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Review article

Direct versus indirect inlay/onlay composite restorations in posterior teeth. A systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate the long-term clinical performance of direct versus indirect composite inlays/onlays in posterior teeth.
Data: Screening for inclusion eligibility, quality assessment of studies and data extraction was performed independently by two authors.
Sources: The electronic databases MEDLINE, EMBASE, Cochrane Oral Health Group's Trials Register and CENTRAL were searched (14.12.2015), with no restriction to publication date or language. We included only randomised controlled trials (RCTs) and evaluated them according to Cochrane risk of bias tool. The main outcome assessed was the restoration failure, determined by several clinical parameters.
Study selection: Two studies concerning direct and indirect inlays (82 patients with 248 restorations) and one study for onlays (157 patients with 176 restorations) satisfied the inclusion criteria. Two trials, one of unclear and one of high risk of bias, could be mathematically combined. The meta-analysis indicated no statistically significant difference in the risk failure between direct and indirect inlays, after 5 years (RR: 1.54; 95% CI: 0.42, 5.58; p = 0.52) or 11 years of function (RR: 0.95; 95% CI: 0.34, 2.63; p = 0.92). Only one parameter, the marginal discoloration, slightly favored direct inlays after 11 years (RR: 0.41; 95% CI: 0.17, 0.96; p = 0.04). Only one study dealt with onlays; an overall 5-year survival of 87% (95% CI: 81–93%) was reported.
Conclusion: The difference of the two techniques did not reach statistical significance in order to recommend one technique over the other. The scarcity of primary studies support the need for further well-designed long-term studies in order to reach firm conclusions about both techniques.
Clinical significance: Resin composite materials, placed directly or indirectly, exhibit a promising long-term clinical performance when rehabilitation of posterior teeth is needed. Although many years in clinical practice, the selection of the best treatment protocol still remains subjective. The available studies, and their synthesis, cannot provide reliable evidence in this field.

1. Introduction

Failure of dental restorations presents a major complication in everyday dental practice. It has been reported that about 60% of all operative dental workload refers to placement and replacement of restorations [1]. Correct material manipulation and proper technique selection may be regarded as the key factors that affect restoration success or failure [2].

Contemporary dentistry evolves along with patient's demand for high aesthetics. Even though amalgam and gold have been materials with a long history of clinical success and biocompatibility, patients often reject these treatment options, as the desire of a restoration that resembles natural tooth structure, even for posterior teeth, is high [3].

Conservative restorative dentistry is provided with a wide range of techniques and systems for the rehabilitation of posterior teeth in a minimal invasive way. Resin composite materials, placed directly or indirectly, are among the best alternative non-metallic, tooth-colored restorative treatments [4].

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Composite resin materials usually consist of a matrix (organic polymer) and fillers (combination of inorganic particles) of different types. Some of these resinous materials are based on Bisphenol-A (BPA), which is used as a precursor of BPA glycidyl dimetha-crylate (Bis-GMA) or BPA dimethacrylate (Bis-DMA). The BPA structure assembles a bulk, stiff chain that offers low susceptibility to biodegradation as well as great rigidity and strength [5]. Clinical, physical and mechanical properties of composite resins depend on the percentage of fillers in their volume, the particle size, and load and matrix bonding of the filler. In fact, the more the loading of the filler particle is, the less the wear resistance [6]. However, these resins are less polishable. Resin composites have gone through generations of traditional (macro-filled) composites, microfilled composites, hybrid composites, microhybrid composites and nano-composites. Newer resin formulations of smaller filler particles but higher filler loading percentage (approximately 66% inorganic fillers and 33% resin matrix) have been developed to enhance mechanical characteristics. The submicron-particle fillers provide abrasion resistance, more color stability and less polymerization shrinkage, while increasing flexural and tensile strength. Resins are converted from monomer to polymer by various methods of polymerization devices. The controlled degree of polymerization also enhances tensile strength, wear resistance, fracture toughness and color stability [7,8].

In direct restorations, light-cured resin composite material is placed directly into the prepared cavity. The greatest advantage presented by this procedure, is that it permits the maximum preservation of tooth structure, which collaborates with the modern concept of a minimal-invasion conservative restorative dentistry. In addition, they are usually performed in one treatment appointment, at relatively low costs. However, direct restorations are associated with polymerization shrinkage and low wear resistance [9,10].

Indirect technique involves fabricating the restoration outside the oral cavity, using an impression of the prepared tooth. This technique overcomes some of the disadvantages of direct resin composites, such as polymerization shrinkage to the width of the luting gap [11]. Furthermore, it provides better physical and mechanical properties by post-curing the inlay/onlay with light or heat, ideal occlusal morphology, proximal contouring and wear compatibility with opposing natural dentition [12,13]. However, this technique is more time consuming and requires extra cost and appointments that may, in turn, be out of patient wishes and budget.

