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Original

Demineralization of hard tooth tissue adjacent to resin-modified glass-ionomers and composite resins: a quantitative systematic review

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Abstract: The purpose of this systematic review was to quantitatively find out whether resin-modified glass-ionomers (RM-GIC), in comparison to fluoride-containing composite resin and composite resin without fluoride, are associated with a more effective reduction of demineralization in hard tooth tissues under caries challenge. Five databases were systematically searched on clinical trials up to 6 April 2009. Article inclusion criteria: titles/abstracts relevant in answering the review question, published in English, two-arm (prospective) longitudinal trial; Exclusion criteria: not all included subjects accounted for at the end of the trial; subjects of both groups not followed up the same way; no randomized, quasi-randomized controlled study design for *in situ* and clinical trials; contains no computable continuous data. Quality assessment of the accepted *in situ* and clinical trials was performed. Data were extracted in the form of datasets, containing numbers of evaluated samples and mean result with standard deviation for both groups. Fifteen articles were selected for review. Two lacked computable data and were excluded; nine laboratory trials, three randomized *in situ* trials and one randomized control trial were accepted. From these, 97 continuous datasets were extracted. The evidence suggests that RM-GIC is associated with a higher reduction of demineralization in adjacent hard tooth tissue than composite resin without fluoride. No difference was found when RM-GIC was compared with fluoride-containing composite resin. RM-GIC showed efficacy in reducing demineralization. However, the internal validity of the current evidence is limited and further high-quality trials are needed. (J Oral Sci 52, 347-357, 2010)

Keywords: demineralization; resin-modified glass-ionomer; composite resin; systematic review.

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Introduction

An important part of caries management is encouraging hard tooth tissue remineralization (1). Ten Cate and van Duinen have shown, *in situ*, a hyper-remineralization effect in demineralized tooth tissues bordering glass-ionomer cement (GIC) type restorations (2). The significant remineralizing potential of GIC has been ascribed to the release of fluoride ions, facilitated by a hydrophilic environment (3). The remineralizing effect has been explained clinically (4) on the basis of its fluoride release into saliva, leading to an increase in the salivary fluoride content from 0.04 to 0.30 ppm after one year (5). However, the actual amount of fluoride in saliva required to have any effect on the mineral content of teeth is still unclear (6). Two recent systematic reviews with meta-analyses of RCTs have confirmed the caries-preventive effect of GIC on restoration margins (7) and on pits and fissures sealed with GIC (8). These findings have been established for conventional glass-ionomers (C-GIC) which set through an acid-base reaction between fluoroaluminosilicate glass powder and polyalkenoic acid liquid. However, C-GICs remain sensitive to water uptake and are lost in the first hours after setting, which led to the development of 'resin-modified' GICs (RM-GIC). In the set material, approximately 10% of RM-GIC is resin, usually hydroxyethyl-

methacrylate (HEMA) (9). Compared to other dental materials, such as non-fluoride-containing composite resins, laboratory research has shown a higher caries-resistance in bovine enamel located considerably distant from the margins of RM-GIC restorations (10). The *in situ* trial by Cenci et al. showed lower demineralization in both enamel and dentine around RM-GIC restorations (11) and the RCT by Pascotto et al. reported RM-GIC to be statistically more efficient in reducing enamel demineralization around orthodontic brackets in clinics than composite resin without fluoride (12).

One systematic review without quantitative synthesis has been published regarding the secondary caries treatment effect of GIC restorations (13). This review included C-GIC and RM-GIC but did not distinguish differences between these types of material. A more recent review by Wiegand et al. included an overview covering the influence of RM-GIC on the demineralization of enamel and dentin (14). The results of this review indicated a reduction of carious lesions adjacent to RM-GIC in laboratory trials. However, no conclusive evidence was obtained from *in situ* and clinical trials. Although the review by Wiegand et al. included a systematic search strategy, it did not report on quality aspects related to the internal validity of the included trials and employed only a qualitative synthesis during the assessment of the trial results (14).

To date, no systematic review using quantitative synthesis, with or without meta-analysis, has been attempted on this topic. Thus, the aim of this systematic review was to quantitatively appraise the current evidence and to answer the review question about whether RM-GIC, in comparison to fluoride-containing composite resin and composite resin without fluoride, is associated with a higher reduction of demineralization in hard tooth tissues under caries challenge.

Materials and Methods

Data collection

Five databases: Biomed Central, Cochrane Library, Directory of Open Access Journals, PubMed and Science-Direct were systematically searched for articles reporting on clinical trials up to 6 April 2009. The strings of MeSH/text search terms with boolean operators: i) "*Tooth Remineralization OR Tooth Demineralization AND Glass Ionomer Cements AND Composite Resins*" and ii) "*Dental Caries OR Dental Caries Susceptibility OR Root Caries AND Glass Ionomer Cements AND Composite Resins*" were used to search the databases. Articles were selected for review from the search results on the basis of their compliance with the inclusion criteria:

1. Titles/abstracts relevant in answering the review question;
2. Published in English;
3. Two-arm (prospective) longitudinal trial;
4. Focus on materials used for orthodontic and restorative application.

