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Therapeutic effect of glass-ionomers: an overview of evidence

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ABSTRACT

The requirements for an ideal restorative material include adhesion to tooth structure (enamel and dentine) and an ability to withstand the traumas of occlusion. However, some level of an anticaries effect is also desirable. After a long history of glass-ionomer cement (GIC) development, an evidence base in support of the therapeutic effect of GIC, particularly with regard to its anticaries effect, is emerging. This evidence is increasingly presented through systematic reviews of clinical GIC application and, to a certain extent, relates to a caries-preventive effect of the material itself. However, the strength of evidence supporting other aspects of GIC, such as a higher remineralizing effect, fluoride uptake in hard tooth tissue and fluoride release of GIC, is limited. Nevertheless, the results of these *in situ* and laboratory trials provide valuable insights into factors that facilitate understanding of the clinical efficacy of GIC.

Keywords: Glass-ionomer cement, caries, systematic review evidence.

Abbreviations and acronyms: ART = Atraumatic Restorative Treatment; ASPA II = alumino-silicate polyacrylic acid; GIC = glass-ionomer cement; KHN = Knoop hardness number; RCT = randomized control trial; RR = restorative risk.

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INTRODUCTION

The requirements for a dental restorative material are very demanding, from both a physical and a chemical point of view. Amalgam, gold and silicate cements all have long histories and it was not until the 1950s that researchers turned their thoughts to the development of entirely new products which eventually evolved to the resin composites and glass-ionomer cements (GIC) of today. The requirements for an ideal restorative material include good adhesion to tooth structure (enamel and dentine) and an ability to withstand the traumas of occlusion. However, some level of an anticaries effect is also desirable.

This article aims to provide an overview of the history and development of GIC, as well as a critique of the evidence concerning its therapeutic and caries-preventing efficacy.

History and development of glass-ionomer cement

Progress in the development of dental restorative materials has been slow over the last century and the profession has remained more or less under the recommendations of Black since the publication of his seminal text – *A work on operative dentistry* – in 1908.[1] His techniques were based upon the use of amalgam as the restorative material of choice.

During the 1950s a small group of dentists and scientists in England recognized the dearth of research into new materials for use in restorative dentistry. Their goal was to develop a material that had thermal, mechanical and optical properties, which could match those of a tooth and would also, hopefully, have some therapeutic effect. The rationale was that restorative materials should no longer merely be regarded as 'fillings' but should also be enamel and dentine substitutes.

At first an improvement of the existing silicate cements was attempted.[2] This was no easy task and led to several years of concentrated investigation – both scientific and clinical. About this time Smith began an investigation into the standard zinc oxide and eugenol cement, which was already notable for its sedative effect on an inflamed pulp.[3] He decided to use a polyalkenoic acid as the liquid, rather than eugenol, and found that the resultant cement demonstrated a level of adhesion to both tooth structure and gold.[4] However, its physical properties were less than ideal and this class of cement failed to succeed.[5]

Meanwhile, Wilson and his team at the Laboratory of the London Government Chemist pursued their chosen path to find out more about the silicate cements. Modern thinking and technology revealed the true nature of the chemical setting reaction and Wilson decided to adopt Smith's use of a polyalkenoic acid as the liquid. The result was a surprise and the beginnings of a success.[6] It was recognized that a dental adhesive must be hydrophilic because it needs to compete with water for the surface of the tooth, while at the same time being resistant to hydrolysis. Because the group of polyalkenoic acids is both ionic and polymeric, this proved effective. Their carboxyl groups, which enter the structure of hydroxyapatite by displacing phosphate from the surface, are the principal agents of their bonding with the hydroxyapatite constituent of the tooth. Thus, adhesion is permanent because of the development of a multiplicity of adhesive groups that are connected by covalent bonds. For adhesion to be lost, all bonds will need to be broken simultaneously. However, it appears that if one bond breaks it can reform, as long as the others are maintained.[7]