As evident in the literature, many *in-vitro* studies have examined the behavior and durability of direct composite restorations and indirect composite inlays [14,15]. Although, several studies have verified the long-term *in-vivo* performance of those materials separately [16,17], only few have compared these techniques [18,19]. In a recent systematic review, Grivas et al. concluded that there was insufficient evidence to make recommendations for the use of indirect composite inlays over direct. In this review, the variety of methodology, the heterogeneity of the trials – 3 randomized controlled trials (RCTs) and 4 controlled clinical trials CCT until 2013 were considered eligible- as long as the unlimited observation time could not permit a valid assessment on the basis of a meta-analysis regarding the longevity of the composite inlays [20]. Even though there is a systematic review that compares clinical effectiveness of composite versus ceramic inlays/onlays [21], there is no systematic review apparent in the literature that has evaluated effectiveness of direct versus indirect composite inlays/onlays.

The aim, therefore, of this systematic review was to provide updated evidence stemming from randomized controlled trials comparing direct and indirect composite restorations in posterior teeth, with at least 3 years of follow-up after initial restoration. Comparison results relied on the clinical parameters of longevity, secondary caries, post-operative sensitivity, marginal discoloration and color match between intervention modalities.

2. Materials and methods

This systematic review was based on the guidelines of the PRISMA Statement for reporting Systematic Reviews and Meta Analyses of studies evaluating health-care interventions [22].

2.1. Protocol and registration

Not available.

2.2. Selection criteria applied for the review

- Study design: Only randomized clinical trials were eligible for inclusion in this review. Non-randomized or quasi-randomized controlled trials were not eligible for inclusion
- Types of participants: Patients of any age who received direct or indirect composite inlays/onlays
- Type of intervention: All direct/indirect composite inlays/onlays irrespectively of the resin and bonding material and the type of tooth (molar, premolar)
- Outcome: Failure rate of direct and indirect composite inlays/onlays, (restorations which need replacement or repair) and risk ratio of (1) secondary caries, (2) postoperative sensitivity, and (3) marginal discoloration, color match between the two groups
- Follow-up: At least three years of observation
- Exclusion criteria: Animal and *in-vitro* studies.

2.3. Search strategy for identification of studies

Detailed search strategies were developed and appropriately revised for each database, considering the differences in controlled vocabulary and syntax rules. The following elec-tronic databases were searched: MEDLINE (via Ovid and Pubmed, Appendix A, from 1946 to December 14th, 2015), EMBASE (via Ovid), the Cochrane Oral Health Group's Trials Register and CENTRAL.

Unpublished literature was searched on ClinicalTrials.gov, the National Research Register, and Pro-Quest Dissertation Abstracts and Thesis database. The search attempted to identify all relevant studies irrespective of language. The reference lists of all eligible studies were hand-searched for additional studies.

2.4. Selection of studies

Two authors (F.A. and A.G.) of the review independently and in duplicate performed the study selection. The procedure composed of three stages: title-reading, abstract reading and full-text reading in order to identify studies that potentially met the eligibility criteria. After exclusion of not eligible studies, the full report of publication was obtained and assessed independently. Any disagreements were discussed and resolved by discussion and consultation with the other two authors. Reasons of exclusion and all decisions on study identification were recorded.

2.5. Data extraction and management

Data extraction was performed independently and in duplicate by the first two authors. In order to record the desired information, the following customized data collection forms were used.

- Author/title/year of study

- Design of study
- Number/age/gender of patients recruited
- Type of restoration, direct or indirect technique
- Number of tooth
- Composite used
- Bond system used
- Observation period (Follow up of patients)
- Outcome assessed
- Failure rate of direct and indirect inlays/onlays

2.6. Measures of treatment effect

For continuous outcomes, mean differences and standard deviations were used to summarize the data from each study. For dichotomous data, number of participants with events and total number of participants in experimental and control groups were analyzed. Regarding meta-analysis for dichotomous data risk ratios (RR) and their 95% confidence intervals (Cls) were calculated.

Table 1
Characteristics of included studies ordered by study design and date.