It was expected that only a few RCTs would be found relating to this topic. The investigation of the mineral content of hard tooth tissue often requires evaluation of extracted teeth under laboratory conditions. For this reason, clinical trials in this field are challenged by ethical considerations and randomized, double-blind short-term *in situ* trials involving a small number of subjects appear to be the study design of choice. Moreover, laboratory trials may also provide additional valuable data on this topic. However, laboratory trials present weak evidence only, owing to the uncertainty of extrapolating their results to physiological effects in humans (15). Thus, it was decided to include laboratory, *in situ* and clinical trials in this review but to assess their outcomes separately in accordance with the evidence hierarchy (16). Where only a relevant title without a listed abstract was available, a full copy of the article was assessed for inclusion. References of the included articles were checked, in order to identify further trials suitable for inclusion.

Article review

Only articles that complied with the inclusion criteria were reviewed further. Full copies of articles were reviewed independently by two reviewers (VY and SM) in accordance with the exclusion criteria (15):

1. Not all entered subjects accounted for at the end of the trial;
2. Subjects of both groups not followed up the same way;
3. No randomized, quasi-randomized controlled study design for *in situ* and clinical trials;
4. Contains no computable continuous data for extraction (including the number of evaluated samples (n) and the mean result of the measured outcome with standard deviation (SD) for both material groups).

When several articles reporting on the same trial over similar time periods were available, the article covering the trial most comprehensively in accordance with the exclusion criteria was accepted. Disagreements between reviewers were resolved by discussion and consensus.

Quality of studies

The quality assessment of the accepted *in situ* and clinical trials followed guidelines concerning the internal validity of clinical studies (17) and was undertaken

independently by two reviewers (VY and SM). Trials not included in this review were used to pilot the process. Subsequently, quality assessment rating scored by both reviewers was derived through consensus. The following criteria were used:

1) Generation of randomization sequence (allocation), recorded as:
   (A) Adequate – e.g., computer-generated random numbers, table of random numbers,
   (B) Unclear – not reported,
   (C) Inadequate – e.g., case record number, date of birth, date of administration, alternation;
2) Allocation concealment, recorded as:
   (A) Adequate – e.g., central randomization, sequentially numbered sealed opaque envelopes;
   (B) Unclear – not reported;
   (C) Inadequate – e.g., open allocation schedule, unsealed or non-opaque envelopes;
3) Blind outcome assessment, recorded as:
   (A) Adequate – Yes;
   (B) Unclear – No information given as to whether assessment was blinded;
   (C) Inadequate – Reported in text that assessment was not blinded;
   (D) Not possible.

No quality assessment was done for accepted laboratory trials.

Data extraction from accepted trials

Outcome measures related to the mineral content of hard tooth tissue under caries challenge in contact with or adjacent to either material were assessed. Two reviewers (VY and SM) independently extracted data from the accepted articles. Individual continuous datasets for the control- and test-group were extracted from each article. Where possible, missing data were calculated from information presented in the text or tables. Authors of articles were also contacted, in order to obtain missing information. Data were extracted in the form of datasets, each containing the number of evaluated samples (n) and the mean result of the measured outcome with standard deviation (SD) for both material groups. Disagreements between reviewers during data extraction were resolved through discussion and consensus.

Statistical analysis

A random effects model in RevMan Version 4.2 statistical software by The Nordic Cochrane Centre, The Cochrane Collaboration (Copenhagen; 2003) was used. Differences in treatment groups were computed on the basis of mean difference (MD) with 95% confidence intervals (CI). From the accepted articles, extracted datasets were assessed for their clinical and methodological heterogeneity, following Cochrane guidelines (18). Datasets were considered heterogeneous if they differed in type of study (laboratory, *in situ* or clinical study type); whether the control material (composite resin) contained fluoride or not; aspect and definition of outcome measure; and type of hard tooth tissue. In addition, datasets within each study type were considered heterogeneous if they differed in the following aspects: i) Laboratory study: initial exposure period; tissue distance from material ii) *in situ*: saliva function; fluoride exposure from other sources; tissue distance from material; follow-up period iii) Clinical study: saliva function; fluoride exposure from other sources; type of dentition; type of cavity; follow-up period. The percentage of total variations across datasets (I^2), together with its associated *P*-value (<0.10), was used in assessing statistical heterogeneity (19). Only identified homogeneous datasets were considered suitable for meta-analysis. All datasets were assigned a Mantel-Haenszel weight directly proportionate to their sample size.

Results

Systematic literature search and review

An initial search of PubMed, using both strings of MeSH/Text words (i. and ii.), resulted in 403 and 490 articles, respectively. Of these, 15 articles (10-12,20-31) complied with the inclusion criteria and were selected for review. No further articles were identified for selection during the subsequent search of the other four databases, and during the reference check. From the 15 selected articles, two were excluded because they lacked computable data (20,21).

Thirteen articles; nine laboratory trials (10,22,23,26-31), three randomized *in situ* trials (11,24,25) and one RCT were accepted for further quality assessment and data extraction (12).

Quality assessment and data extraction

For all *in situ* and clinical trials random allocation of subjects, concealment of random allocation and evaluator blinding were rated “B” (unclear), since no information about these items was given in the text.