Wilson and his team continued to modify the constituents of the glass powder and the polyalkenoic acid liquid, seeking to find a material compatible with clinical requirements. Ultimately, Wilson's years of experience in other scientific endeavours paid off when he recognized that precipitation of aluminium could be controlled by use of tartaric acid.[8] The result was the generation of a useful clinical material, which was marketed as ASPA II (alumino-silicate polyacrylic acid). Clinical trials began in 1972 and by 1975 a usable material was marketed by Amalgamated Dental as De Trey ASPA II. The first formal lectures were presented by McLean at a Congress in Adelaide, South Australia, and this was followed by a series of clinically-orientated articles in the *Australian Dental Journal*.[9]

One of the most significant features of GIC is its ability to adhere to both enamel and dentine through an ion exchange mechanism. From the clinical point of view this is invaluable. No other material shows any sign of such a chemical union and microleakage has always been regarded as a serious problem in restorative dentistry because of the potential for bacterial invasion at the interface between tooth and restoration. The cavity surface must be cleaned to develop a surface that is in a condition to accept the ion exchange and this can be achieved simply by applying a 10% polyacrylic acid to the surface for 10 seconds and then washing vigorously. The dentine tubules will remain more or less sealed with remnant plugs, thus limiting the dentine fluid flow, but otherwise the surface will be clean, fully mineralized and ready for the ion exchange.[10]

From this point other manufacturers took up the challenge to continue research in an attempt to improve the physical properties, the translucency and the aesthetics. By 1977 the team at the GC Company in Tokyo, consisting of Mr Tezuka, followed by Drs Hirota and Akahane, had developed a series of materials under the label of Fuji. The ESPE Company of Germany, under the leadership of Drs Purrmann and Gasser, developed the Ketac line of materials. They were the first to place the material in capsules and this was an important step forward. As with any material that is dispensed as a powder and a liquid, the powder-to-liquid ratio is very important. Capsulation is the best solution to this problem, even if it increases the initial cost to the operator. Both companies modified the constituents as a result of their own research and the properties of their materials improved steadily.[11]

During the manufacture of the glass it is necessary to use a fluoride flux to avoid oxidation.[12] This facilitates incorporation of fluoride into the glass, regardless of what specific material is used. Fluoride will then be released after mixing with the polyalkenoic acid and will be available for uptake into tooth structure.[13]

The fluoride release from GIC is initially high but declines fairly rapidly to a level where the set cement remains mildly antibacterial. However, it is not only fluoride ions that are available. Smith[14] showed that as fluoride ions are released from the surface of a restoration, absorption of calcium and phosphate ions is needed to maintain electrolytic balance.

In 1988, Purton and Rodda[15] showed that the cement released not only fluoride ions, but also calcium and phosphate, into the tooth structure. This was subsequently confirmed by ten Cate and van Duinen in 1995[16] and eventually, by Ngo *et al.*[17] This last group conducted a clinical experiment using a newer material in which strontium had been substituted for calcium, in order to make the cement radiopaque. Calcium and strontium can more or less be regarded as substitutes for each other and the strontium could be traced to the depth of the demineralized dentine on the floor of a cavity. This confirmed the possibility of a remineralizing effect.

Research to this point has improved our knowledge of the physical properties of these materials as well as their level of bioactivity. They represent the first of the bioactive restoratives but it is suggested that some further development is needed to evolve a true substitute for enamel and dentine.

Therapeutic efficacy of glass-ionomer cement

Fluoride in the surrounding oral environment has been shown to provide a situation conducive to remineralization and a subsequent cariostatic effect.[18] Laboratory findings indicate that a fluoride concentration of 2 mg/l inhibits the formation of carious lesions by inhibiting bacterial plaque formation and encouraging the formation of hydroxyfluoroapatite which is resistant to acid dissolution.[19] Sources of the fluoride ion can be fluoride-containing restorative materials such as polyacid-modified resin composites ('compomers'), resin composites and GICs.