Reference type of study Country Operator-evaluation	Assessment criteria Statistical analysis	No of patients	No of restorations	Tooth	Materials	Cement	Follow up
Pallesen and Qvist [19]	Modified USPHS	28	140	88 Premolars 52 Molars	Briliant Dentin (BD) by Coltene. For inlays and direct restorations	Cements: BD by Coltene	11 y (2-5-8-11y).
RCT	X^2 and sign test	(20 female, 8 male)	28 sets (2 direct, 3 inlays)	85 MO/DO (two surfaces cavities-class II)	Estilux Posterior (EP) by Kulzer. For direct restorations	EP by Microfil Pontic C, Heraeus	
Denmark University of Copenhagen Operator:One clinician (UP) Evaluation by either UP or UP and VQ		Range: 19–64 years old (av35)	84 inlays 56 direct	55 MOD (3 surfaces cavities) Vital teeth	SR-Iso-sit (ISO) by Ivoclar. For indirect inlays	ISO by Vivadent	
Fennis et al. [23]	Authors criteria	157	92 direct 84 onlays	176 Premolars	hybrid resin composite 70% vol, 86% wt filler load; AP-X, Kuraray(direct)	Clearfil Photobond, Kuraray	Mean follow-up time was 5.6 yrs (SD, 0.9 yrs; range, 4.5–8.8 yrs) for the direct and 6.0 yrs (SD, 1.3 yrs; range, 4.5–8.5 yrs) for the inlays
RCT	Kaplan-Meier	77 males, 80 females	Vital teeth	All Class II,			
Radbound university Nijmegen, The Netherlands Evaluated by two clinicians		Mean age 54.9 yrs (range, 35.0–81.0 yrs)		Fracture of buccal or palatal cusps	Estenia(indirect)		
Cetin et al. [18]	Modified USPHS,	54	108	Molars	Indirect: 1.(Estenia [E] 2.Tescera ATL [TATL])	DC for E inlays (Panavia)	5yrs
RCT	Statistical analysis fisher exact test and McNemar x2test	22 males and 32 females 20–28yo, mean:23yo	41 Indirect inlays 21(Estenia [E] and 20Tescera ATL [TATL])	57 Class I 51 Class II	Direct: 1. Filtek SupremeXT [FSXT], 2. Tetric Evo Ceram [TEC 3. AELITE Aesthetic [AA])	Talt with Duo Link (Bisco)	
Selcuk university Konya, Turkey One clinician Evaluation by two independent dentists (blind)		Each patient 1 class one and 1 class II resto-ration	67Direct inlays (Filtek SupremeXT [FSXT], Tetric Evo Ceram [TEC], AELITE Aesthetic [AA])	Vital teeth			

MO/DO = Mesial Occlusal/ Distal Occlusal.
MOD = Mesial Occlusal Distal.
SD = Standard Deviation.

For continuous data mean difference (MD) and 95% Cls were calculated.

2.7. Unit of analysis issues

In all cases, the unit of analysis was the restored tooth (number of teeth treated).

2.8. Dealing with missing data

We contacted study authors via e-mail to request information where missing. In case of no response, only the available data were reported and analyzed. Following our request, Dr. Fennis provided additional data, concerning the exact time-point that onlays' failures had occurred during her trial [23].

2.9. Assessment of heterogeneity

We assessed clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, the interventions and the outcomes as specified in inclusion criteria.

2.10. Quality assessment

The methodological quality of RCTs was assessed by two review authors, independently and in duplicate, using the Cochrane risk of bias tool [24]. Risk of bias was assessed and judged for seven separate domains.

- Sequence generation: was the allocation sequence adequately generated?
- Allocation concealment: was allocation adequately concealed?
- Blinding of participants and investigators: was knowledge of the allocated intervention adequately prevented during the study?
- Blinding of outcome assessors: was knowledge of the allocated intervention adequately prevented before assessing the outcome?
- Incomplete outcome data: were incomplete outcome data adequately addressed?
- Selective outcome reporting: were reports of the study free of suggestion of selective outcome reporting?
- Other sources of bias: was the study apparently free of other problems that could put it at a high risk of bias?

Each study received a judgment of low risk, high risk or unclear risk of bias (indicating either lack of sufficient information to make a judgment or uncertainty over the risk of bias) for each of the seven domains. Studies were finally grouped into the following categories:

- Low risk of bias (plausible bias unlikely to seriously alter the results) if all key domains of the study were at low risk of bias.
- Unclear risk of bias (plausible bias that raises some doubt about the results) if one or more key domains of the study were unclear.
- High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more key domains were at high risk of bias.

2.11. Assessment of reporting bias

In the presence of more than 10 studies in a meta-analysis, the possible presence of publication bias was investigated.

2.12. Data synthesis

We planned to conduct meta-analyses if there were studies of similar comparisons reporting the same outcomes at the same follow-up periods. Risk ratios were combined for dichotomous data using fixed-effect models, unless there were more than three studies in the meta-analysis, when random-effects models would have been used.

3. Results

3.1. Description of studies

A total number of 42 studies were identified as relevant, as screened from the electronic searches and after the specific inclusion criteria were applied. Many studies concerning direct or indirect composite inlays separately or in comparison with ceramic inlays as well as *in-vitro* studies and studies assessing veneers were found, but their outcome was not relevant for this review. After exclusion of all duplicates, the studies were screened and assessed for eligibility. 24 studies were discarded after the title-reading stage and finally 18 abstracts were screened. 4 records met all eligibility criteria but one was excluded after full text reading, leaving 3 RCTs (2 regarding direct versus indirect inlays [18,19] and 1 regarding direct versus indirect onlays [23]) to be included in this review (Table 1). The process of study identification is presented in Fig. 1.