From the accepted laboratory, *in situ* and clinical trials, 51, 24 and 22, separate computable continuous datasets with relevance to the review question were extracted, respectively. The outcome measures of these datasets related to the mineral content of hard tooth tissue were:

(A) Outcome measures that indicate the mineral loss after

caries challenge:

a. Laboratory trials: Volume% mineral loss; Knoop microhardness loss value; Reciprocal microhardness value, as well as the difference in surface microhardness before and after artificial caries challenge; Lesion area and Lesion area + lesion depth
b. *In situ* trials: Mineral loss; Lesion depth; Increase of indention length

(B) Outcome measures that indicate the remaining mineral content after caries challenge:

a. Laboratory trials: Mean density; Knoop microhardness
b. Clinical trial: Knoop microhardness

The main characteristics of the extracted datasets are described in Table 1-3. Large clinical and methodological heterogeneity was observed between all datasets and

Table 1 Characteristics of datasets (DS) with potential influence on study outcome (laboratory trials)

Article	DS	RM-GIC	Composite resin		Outcome measure		Hard tooth tissue	Artificial caries challenge			Lesion distance from material
			Type	With fluoride	Aspect	Definition		Cycle / exposure	Demineralising solution content	Initial exposure period	
Lee et al. (26)	01 02 03	Vitremer	Z250	No	Mean density	The mean of 25 values from 5 randomly selected on each of randomly selected slices of specimen. Density measured using Vworks software	E	Suspended in demineralising solution for 3 days, afterwards placed into artificial saliva at 37°C	2.2 mM Ca^{2+}, 2.2 $mMPO_4^{3-}$, 50 mM acetic acid, pH 4.4	After 3 months in arti-ficial saliva	Adjacent
Samuel and Rubinstein (28)	04 05	Vitremer	Helio -molar Z100	Yes No	Knoop micro-hardness (KHN)	Measure of the length of the major diagonal left by penetration of a diamond and calculated with Standard deviation	E	Placed in demineralising solution for 30 min, artificial saliva 3hrs, demineralising solution for 30 min	According to Serra (1992), pH 4.3	30 min	Opposite in neighboring tooth at contact point
Tantbirojn et al. (10)	06 07 08 09 10 11	Vitremer	Bis-GMA resin	No	Volume % mineral loss (ΔZ)	Knoop microhardness value converted into Vol% mineral = 4.3 √KHN+11.3	BE	Placed in demineralising solution	6% by weight hydroxyethylcellulo se in 0.1 mol/l lactic acid, pH 5.1	3 weeks	0.2 mm 0.5 mm 1.0 mm 2.0 mm 4.0 mm 7.0 mm
Hara et al. (22)	12 13	Fuji II LC	Z250	No	Knoop micro-hardness-loss value	Difference between KHN before and after artificial caries challenge	RD	1 hr in demineralising solution, 23 hrs in remineralising solution	2.0 mM Ca^{2+}, 2.0 $mMPO_4^{3-}$, 74 mM acetic acid, pH 4.3	3 days	Adjacent
Hara et al. (23)	14 15 16 17 18 19 20 21 22 23 23	Fuji II LC Improved	Z250	No	Reciprocal micro-hardness values	= 1 : KHN	BRD	30 min in demineralising (DE) solution, 3 hrs in remineralising (RE) solution 30 min in DE solution, 20 hrs in RE solution	2.0 mM Ca^{2+}, 2.0 $mMPO_4^{3-}$, 74 mM acetic acid, pH 4.3	2 days	50 µm 100 µm 150 µm 300 µm 600 µm 900 µm 1200 µm 1500 µm 1800 µm 2100 µm 2100 µm

Table 1-2 Characteristics of datasets (DS) with potential influence on study outcome (laboratory trials) - contd.

Article	DS	RM-GIC	Composite resin		Outcome measure		Hard tooth tissue	Artificial caries challenge			Lesion distance from material	
			Type	With fluoride	Aspect	Definition		Cycle / exposure	Demineralizing solution content	Initial exposure period		
Takeuti et al. (29)	24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41	Vitremer	Tetric Ceram Z250	Yes No	Knoop micro-hardness (KHN)	Measure of the length of the major diagonal left by penetration of a diamond and calculated with Standard deviation	E (prim)	3 hrs in demineralising solution, 21 hrs in remineralising solution	2.2 mM Ca^{2+}, 2.2 $mMPO_4^{3-}$, 50 mM acetic acid, pH 4.8	10 days	Depth: 100 µm 200 µm 300 µm 100 µm 200 µm 300 µm	50 µm 150 µm 250 µm 50 µm 150 µm 250 µm 50 µm 150 µm 250 µm 50 µm 150 µm 250 µm 50 µm 150 µm 250 µm
Rodrigues et al. (27)	42 43 44 45	Vitremer	Z100	No	Percentage change of surface micro-hardness (%SMH_C)	Difference in surface microhardness before and after artificial caries challenge X 100%	BE	6 hrs in demineralising solution, 18 hrs in remineralising solution	2.0 mM Ca^{2+}, 2.0 $mMPO_4^{3-}$, 75 mM acetic acid, pH 4.7	5 days		150 µm 300 µm 450 µm 600 µm
Vorhies et al. (30)	92 93 94 95	Fuji Ortho LC Advance Fuji Ortho LC Advance	Trans-bond XT	No	Area plus depth of demineralized lesion around bracket	Average depth (in µm) and a standardized area of demineralization with 0.5 mm occlusogingival width (in $µm^2$)	E	3x 20 min intervals for a total of 60 min at 7:00 a.m; 12:00 p.m.; 6:00 p.m. 3x 20 min intervals for a total of 60 min at 7:00 a.m; 12:00 p.m.; 6:00 p.m. + 2x daily with 1500 ppm fluoride dentifrice	2.2 mM Ca^{2+}, 2.2 $mMPO_4^{3-}$, 50 mM acetic acid, pH 4.4	30 days	In contact with bonded brackets	
Wilson and Donly (31)	96 97	Fuji Ortho LC	Concise Light Bond	No Yes	Area of demineralized lesion around bracket	As measured 100 µm from residual bonding agent with a computerized imaging system (in $µm^2$)	E	Suspension into demineralising solution	2.2 mM Ca^{2+}, 2.2 $mMPO_4^{3-}$, 50 mM acetic acid, pH 4.5	5 days	100 µm from bonded bracket	