Fluoride release

Many laboratory trials have studied the fluoride release of GIC in comparison to that of other materials. However, no systematic review with or without meta-analysis has been conducted. Results from one trial, with one of the longest follow-up periods, found that conventional GIC released cumulatively over five times more fluoride than compomer and over 21 times more than fluoride-containing composite resin after 12 months (480+/−42) µg/cm^2; (87+/−17) µg/cm^2 and (22+/−2) µg/cm^2, respectively – ANOVA $p < 0.001$).[18] The amount of fluoride released by GIC, during a 24-hour period one year after curing, was five to six times higher than that of either compomer or a fluoride-containing composite (1.3+/−0.20) µg/cm^2; (0.21+/−0.04) µg/cm^2 and (0.23+/−0.02) µg/cm^2, respectively – ANOVA $p < 0.001$).[18]

Fluoride uptake in dental plaque

The absorption of fluoride from GIC into dental plaque has been compared to that from fluoride-containing composite resin *in situ*.[20] After 28 days, plaque accumulated around GIC restorations in enamel blocks carried by patients using removable intraoral appliances, contained over six times more fluoride than similar restorations with composite resin (median 21.18 µg/g and 3.47 µg/g, respectively, $p = 0.048$).[20] These findings are in line with the observed difference between GIC and fluoride-containing resin composite regarding the amount of fluoride released during a 24-hour period in the laboratory.[18]

Fluoride uptake in hard tooth tissue

In contrast to the fluoride absorption into dental plaque, fluoride absorption from GIC into adjacent enamel has been observed to be only twice as high as that from fluoride-containing resin composite *in situ*.[20] However, *in situ* measurements of enamel blocks restored with either material show that after 28 days, enamel adjacent to GIC contained 1181.03 ppm (95% CI 1141.34–1120.72; $p < 0.00001$) more fluoride than enamel adjacent to composite contained.[20]

Remineralizing effect

The comparatively higher fluoride uptake in enamel from GIC than from fluoride-releasing resin composite has been associated with a higher microhardness of enamel after 28 days, at various depths from the enamel surface and at a distance from the restoration of 100 to 400 µm.[20] The measured Knoop hardness number (KHN) at 20, 40 and 60 µm depth was 169.11; 102.08 and 75.30; higher, respectively ($p < 0.00001$) for enamel adjacent to GIC than for enamel adjacent to fluoride-containing resin composite.[20]

Caries-preventive effect: glass-ionomer cement compared with resin composite

There are few trials comparing the caries-preventive effect of GIC with that of resin composite. The results of two randomized control trials indicated no difference between both materials after two years in primary[21] and permanent teeth.[22]

Caries-preventive effect: glass-ionomer cement compared with amalgam

The margins of single-surface GIC restorations in permanent teeth have been shown to have significantly less carious lesions ($p = 0.003$) after six years than the margins of similar teeth restored with amalgam (OR = 2.64; 95% CI 1.39–5.03).[23] The difference between both materials regarding the numbers of carious lesions of multiple-surface GIC restorations in primary teeth after three years was not statistically significant (OR 2.00; 95% CI 0.06–5.06; $p = 0.10$) but tended to favour GIC.[23] This trend was confirmed when the three-year results were combined with data from an eight-year study[24] using meta-analysis (OR = 2.35; 95% CI 1.18–4.71; $p = 0.02$).[23]

Clinical application

GIC-based fissure sealants

Systematic reviews[25,26] have reported a poorer retention rate for GIC fissure sealants (Fig 1) than for resin-based sealants. However, when the absence of caries on permanent teeth protected by either type of sealant is compared, the pooled odds ratio (OR 0.96, 95% CI 0.62–1.49; $p = 0.87$) suggests that GIC is as effective in preventing dental caries in pits and fissures as the current 'gold standard', resin-based fissure sealants.[27] Although the GIC sealants appear clinically to be 'partially' or 'totally' lost, the openings of the fissures remain sealed. It has been hypothesized that the effectiveness of GIC is attributable to the isolation of bacteria from nutrients in the substrate below early carious lesions that have been sealed, the release of fluoride into the dentine or a combination of both factors.[28] In contrast, resin-based sealants have been shown to lose almost all of their protective effect once