3.2. Quality assessment

The methodological quality of the 3 included RCTs assessed on the basis of the Cochrane risk of bias tool is shown in Fig. 2. Only one study reported an adequate randomization procedure [23]. One study was unclear about the randomization method, due to an obvious imbalance between groups and the poor description of the restriction methods [19]. One study claimed to having performed randomization after author's decision and thus it was considered as at high risk of bias in this aspect [18]. Allocation concealment was, overall, unclear. Blinding of the clinicians and patients was not always possible due to the nature of the interventions. Losses of follow-up were few and if present, they were appropriately described. There was no evidence of selective outcome reporting. Two studies, therefore, were classified as at unclear risk of bias [18,23] and one at high risk of bias [19].

3.3. Quantitative synthesis of included studies

Substantial differences in the interventions, participants, and outcomes among studies were observed. Since only one trial concerned onlays [23], quantitative analysis was only feasible between two studies, regarding direct composite inlays versus indirect composite inlays [18,19]. Moreover, some variations with respect to the type of the cavity, the number of participants and the observation period with in the studies included in the meta-analysis were also evident.

3.3.1. Effects of interventions

Two trials could be mathematically combined for this comparison [18,19]. The inlays compared, were direct or indirect placed and made of different composite resin materials. For direct inlays, Pallesen and Qvist [18] used *Brilliant Dentin (BD)* and *Estilux Posterior (EP)* and for indirect, *Brilliant Dentin (BD)*, *Estilux Posterior (EP) and SR-Isosit (ISO)*. Cetin [19] selected three nanofilled composite restorative systems *(Filtek Supreme XT [FS], 3 M ESPE, St. Paul, MN, USA; Tetric EvoCeram [TEC], Ivoclar Vivadent, Schaan, Liechtenstein; AELITE Aesthetic [AA], Bisco, Schaumburg, IL, USA*) and

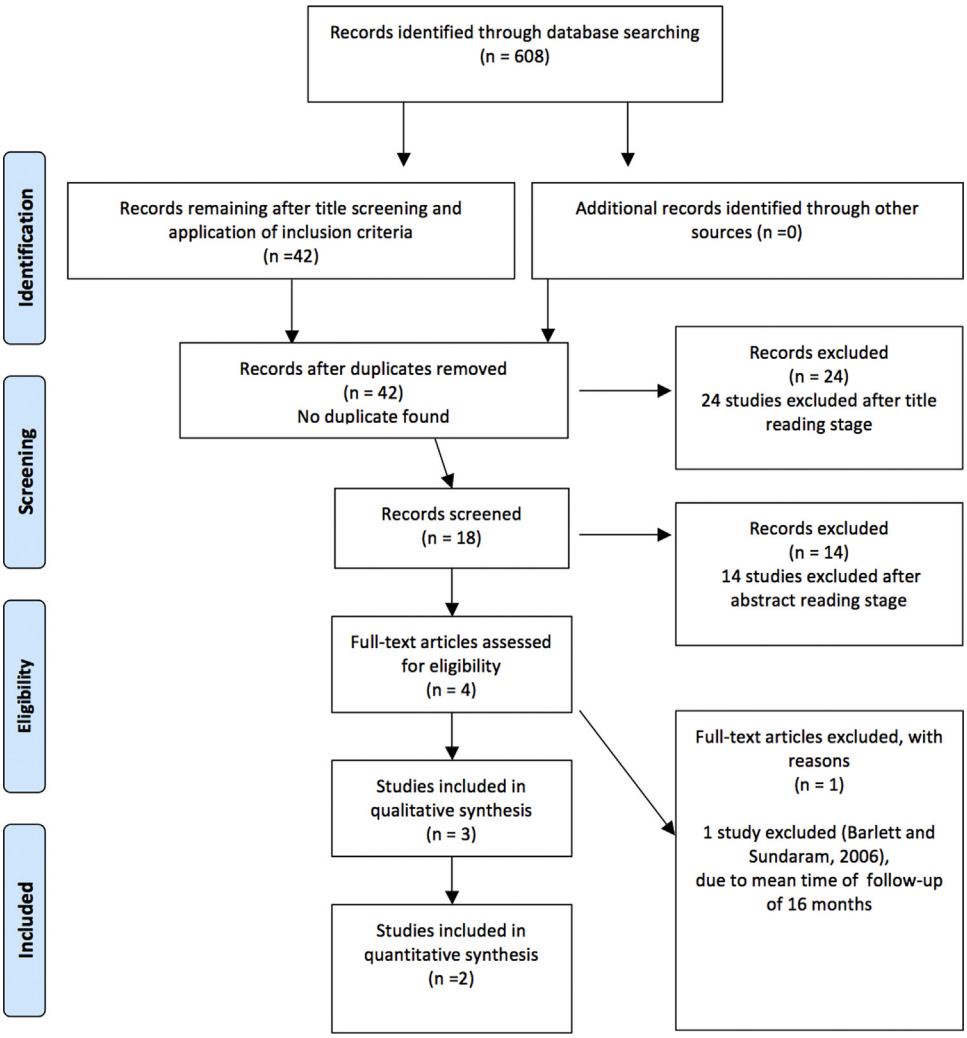

Fig. 1. Study flow diagram.