RM-GIC = Resin-modified class ionomer cement; E = Enamel (permanent dentition), E (prim) = Enamel (primary dentition); BE = Bovine enamel; RD = Root dentin; BRD = Bovine root dentin

therefore, no meta-analysis was attempted and statistical heterogeneity was not further investigated. Instead, the mean difference between the outcome effects of both material groups was calculated with 95% confidence intervals (MD; 95% CI) for each dataset. The results are presented per study design in Figs. 1-3.

Comparison of RM-GIC versus fluoride-containing composite resin

The results of the laboratory trials (Fig. 1) revealed no

Table 2 Characteristics of data sets (DS) with potential influence on study outcome (*in situ* trials)

Article	DS	RM-GIC	Composite resin		Outcome measure		Hard tooth tissue	Patients				Hard tooth tissue distance from material	Follow-up period
			Type	With fluoride	Aspect	Definition		Age	Gender	Saliva function	Fluoride exposure from other sources		
Cenci et al. (11)	46	Vitremer	Z250	No	Mineral loss (vol% min x µm)	Mineral loss was quantified by transversal microradiography	E	18-31 years	7 male / 7 female	No info	No	50 µm	14 days
	47											100 µm	
	48											150 µm	
	49											200 µm	
	50						D					50 µm	
	51											100 µm	
	52											150 µm	
	53											200 µm	
	54						E				Fluoride containing dentifrice (1.1 µg F/g)	50 µm	
	55											100 µm	
	56											150 µm	
	57											200 µm	
	58						D					50 µm	
	59											100 µm	
	60											150 µm	
	61											200 µm	
Kielbassa et al. (24)	62	Vitremer	Tetric Ceram	Yes	Mineral loss (vol% min x µm)	Calculated by integrating the difference between mineral content in sound (= 88 vol%) and demineralized enamel over the depth of lesion	E	21-46 years	4 male / 7 female	No info	Fluoridated water (0.3 ppm)	<100 µm	4 weeks (storage in 10% sucrose solution during extra-oral periods)
	63				Lesion depth (µm)	Distance from the original flat surface to the site of the lesion where mineral content was more than 95% of the mineral content in sound enamel.							
	64				Mineral loss (vol% min x µm)	Calculated by integrating the difference between mineral content in sound (= 88 vol%) and demineralized enamel over the depth of lesion						>500 µm	
	65				Lesion depth (µm)	Distance from the original flat surface to the site of the lesion where mineral content was more than 95% of the mineral content in sound enamel.							
Kotsanos (25)	66	Vitremer	Pertac II	No	Micro-hardness (µm)	Increase of indentation length	BE	60 and 75 years	1 male / 1 female	Normal (UWS >15 ml/min)	No info	0	70 days (No brushing, storage in 3% sucrose solution for 10 min x 4 per day)
	67											0.4 mm	
	68											0.8 mm	
	69											12 mm	

Table 3 Characteristics of data sets (DS) with potential influence on study outcome (clinical trials)

Article	DS	Type of study	RM-GIC	Composite resin		Outcome measure			Hard tooth tissue	Patients			Dentition / Type of tooth	Type of cavity	Follow-up period
				Type	With fluoride	Aspect	Definition			Age	Saliva function	Fluoride exposure from other sources			
Pascotto et al. (12)	70	RCT	Fuji Ortho LC	Concise	No	Knoop-microhardness	Hardness increase due to reduction of demineralisation at different depths from enamel surface:	10 µm	E	12-17 years	Normal flow rate (>1.0 ml/min); Buffer capacity (final pH 6 – 7)	Fluoridated piped water	Permanent premolars	Ortodontic brackets	30 days
	71							20 µm							
	72							30 µm							
	73							50 µm							
	74							70 µm							
	75							90 µm							
	76						For materials at different proximity, under, occlusal and cervical to the brackets on labial and lingual (control) surface:	Oclusal / 0 µm							
	77							Occlusal / 100 µm							
	78							Occlusal / 200 µm							
	79							Cervical / 0 µm							
	80							Cervical / 100 µm							
	81							Cervical / 200 µm							
	82							Lingual							
	83							Underneath							
	84						For materials and positions at depth of 10 µm:	Oclusal / 0 µm							
	85							Occlusal / 100 µm							
	86							Occlusal / 200 µm							
	87							Underneath							
	88							Cervical / 0 µm							
	89							Cervical / 100 µm							
	90							Cervical / 200 µm							
	91							Lingual							

RM-GIC = Resin-modified glass ionomer cement; RCT = Randomized control trial with parallel group design; E = Enamel (permanent dentition).