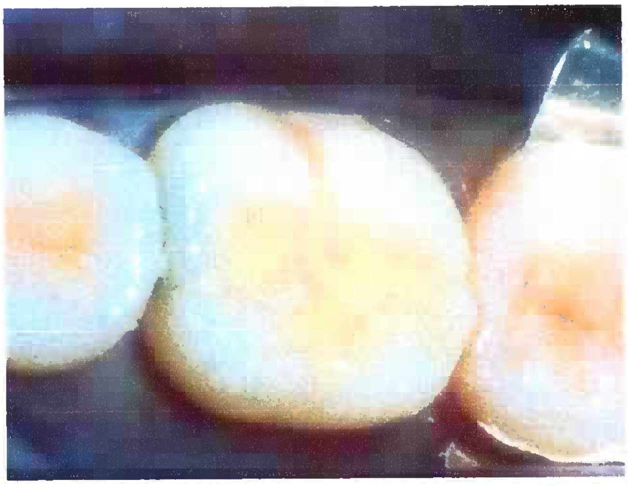

Fig 1. GIC-based fissure sealant (Image by G Mount).

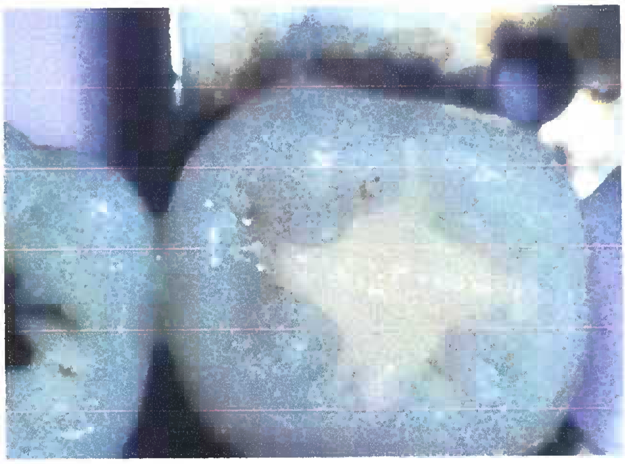

Fig 2. Restoration placed following the ART approach (Image by G Mount).

their retention is lost.[29] The pooled odds ratio (OR 0.96, 95% CI 0.62–1.49; p = 0.87) is based on a systematic review, with meta-analysis of trials that investigated only obsolete, low-viscosity GIC materials and were restricted to 2–3 years. New, high-viscosity GIC materials for sealing pits and fissures have been introduced.[30] Clinical application of these materials for sealing fissures differs from the application of low-viscosity GICs. While the latter are applied onto pits and fissures in thin consistency, using a hand instrument, a gloved index finger coated with petroleum jelly[31] is used with pressure to apply high-viscosity glass-ionomer materials. This procedure may achieve deeper fissure penetration of the GIC material than is achieved through application of thin, low-viscosity GIC with a hand instrument. Such deeper fissure penetration of the material may support its higher retention in pits and fissures. A full retention rate of 72% in high-viscosity GIC fissure sealants, as compared to 50% in low-viscosity GIC material, after three years, has been shown.[32] High-viscosity GIC applied through finger pressure has also been reported to have a four times higher chance of preventing caries in pits and fissures than resin-based fissure sealants, after five years.[30]

GIC-based tooth restorations

GIC is considered to be the material of choice for Atraumatic Restorative Treatment (ART),[33] as it has been shown to have a (hyper-) remineralizing effect on hard tooth tissue.[16,17] A systematic review with meta-analysis identified similar success rates of ART (Fig 2) and amalgam restorations of the same size.[33] In addition, the systematic review showed a relative risk (RR), calculated for one dataset, indicated that ART restorations in posterior Class V cavities in permanent teeth have a 28% higher chance of being rated successful than that of amalgam restorations, after 6.3 years (RR 1.28; 95% CI 1.08–1.51; p = 0.004). Two datasets indicated that ART restorations in posterior Class I cavities of permanent teeth have a 6% higher chance after 2.3 years (RR 1.06; 95% CI 1.01–1.10; p = 0.02) and a 9% higher chance after 4.3 years (RR 1.09; 95% CI 1.03–1.15, p = 0.004), of being rated more successful than amalgam restorations. The relative risk calculated for one further dataset (RR 1.61; 95% CI 1.11–2.34; p = 0.01) indicated that ART restorations in posterior Class II cavities in permanent teeth have a 61% higher chance of being rated more successful than amalgam restorations after 2.3 years.[33]