two indirect inlay restorative systems (*Estenia [E], Kuraray, Tokyo, Japan; Tescera ATL [TATL], Bisco, Schaumburg, IL, USA)* in his study. The duration of the studies was 5 [19] and 11 years [18]. Clinical outcomes were assessed at baseline, 1 and 5 years and at baseline, 2, 5, 8 and 11 years respectively. For both studies included in the meta-analysis, clinical outcome assessment involved the modified USPHS (United Stated Public Health) criteria [26]. In the Pallesen and Qvist study [18] the clinical aspects evaluated were: anatomic form, marginal adaptation, color match, marginal discoloration, surface discoloration, cracks and secondary caries. Post-operative sensitivity symptoms were performed after 1 month, then 6 months and at two years recall. In the Cetin et al. trial [19], the clinical aspects assessed were: surface texture, marginal integrity, marginal discoloration, gingival adaptation, postoperative sensitivity, color match, retention and secondary caries. The numbers of events (direct and indirect composite inlays that received the worst grades) by the four common criteria (marginal discoloration, color match, post-operative sensitivity, secondary caries) reported by both studies are presented in Figs. 3–6.

The Pallesen and Qvist study [18] reported assessment grades using the 4-step USPHS rating system which reflects absolute differences (restorations scored optimal/acceptable or unacceptable with detailed number of patients and restorations) after 2, 5, 8 and 11 years. The Cetin et al. study [19] reported 5-year grades as restorations scored A (Alpha), B (Bravo), C (Charlie), D (Delta) and results were given in percentage (%) with no detailed number of patients with missing outcome data.

Since the outcome was measured on individual teeth and not on patients (clusters), clustering needed to be taken into account for the meta-analysis. We implemented Generic Inverse Variance (GIV) with adjusted standard error. We inflated the variance of the estimate by an amount equal to (1 + (m-1)* ICC), where m is the average cluster size and ICC the interclass correlation coefficient. A conservative value of 0.1 for the ICC was used since we could not find an ICC from this or any similar trial. Average cluster size (m) was calculated to be 3.5. Design effect was, therefore, 1.25. Standard Error was, in turn, inflated by the square root of design effect (1.25), thus by 1.118.

In the Fennis et al. study [23], the onlays compared, were direct or indirect composite cuspal restorations made of two composite resin materials. For direct onlays, Fennis applied a highly filled hybrid resin composite 70% vol, 86% wt filler load; AP-X, Kuraray and for indirect 82% vol, 92% wt filler load; Estenia, Kuraray. Mean follow-up time was 5.6 years (SD: 0.9 years; range, 4.5–8.8 years) for the direct technique and 6 years (SD: 1.3 years; range, 4.5–8.5 years) for the indirect. Clinical outcome assessment was recorded on the basis of authors' predefined criteria and considered as reparable and complete failure.

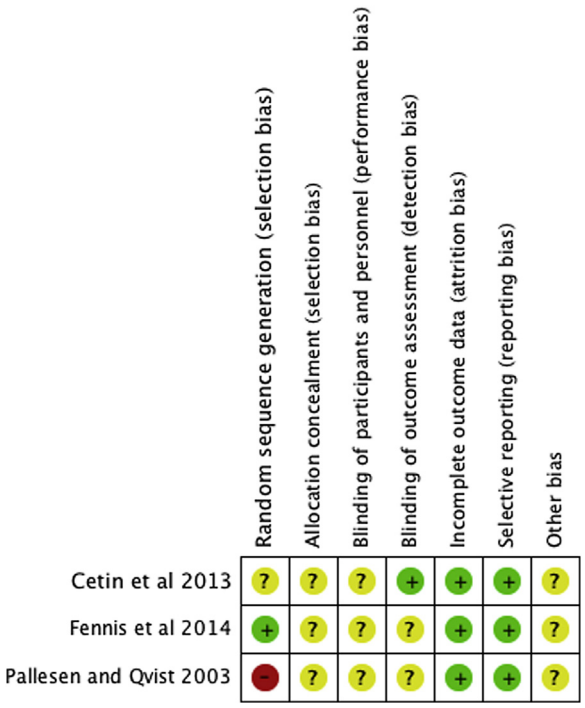

Fig. 2. Risk of bias summary for included RCTs: the plus sign indicates low risk of bias; the circle with question mark indicates unclear risk of bias; the minus sign indicates high risk of bias.