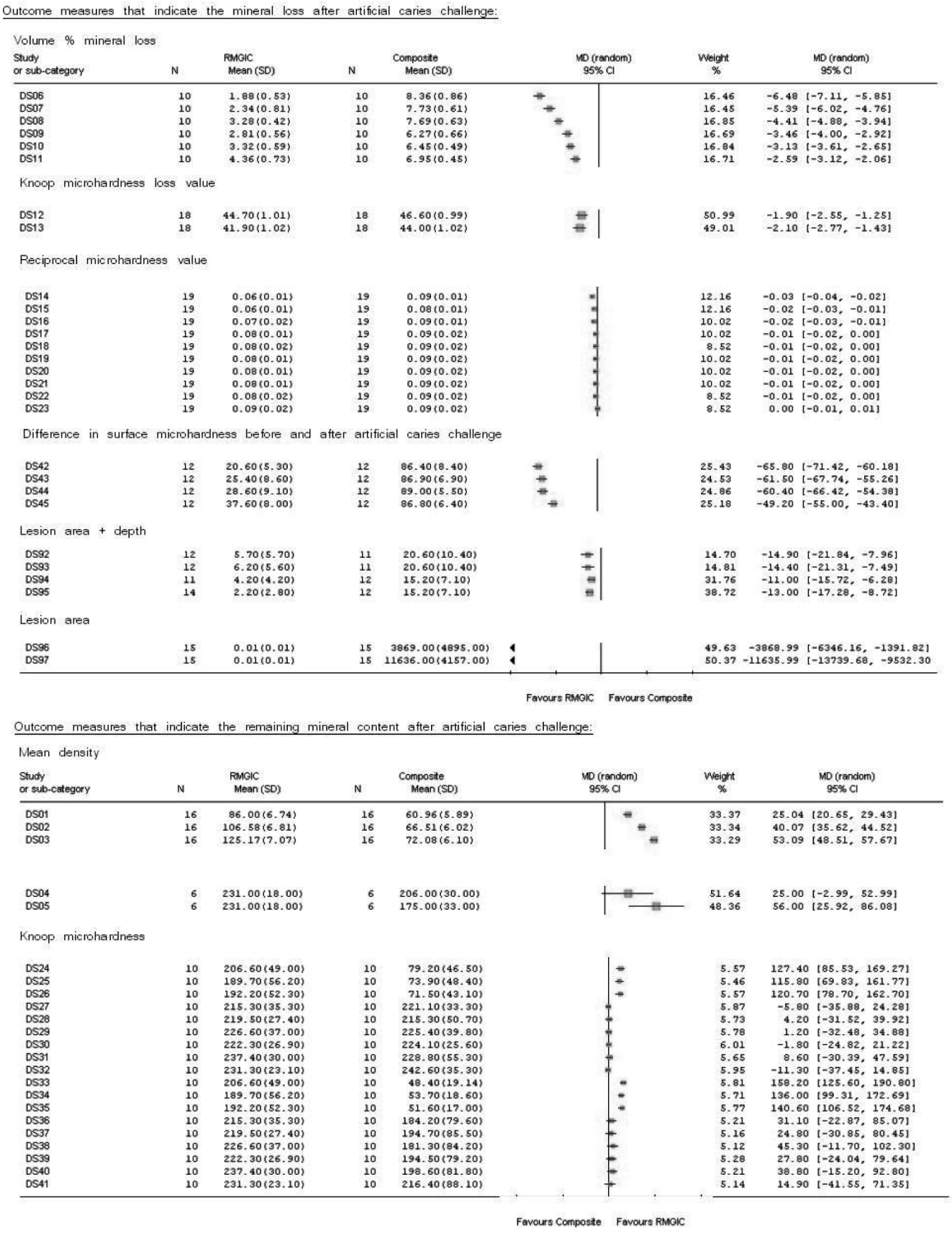

Fig. 1 Demineralization of hard tooth tissue adjacent to RM-GIC or Composite resin (Laboratory trials).
DS = Dataset number; N = Number of analyzed items; SD = Standard deviation; MD = Mean difference; CI = Confidence interval; Weight % = Mantel-Haenszel weight directly proportionate to sample size.

statistically significant mean difference (MD) between the mean density values of both materials (Dataset #04: MD 25.00; 95% CI -2.99, 52.99; $P = 0.08$) after a 30 min artificial caries challenge (28). The mean difference in the Knoop microhardness ranged between MD -11.30 (Dataset #32: 95% CI -37.45, 14.85; $P < 0.00001$; in favor of RM-GIC) and MD 127.40 (Dataset #24: 95% CI 85.53-169.27; $P = 0.40$) after 10 days of artificial caries challenge (29). One dataset (#97), reporting on the area of demineralized enamel at a distance of 100 μm from the materials, showed a significantly smaller demineralized area (in μm^2) around RM-GIC (MD -11635.99, 95% CI -13739.68, -9532.30, $P < 0.00001$) (31).

The results from one *in situ* trial (30) showed statistically non-significant mean differences (MD) between mineral loss values (datasets #62 and 64) and in lesion depth (datasets #63 and 65) of both types of material after four weeks (Fig. 2). No results from clinical trials were identified during this review.