Strength of current evidence

The strengths of evidence for the various key points that describe the therapeutic effect of GIC vary (Table 1). The current evidence regarding clinical application of GIC as a fissure sealant or as a restorative material is based on quantitative systematic reviews.[27,33] Systematic reviews of randomized control trials (RCT), with or without meta-analysis, have been rated as providing level I evidence.[34] Such evidence provides results with a low risk of systematic error or bias and is thus considered as the most reliable.[35] Bias may affect studies, causing either an over- or an underestimation of the treatment effect of an investigated clinical procedure. Overestimation has been observed to be the most common.[36] Kjaergard *et al.*[37] reported a treatment effect overestimation of 48% due to selection bias alone and Egger *et al.*[38] reported one of 54%. Systematic reviews include: (i) a systematic search for clinical trials of all known and relevant information sources; (ii) the selection of trials with highest internal validity – or if not many trials can be found, the subgrouping of available trials in line with their various internal validity strengths; (iii) quality assessment of trials in line with internal validity criteria and, if

Table 1. Therapeutic effect of glass-ionomer cement

Key points	Outcome		Study design	Level of evidence[35]	Reference
Fluoride release	GIC versus compomer	GIC releases cumulatively 5x more fluoride during 12-month period; GIC releases 6x more fluoride during a 24-hour period, one year after curing	Two-arm laboratory trial	III-3	18
	GIC versus composite resin*	GIC releases cumulatively 21x more fluoride during 12-month period; GIC releases 6x more fluoride during a 24-hour period, one year after curing			
Fluoride uptake in plaque	GIC versus composite resin*	Plaque accumulated around GIC restorations contained over 6x more fluoride after 28 days	Randomized *in situ* trial	III-1	20
Fluoride uptake in hard tooth tissue	GIC versus composite resin*	Hard tooth tissue adjacent to GIC restorations contained over 2x more fluoride after 28 days			
Remineralizing effect	GIC versus composite resin*	Statistically significant higher microhardness of enamel adjacent to GIC			
Caries preventing effect	GIC versus composite resin*	No difference	Randomized controlled trial	II	21,22
	GIC versus amalgam	Statistically significant less carious lesions after 6 years on GIC restoration margins	Quantitative systematic review	I	23
Clinical application	GIC versus resin-based fissure sealants	No difference in caries protective effect after 3 years	Quantitative systematic review	I	27
	ART (GIC) versus amalgam	No difference in success rates	Quantitative systematic review	I	33

GIC = Glass-ionomer cement; ART = Atraumatic restorative treatment.
*Containing fluoride.

possible; (iv) meta-analysis of the data from combined trials. Through this process, systematic reviews provide the most comprehensive answer to clinical questions, with least possible systematic error/bias.

The evidence regarding the caries-preventive effect of GIC (Table 1) in comparison to that of amalgam has also been established through systematic review (Evidence level I).[25] However, the comparison of GIC to fluoride-containing resin composite is only based on level II evidence from single RCTs.[21,22] Evidence for the fluoride uptake and remineralizing effect of GIC is based on *in situ* trial results (Evidence level III-1) and evidence for the comparative amount of fluoride released by GIC is based on two-arm laboratory studies (Evidence level III-3). These levels of evidence need to be regarded as 'fair', only as they reflect varying degrees of error and thus, do not provide strong evidence for clinical practice.[35]