As failures, were considered restorations, in need of repair or replacement. Type and time they occurred are described in Tables 2a and 2b. Regarding inlays, the random-effects meta-analysis indicated no statistically significant difference in the risk failure between direct versus indirect inlays, after 5 years of function (RR: 1.54; 95% CI: 0.42, 5.58; $p = 0.52$) (Fig. 7), although results turn slightly in favor of indirect. However, when the observation time exceeds to 11 years, results are gravitated towards direct composite restorations, although no statistical significant difference was observed (RR: 0.95; 95% CI: 0.34, 2.63; $p = 0.92$) (Fig. 8). The degree of heterogeneity between studies was found to be overall low ($I^2 = 0\%$). Statistical analysis of the publication bias was not possible, as only two studies were included in the quantitative synthesis.

Regarding onlays, the distribution of failure categories is shown in Table 2b. The mean follow up time of failures was 35.4 months (SD, 20.9 months) for the direct technique and 37.4 months (SD, 14.4 months) for the indirect technique. An overall five-year survival of 87% (95% CI = 81–93%) of Class II cavity and a missing cusp restorations was obtained (pooled Kaplan-Meier analyses). Five-year survival rate was higher for direct than indirect restorations for both repairable (89.9% vs 83.2%) and complete failures (91.2% vs 83.2%), however differences were not statistically significant (reparable failure 95% CI = −5.1–18.5%, $p = 0.23$, complete failure, 95% CI = −3.6–19.6%, $p = 0.15$).

3.3.2. Secondary caries

In the Pallesen and Qvist study [18], a relatively low frequency of secondary caries was detected for the direct and indirect composite restorations. More specifically, two direct restorations (4%) had been detected with secondary caries in the proximal gingival area at 5 and 9.2 years. Four indirect inlays (6%) in four teeth were diagnosed with secondary caries at 6.5, 6, 8 and 8.8 years respectively. Cetin et al. in his RCT [19] required replacement of only one direct composite restoration (member of TEC group) due to secondary caries, after three years. The meta-analysis indicated no statistically significant differences in the risk ratio between direct versus indirect composite inlays in this aspect (RR: 0.93; 95% CI: 0.21, 4.04; $p = 0.92$), (Fig. 3). Cluster analysis was not performed for this parameter, as in Cetin et al. study [19] only one event was present. Finally, in the Fennis et al. study [23], secondary caries has been reported at only one indirect inlay.

3.3.3. Postoperative sensitivity

Regarding postoperative sensitivity, Cetin et al. [19] reported sensitivity to 4% of the restorations (three indirect, one direct); however only one indirect inlay required canal treatment and replacement after two years. Similarly, Pallesen and Qvist [18] found 7% and 10% of post-operative sensitivity for direct and indirect inlays respectively. The findings suggest that there is insignificant difference between the two methods and meta-analysis risk ratio results also confirm that (RR: 0.60, 95% CI: 0.19, 1.90; $p = 0.38$), (Fig. 4). According to Fennis et al. [23], one direct onlay restoration had to be replaced due to post-operative sensitivity and was considered failed.

3.3.4. Esthetic quality

Regarding color match and marginal discoloration, a detailed report was given by Pallesen and Qvist [18], where inlays scored better than fillings. Color match and discoloration of the margin were 44%–50% respectively for indirect inlays and 33%–26% for fillings which is reported as a significant difference only for marginal discoloration, in favor of fillings. In the Cetin trial [19], at five-year evaluation, color match was predominately scored as Alpha for all groups. At the same time marginal discoloration was scored as Alpha for both direct and indirect composite restorations but there was statistical significant differences between two direct materials (AA 64%: AELITE Bisco, Schaumburg, IL, USA and TEC 95% Tetric Evo Ceram). The meta-analysis of Pallesen & Qvist and Cetin trials [18,19], indicated no statistically significant differences in the risk of color match between the two techniques (RR: 0.62; 95%CI: 0.26, 1.47; p = 0.28), (Fig. 6). However, overall marginal discoloration risk ratio was statistically in favor of direct inlays (RR: 0.41; 95% CI: 0.17, 0.96; p = 0.04), (Fig. 5). No information was reported by Fennis et al. in their RCT [23] regarding those parameters.

4. Discussion

The aim of the present systematic review was to search the relevant literature for RCTs assessing the long-term clinical behavior of direct and indirect composite inlays/onlays as well

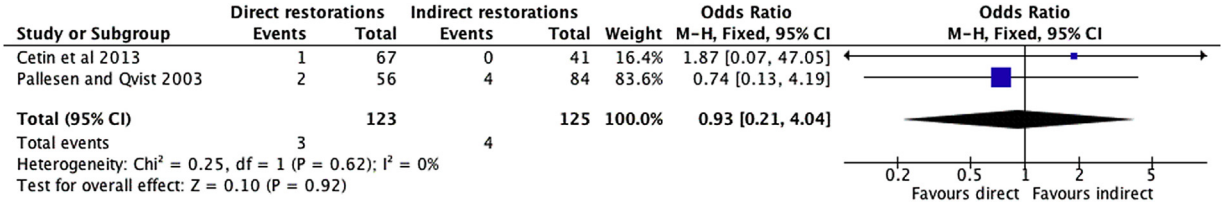

Fig. 3. Forest plot of comparison of direct vs indirect inlays regarding secondary caries during 11 years.