Comparison of RM-GIC versus composite resin without fluoride

The results of the laboratory trials (Fig. 1) showed statistically significant ($P < 0.05$) lower mineral loss after artificial caries challenge in hard tissues adjacent to RM-GIC, with exception of four datasets (#17-20) that found no difference between the reciprocal microhardness values of the two material types (10,22,23,27). In addition, the mean density of hard tooth tissues adjacent to RM-GIC was significantly higher than for composite resin after 30 min (Dataset #05) and after 3 months (Datasets #01-03) of artificial caries challenge (26,28). The laboratory results for the Knoop microhardness values (Datasets #33-41) showed a range of the mean difference between the two materials; from MD 14.90 (Dataset #41: 95% CI -41.55, 71.35; $P = 0.60$) to MD 158.20 (Dataset #33: 95% CI 125.60, 190.80; $P < 0.00001$; in favor of RM-GIC) (29). Datasets (#92-96) that measured the demineralized areas around both materials after artificial caries challenge found significantly smaller lesion areas surrounding RM-GIC

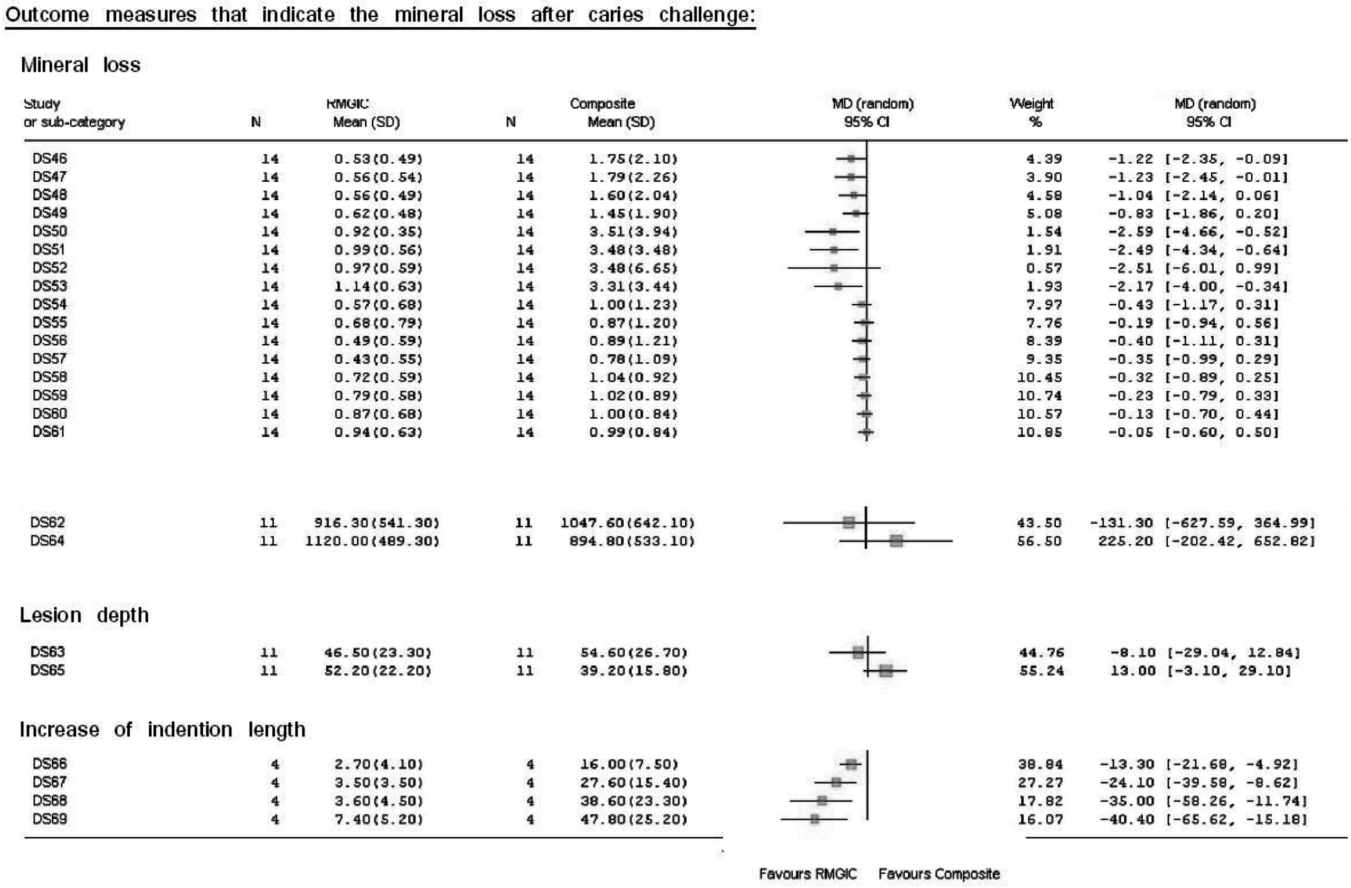

Fig. 2 Demineralization of hard tooth tissue adjacent to RM-GIC or Composite resin (*in situ* trials).
DS = Dataset number; N = Number of analyzed items; SD = Standard deviation; MD = Mean difference; CI = Confidence interval; Weight % = Mantel-Haenszel weight directly proportionate to sample size.

(Fig. 1) (30,31).

The results of *in situ* trials (Fig. 2) indicated a significantly lower increase of indention length for RM-GIC after 70 days (25) and a mean difference in mineral loss after 14 days, ranging from MD -0.05 (Dataset #61: 95% CI -0.60, 0.50; $P = 0.87$) to a statistically significant MD -2.59 (Dataset #50: 95% CI -4.66, -0.52; $P = 0.01$) in favor of RM-GIC (11).