The obvious limitation of *in situ* trials, requiring participants to wear appliances containing enamel slabs analysed in a laboratory after exposure, is that the length of exposure is relatively short and the number of participants in this type of study is limited. 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.[37]

The advantage of *in situ* and laboratory trials is that both provide objectively assessed outcomes. Such outcomes are established through recognized laboratory procedures and include objective, instrument-based, measurements. This especially relates to laboratory study designs where confounding clinical factors are absent. It has been suggested that bias or systematic error caused by a lack of randomized sequence allocation, allocation concealment or evaluator blinding has less influence on objectively assessed outcomes trials.[39] However, laboratory trials carry the uncertainty of extrapolation of their results to physiological effects in humans.[40]

CONCLUSIONS

After a long history of GIC development, there is today an emerging evidence-base in support of the therapeutic effect of GIC, particularly against caries. This evidence is increasingly presented through systematic reviews covering clinical GIC application and, to a certain extent, a caries-preventive effect of the material itself. However, the evidence supporting other aspects of GIC, such as a superior remineralizing effect, fluoride uptake in hard tooth tissue and fluoride release of GIC is only of limited strength. Notwithstanding this limitation, the results of these *in situ* and laboratory trials provide valuable insights into factors that facilitate understanding of the clinical efficacy of GIC.

REFERENCES

1. Black GV. A work on operative dentistry. The technical procedures in filling teeth. Chicago: Medico-Dental Publishing Company, 1917.