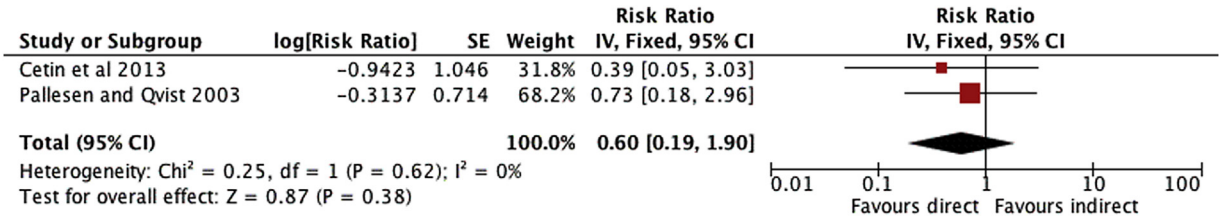

Fig. 4. Forest plot of comparison of direct vs indirect inlays regarding post-operative sensitivity (Cluster level analysis).

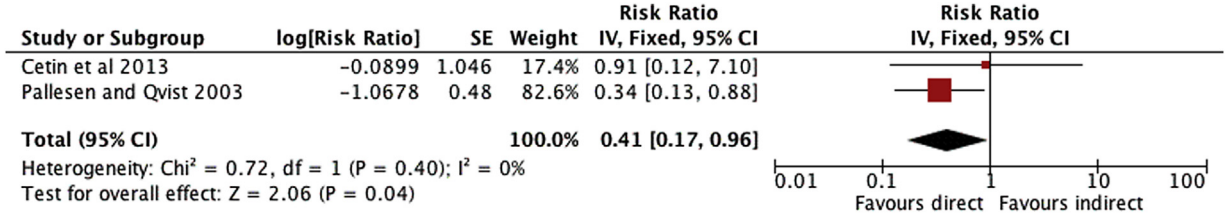

Fig. 5. Forest plot of comparison of direct vs indirect inlays regarding marginal discoloration during 11 years (Cluster level analysis).

Fig. 6. Forest plot of comparison of direct vs indirect inlays regarding color match during 11 years (Cluster level analysis).

Table 2a
Types and time of failure (Inlays).

Study	Pallesen and Qvist [18]				Cetin et al. [19]			
	Direct		Indirect		Direct		Indirect	
Failures	N	Years	N	Years	N	Years	N	Years
Secondary caries	2	5; 9.2 (replaced)	4	6; 8; 8.8 (replaced) 6.5 (repaired)	1	3 (replaced)	0	
Loss of proximal contact	2	1; 1 (replaced)	0		0		0	
Occlusal Fracture	4	5; 5; (repaired) 9.9; 10 (replaced)	1	5 (replaced)	0		0	
Fracture of the marginal ridge	0		4	1.5; 7; 10.1 (replaced) 5 (repaired)	0		0	
Debonding of the restoration	0		1	2.7 (replaced)	0		0	
Cusp Fracture	0		2	7; 8 (replaced)	0		0	
Endodontic treatment							1	2 (replaced)

Table 2b
Types and time of failure (Onlays).

Study	Fennis et al. [23], after e-mail communication			
	Direct		Indirect	
Failures	N	Years	N	Years
Secondary caries	0		1	2.6 (replaced)
Debonding of the restoration	1	3.8 (replaced)	4	1.8; 2.3; 2.5 (repaired) 3.2 (replaced)
Cusp Fracture	3	1.8; 3.7; 4.2 (replaced)		
Cohesive failure	2	0.6 (replaced) 4.1 (repair)	1	0.6 (replaced)
Dislodgement and cohesive failure			3	2.8; 4; 4.4 (replaced)
Endodontic treatment			2	2.2; 3.1 (replaced)

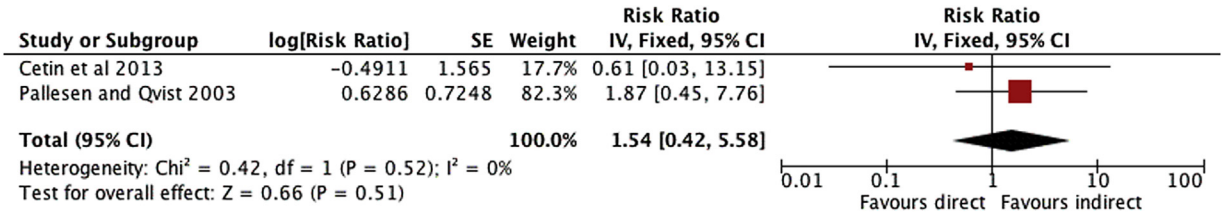

Fig. 7. Forest plot of comparison of direct vs indirect inlays, regarding restorations' failure (restorations in need of repair or replacement at 5 years), (Cluster level analysis).