The results of the single RCT (Fig. 3) indicate a mean difference in the Knoop microhardness of hard tooth tissue after 30 days, ranging from MD -3.60 (Dataset #73: 95% CI -13.54, 6.34; $P = 0.48$) to a statistically significant MD 70.80 (Dataset #88: 95% CI 50.75, 90.85; $P < 0.00001$) in favor of RM-GIC (12). The results of this trial were obtained in the laboratory after extraction of the teeth for orthodontic reasons and with the informed consent of the patients (12).

Factors with influence on measured outcomes

The Knoop microhardness results of the laboratory trials (Fig. 1) indicate that RM-GIC was found in favor when the point of measurement in the tissue was at shallow depth range, even if the RM-GIC was compared to fluoride-containing composite resin (datasets #24-26). Both materials were found to have an equal effect if the point of tissue measurement was chosen at greater depth ranges, even when the RM-GIC was compared to composite resin without fluoride (datasets #36-41) and the tissue measurement was made at close proximity range to the material (datasets #27-31,37-40).

In ten of the extracted datasets, fluoride exposure from fluoridated toothpaste used during the trial period was reported: two laboratory and eight *in situ* datasets #94,95 that measured lesion area plus depth of lesion (Table 1) and #54-61, measuring mineral loss (Table 2), respectively. The laboratory results favored RM-GIC (Fig. 1) (30) and the *in situ* results showed no difference between the compared materials (Fig. 2) (11).

The measurements for two clinical datasets (#82,91 – Table 3) were taken at lingual tooth surfaces, where neither of the two materials was applied (Fig. 3) (12).

Discussion

The aim of this systematic review was to quantitatively appraise the current evidence, in order to answer the review question as to whether RM-GIC is associated with a higher reduction of demineralization in hard tooth tissues under caries challenge than fluoride-containing composite resin and composite resin without fluoride. Quantitative synthesis with, or without, meta-analysis has a greater value than qualitative or narrative synthesis in providing the opportunity for detecting a statistically significant ($P < 0.05$) treatment effect and for improving estimation of such effect by quantifying its outcome (30). In quantitatively

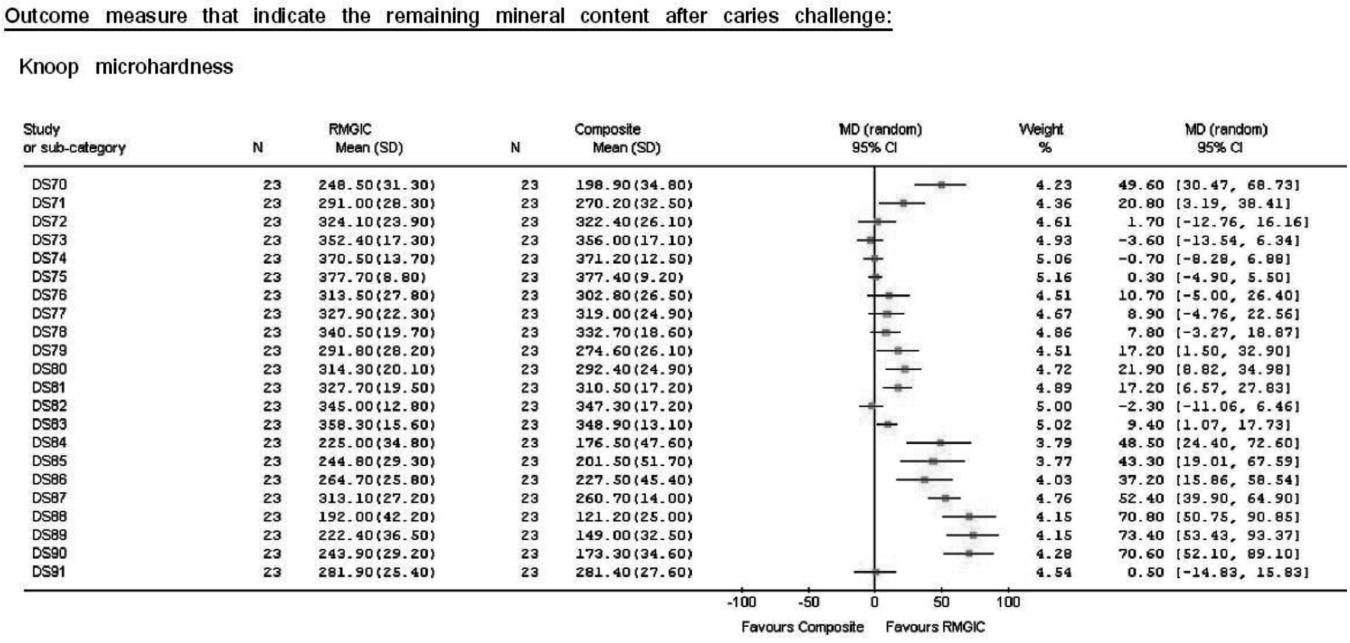

Fig. 3 Demineralization of hard tooth tissue adjacent to RM-GIC or Composite resin (Clinical trial).
DS = Dataset number; N = Number of analyzed items; SD = Standard deviation; MD = Mean difference; CI = Confidence interval; Weight % = Mantel-Haenszel weight directly proportionate to sample size.

