patients at end point.	Low. 4 patients (9%) were lost; 40/44 patients at end point.	High. 2 patients (9%) were lost; 21/23 patients were seen at end point. But only 14/23 patients (61%) could be assessed for morphometry at end point.	Low. 9/9 patients at end point.
ROB Due to Measurement of the Outcome	High. No report that the outcome assessors were masked. (Number of assessors unknown.)	Low. The single assessor was masked and different from the allocation investigator.	High. One investigator for application and evaluation.	Low. Masked outcome assessor.	Low. Masked outcome assessor and statistician.	High. Unmasked and subjective assessment. Unpredictable direction in outcome measurement.
ROB in Selection of the Reported Result	Some. Trial registration after study completion.	Some. No trial registration.	Low. Trial registration after study completion, yet very fair and logical reporting.	High. Trial registration before study start, but groups comparisons and timelines are different than plan. Reported group timeline comparisons are illogical.	High. No trial registration nor statistical analysis preplan reported.	Some. No trial registration.

* ROB: Risk of bias. † RCT: Randomized controlled trial. ‡ FV: Fluoride varnish.

eTable 3. Continued

ROB*	ALKILZY AND COLLEAGUES,[36] 2018	GÖZETICI AND COLLEAGUES,[37] 2019	DOBERDOLI AND COLLEAGUES,[35] 2020	KONDELOVA AND COLLEAGUES,[38] 2020	WELK AND COLLEAGUES,[39] 2020	KOBEISSI AND COLLEAGUES,[40] 2020
Manufacturer Sponsorship	Yes, reported and handled appropriately. "No role in study design, data collection, data analysis, data interpretation, or writing of the report."	Supplied Curodont.	Yes, sponsored, coauthored, without risk management plan.	Supplied Curodont and coauthored, without risk management plan.	Supplied Curodont.	None
Overall ROB	High. Due to unmasked outcome assessors.	Some. Direction of bias risk is unpredictable; results section promotes resin infiltration and FV, not Curodont, despite positive outcomes.	High. Due to unmasked assessor, manufacturer sponsored, and coauthored.	Some. Good masking, but creative reporting and manufacturer coauthorship.	High. Due to creative outcome reporting and missing outcome data.	High. Due to unmasked assessment, although direction unpredictable. Reported sources of support and conflicts of interest are "none."

eTable 4. Grading of Recommendations, Assessment, Development and Evaluations certainty of evidence profile.

STUDIES, NO.	STUDY DESIGN	CERTAINTY ASSESSMENT					PATIENTS, NO. (%)		EFFECT		CERTAINTY
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Curodont Repair	Control	Relative (95% CI)	Absolute (95% CI)	
Primary: Caries Arrest (Visual-Tactile Assessment; 6-12 Mo Follow-up)											
4	Randomized trials	Serious*,†	Not serious	Not serious	Not serious	None	72/95 (75.8)	39/97 (40.2)	RR‡, 1.82 (1.32 to 2.50)	330 more per 1,000 (from 129 to 603 more)	Moderate
Subgroup: Caries Arrest With Fluoride Varnish at Same Visit (Visual-Tactile Assessment; 6-12 Mo Follow-up)											
2	Randomized trials	Serious*,†	Not serious	Not serious	Not serious	None	50/56 (89.3)	20/53 (37.7)	RR, 2.30 (1.62 to 3.26)	491 more per 1,000 (from 234 to 853 more)	Moderate
Subgroup: Caries Arrest With No Fluoride Varnish at Same Visit (Visual-Tactile Assessment; 6-9 Mo Follow-up)											
2	Randomized trials	Serious*,†	Not serious	Not serious	Serious§	None	22/39 (56.4)	19/45 (42.2)	RR, 1.30 (0.84 to 2.02)	127 more per 1,000 (from 68 fewer to 431 more)	Low
Primary: Less Cavitation (by Diagnosis or Restoration; 6-12 Mo Follow-up; Lower Is Better)											
3	Randomized trials	Serious*,†	Not serious	Not serious	Serious§	None	3/73 (4.1)	13/79 (16.5)	RR, 0.32 (0.10 to 1.06)	112 fewer per 1,000 (from 148 fewer to 10 more)	Low
Secondary: Lesion Size Lesions (by Photometry; 6-9 Mo Follow-up)											
2	Randomized trials	Serious†	Not serious	Not serious	Not serious	None	39	45	Hedges *g*, −0.59 (−1.03 to −0.15)	MD, 17% points more shrinking of normalized lesion size (4%-30% points more shrinking)	Moderate
Secondary: Lowers Merged International Caries Detection and Assessment System Categories (by 0, 1-2, 3-4, 5-6 criteria; 6-12 Mo Follow-up)											
2	Randomized trials	Serious*,†	Not serious	Serious¶	Very serious§,#	None	3/56 (5.4)	0/53 (0.0)	RR, 3.68 (0.42 to 32.26)	54 more per 1,000 (from 5 fewer to 167 more)**	Very low

* Studies had nonmasked assessors. † No trials had prior registration or analysis plan. Some industry sponsorship. Some unconventional published analysis, but sufficient data reporting to enable standard by-group comparison here. ‡ RR: Risk ratio. § 95% CI suggests that people undergoing the treatment may experience a large benefit and a negligible harm. ¶ Surrogate outcome. # Studies not powered to detect difference. ** Unrealistic estimation due to 0 control events.