2. Doubleday FN. The translucent filling cement. Dent Rec 1920;40:551–562.
3. Smith DC. A review of the zinc polycarboxylate cements. J Can Dent Assoc 1971;37:22–29.
4. Smith DC. A new dental cement. Br Dent J 1968;124:381–384.
5. Mizrahi E, Smith DC. The bond strength of a zinc polycarboxylate cement. Investigations into the behaviour under varying conditions. Br Dent J 1969;127:410–414.
6. Kent BE, Lewis BG, Wilson AD. The properties of a glass-ionomer cement. Br Dent J 1973;135:322–326.
7. Wilson AD, McLean JW. Glass-ionomer cement. Quintessence Publishing Company, 1988.
8. Wilson AD. Glass-ionomer cement – origins, development and future. Clin Mater 1991;7:275–282.
9. McLean JW, Wilson AD. Clinical development of the glass-ionomer cement. Formulation and properties. Aust Dent J 1977;22:31–36.
10. Mount GJ. Adhesion of glass-ionomer cement in the clinical environment. Oper Dent 1991;16:141–148.
11. Davidson CL. Glass-ionomer cement, an intelligent material. Bull Group Int Rech Sci Stomatol Odontol 1998;40:38–42.
12. Mount GJ. An atlas of glass-ionomer cements. 3rd edn. London: Martin Dunitz, 2004.
13. Marinho VC. Cochrane reviews of randomised trials of fluoride therapies for preventing dental caries. Eur Arch Paediatr Dent 2009;10:183–191.
14. Smith DC. Buonocore Memorial Lecture. A milestone in dentistry. Oper Dent 1982;7:4–25.
15. Purton DG, Rodda JC. Artificial caries around restorations in roots. J Dent Res 1988;67:817–821.
16. ten Cate JM, van Duinen RNB. Hypermineralization of dentinal lesions adjacent to glass-ionomer cement restorations. J Dent Res 1995;74:1266–1271.
17. Ngo HC, Mount G, McIntyre J, Tuisuva J, Von Doussa RJ. Chemical exchange between glass-ionomer restorations and residual carious dentine in permanent molars: an in vivo study. J Dent 2006;34:608–613.
18. Aboush YE, Torabzadeh H. Fluoride release from tooth-colored restorative materials: a 12-month report. J Can Dent Assoc 1998;64:561–564.
19. Wahab FK, Shellis RP, Elderton RJ. Effects of low fluoride concentrations on formation of caries-like lesions in human enamel in a sequential-transfer bacterial system. Arch Oral Biol 1993;38:985–995.
20. Benelli EM, Serra MC, Rodrigues AL Jr, Cury JA. In situ anticariogenic potential of glass ionomer cement. Caries Res 1993;27:280–284.
21. Ersin NK, Candan U, Aykut A, Onçağ O, Eronat C, Kose T. A clinical evaluation of resin-based composite and glass ionomer cement restorations placed in primary teeth using the ART approach: results at 24 months. J Am Dent Assoc 2006;137: 1529–1536.
22. Levy SM, Jensen ME. A clinical evaluation of the restoration of root surface caries. Spec Care Dentist 1990;10:156–160.
23. Mickenautsch S, Yengopal V, Leal SC, Oliveira LB, Bezerra AC, Bönecker M. Absence of carious lesions at margins of glass-ionomer and amalgam restorations: a meta-analysis. Eur J Paediatr Dent 2009;10:41–46.
24. Qvist V, Laurberg L, Poulsen A, Teglers PT. Eight-year study on conventional glass ionomer and amalgam restorations in primary teeth. Acta Odontol Scand 2004;62:37–45.
25. Ahovuo-Saloranta A, Hiiri A, Nordblad A, Mäkelä M, Worthington HV. Pit and fissure sealants for preventing dental decay in the permanent teeth of children and adolescents. Cochrane Database Syst Rev 2008;(4):CD001830.
26. Mejàre I, Lingström P, Petersson LG, *et al.* Caries-preventive effect of fissure sealants: a systematic review. Acta Odontol Scand 2003;61:321–330.
27. Yengopal V, Mickenautsch S, Bezerra AC, Leal SC. Caries-preventive effect of glass ionomer and resin-based fissure sealants on permanent teeth – a meta analysis. J Oral Sci 2009;51:373–382.
28. Oong EM, Griffin SO, Kohn WG, Gooch BF, Caufield PW. The effect of dental sealants on bacteria levels in caries lesions: a review of the evidence. J Am Dent Assoc 2008;139:271–278.
29. Williams B, Laxton L, Holt RD, Winter GB. Fissure sealants: a 4-year clinical trial comparing an experimental glass polyalkenoate cement with a bis glycidyl methacrylate resin used as fissure sealant. Br Dent J 1996;180:104–108.
30. Beiruti N, Frencken JE, van't Hof MA, Taifour D, van Palenstein Helderman WH. Caries-preventive effect of a one-time application of composite resin and glassionomer sealants after 5 years. Caries Res 2006;40:52–59.
31. Frencken JE, Makoni F, Sithole WD. ART restorations and glass ionomer sealants in Zimbabwe: survival after 3 years. Community Dent Oral Epidemiol 1998;26:372–381.
32. van't Hof MA, Frencken JE, van Palenstein Helderman WH, Holmgren CJ. The atraumatic restorative treatment (ART) approach for managing dental caries: a meta-analysis. Int Dent J 2006;56:345–351.
33. Mickenautsch S, Yengopal V, Banerjee A. Atraumatic restorative treatment versus amalgam restoration longevity: a systematic review. Clin Oral Investig 2010;14:233–240.
34. Merlin T, Weston A, Tooher R. Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'level of evidence'. BMC Med Res Methodol 2009;9:34.
35. Evans D. Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions. J Clin Nurs 2003;12:77–84.
36. Chalmers TC, Matta RJ, Smith H Jr, Kunzler AM. Evidence favoring the use of anticoagulants in the hospital phase of acute myocardial infarction. N Engl J Med 1977;297:1091–1096.
37. Kjaergard LL, Villumsen J, Gluud C. Reported methodological quality and discrepancies between large and small randomized trials in meta-analyses. Ann Intern Med 2001;135:982–989.
38. Egger M, Jüni P, Bartlett C, Holenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study Health Technol Assess 2003;7:1–76.
39. Wood L, Egger M, Gluud LL, *et al.* Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ 2008;336:601–605.
40. Rodrigues E, Delbem ACB, Pedrini D, Oliveira MSR. pH-cycling model to verify the efficacy of fluoride-releasing materials in enamel demineralization. Oper Dent 2008;33:658–665.

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