collating clinical information from separate trials in comparison to others, a more objective assessment of the currently available evidence is obtained. Often, owing to the heterogeneity of such trials, the outcome data are not directly comparable. Therefore, restrictive exclusion criteria are used to limit the variation and to strengthen the value of review results. There is a risk, however, that some informative data will be excluded from the review, as they may fall outside the inclusion criteria, thus weakening the overall informative value. In this systematic review, in order to increase the inclusion envelope, two-arm *in situ* and laboratory studies were accepted for data extraction. The authors recognized that ethical challenges exist for clinical trials that follow a RCT study design in attempting to elicit an answer to the review question. For that reason, it was expected that only a few RCTs would be found and a randomized, double-blind *in situ* study design was accepted as an alternative. Besides one single RCT (12), only three *in situ* trials (11,24,25) were identified for review and the further inclusion of nine two-arm laboratory trials (10,22,23,26-31) was, therefore, accepted. The advantage of *in situ* and laboratory trials, in addressing the review question, is that both provide objectively assessed outcomes. Such outcomes are based on recognized laboratory procedures and include objective, instrument-based, measurements. This is especially the case for laboratory study designs where confounding clinical factors, such as fluoride exposure or oral hygiene measurements, are absent. It has been suggested that bias or systematic error caused by the lack of randomized sequence allocation, allocation concealment or evaluator blinding has less influence on objectively assessed outcomes trials (32). For that reason, no quality assessment concerning the internal validity of included laboratory trials was conducted in this review. However, laboratory trials, particularly those involving non-human tissue, carry the uncertainty of extrapolation of their results to physiological effects in humans. For this reason, the laboratory results reported in this systematic review are regarded as weak evidence for clinical considerations trials (27).

The obvious limitation of the *in situ* trials, requiring participants to wear appliances containing enamel slabs that were analyzed in a laboratory after exposure, was that the length of exposure was relatively short and the number of participants was limited (Table 2). It has been suggested that trials with small sample size, inadequate random sequence allocation and inadequate allocation concealment generate higher overestimation of the observed treatment effect in the test group than do trials with larger sample size trials (33). All three *in situ* trials scored "B" (unclear) for randomized sequence allocation, allocation concealment and evaluator blinding, owing to lack of information in the text (Table 1). Thus, the *in situ* results favoring RM-GIC above composite resin may have been overestimated; not only because of the lack of adequate random sequence allocation and allocation concealment, but also because of the very small sample sizes of the *in situ* trials.

Quality assessment of the single RCT (12) also indicated uncertainty about whether the randomized sequence allocation, allocation concealment and evaluator blinding was conducted effectively in order to control bias (Table 1). Such bias or systematic error may affect studies, causing either an over- or an under-estimation of the treatment effect of an investigated clinical procedure. Overestimation has been observed to be the most common (34). Kjaergard et al. reported a treatment effect overestimation of 48% caused by lack of random sequence allocation (33) and Egger et al. reported a treatment effect overestimation of 54% and 53% due to lack of allocation concealment and lack of evaluator blinding (35). As the single RCT (12) included in this review did not provide clear information about these items, its results may have been affected by selection and detection bias.

Despite the danger of bias influence on the accepted *in situ* (11,24,25) and clinical (12) results, the extent of such influence might be limited, as all outcomes were derived by objective (laboratory-based) assessment (32).

As in any systematic review, other aspects in the review methodology may also have contributed to limitations in its results, despite its comprehensive approach to systematically searching for relevant literature: i) not all relevant publications were listed in the selected databases, ii) not all relevant publications were published in the specified review language (English), iii) not all relevant publications could be identified using the constructed strings of search terms. Thus, some relevant studies may not have been included.

Within the limitations of this quantitative systematic review, the results suggest that RM-GIC is associated with a higher reduction of demineralization during caries challenge of hard tooth tissue than non-fluoride containing composite resin. An equal effect between RM-GIC and fluoride containing composite resin was identified in laboratory and *in situ* trials. Owing to the large clinical and methodological heterogeneity of the extracted data (Table 2), it was not possible to express quantitatively the differences of measured outcomes between the compared materials, as combined weighted mean difference (WMD), pooled by meta-analysis. Instead, results were reported quantitatively as individual mean differences (MD) with 95% confidence intervals per dataset (Figs. 1-3). The presented mean differences (MD) were shown to depend

on the proximity of the point of measurement to the material (11,12,23) and the depth of measurement from the tissue surface (29). Furthermore, no preventive effect of RM-GIC superior to that of non-fluoride containing composite resin was observed *in situ* if participants brushed their teeth with toothpaste containing fluoride (1.1 µg F/g) (11).

In conclusion: the evidence, established through this quantitative systematic review, suggests that RM-GIC is associated with a higher reduction of demineralization in adjacent hard tooth tissue under caries challenge than composite resin without fluoride. No difference was found when RM-GIC was compared with fluoride-containing composite resin *in situ*. The observation of such an effect is dependent upon the point of measurement (proximity and depth) in the tissue, as well as upon the exposure of patients to other fluoride sources. The poor internal validity of the included trials warrants further high-quality (clinical or alternatively, *in situ*) RCTs, in order to answer the review question more conclusively. Reporting of such trials should follow the CONSORT statement (36) and, particularly, include a clear description of how the randomized allocation of study subjects to test- and control groups was done and state who generated the allocation sequence, who enrolled the subjects and who assigned subjects to their groups. Reporting should further include information about whether such allocation was concealed from the clinical operators until interventions were assigned and, if it was, about how such concealment was done. Reports should, where possible, indicate whether assessment of the treatment outcome was conducted by evaluators who were blind to allocation of the study subjects into groups and should also discuss details of any possible confounding factors with potential influence on the observed treatment effect.

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