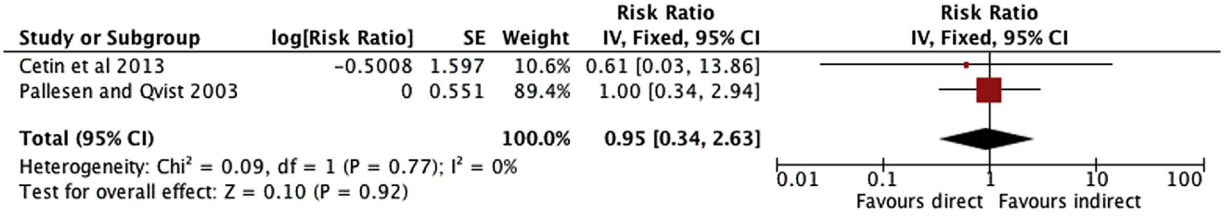

Fig. 8. Forest plot of comparison of direct vs indirect inlays, regarding restorations' failure (restorations in need of repair or replacement at 11 years), (Cluster level analysis).

to identify factors that influence the risk of failure. To our knowledge, a similar systematic review has yet not been published. The review examined reports of 3 randomized controlled trials [18,19,23]. Only one study, by Fennis et al. [23], dealt with onlays, and couldn't, therefore, be part of a quantitative analysis. An overall five-year survival of 87% (95% CI = 81–93%) of Class II cavity and a missing cusp restorations was obtained. That reveals high survival rates of composite restorations in premolars for both techniques (direct or indirect). These results are in agreement with other studies, supporting that both direct [16,17] and indirect onlays composite restorations [25,26] offer a predictable and successful treatment modality in combination with preservation of sound tooth tissue. Furthermore, the minimally cavity preparations applied for both techniques and the possibility of repair, as the nature of the material permits it, makes direct and indirect composite onlays equal recommendable.

Five-year failure rate was higher for indirect onlays than direct. However, differences were not statistically significant (reparable failure, 95% CI = −5.1 to 18.5%, $p = 0.23$ complete failure, 95% CI = −3.6 to 19.6%, $p = 0.15$). The reason of failure was predominantly fracture and cohesive restoration failure for direct restorations and dislodgment together with cohesive failures for indirect. Secondary caries was reported at only one indirect onlay. One direct onlay restoration had to be replaced due to post-operative sensitivity. Although baseline and five years clinical evaluation of the two techniques revealed no statistical significant difference, direct technique seems to be the most favorable mostly due to the lower treatment time and less cost [27]. A similar short-term RCT [28] reported that the indirect and direct cusp-replacing composite resin restorations provided comparable results for proximal and occlusal contacts, post-operative sensitivity and color. Nevertheless, there is a lack of evidence in the literature concerning the selection of direct or indirect resin composite onlay technique.

Regarding inlays, two studies met all eligibility criteria for inclusion in this review [18,19]. Failures necessitating restoration with replacement or repair were well reported for both studies. Failure data for inlays were combined: the resulting overall 5-year failure risk ratio was 1.54 (95% CI: 0.42, 5.58; $p = 0.52$) (Fig. 7) in favor of indirect. The 11-year failure risk ratio was 0.95 (95% CI: 0.34, 2.63; $p = 0.92$) (Fig. 8) in favor of direct composite inlays, although no statistically significant difference was observed at both time-points. However, it should be noted that these results were generated by combining only two trials with a relatively small sample size and at questionable risk of bias.

There are only few clinical studies in the literature that compare direct and indirect composite restoration and these are mostly short-term [4,29,30]. According to the results of a review by Hickel and Manhart in 2001 [31], annual failure rate of composite inlays and onlays ranged from 0% to 11.8%. Individually, concerning direct posterior composite restorations, it has been reported by Manhart et al. annual failure rates from 0,3% to 4.5%, in an observation period of 3–17 years [32]. Regarding indirect composite inlays, different studies have shown annual failure rates from 1.6% to 4.8% after 5–11 years [16,33,34]. In the Pallesen and Qvist study [18] annual failure rate of direct/indirect inlays after 11 years was 1.5% (range 1–2%) and in the Cetin et al. study direct/indirect restoration annual failure rate was 1.6% and 2.5% respectively, which is within the range of the published data.

Regarding aesthetic aspects, in Pallesen and Qvist study [18], 44% of indirect inlays and 33% of direct inlays showed optimal or acceptable color match and BD filling material showed better color match than BD inlay material ($p < 0.05$). Additionally, in Cetin et al. study color match was 100% A for the 2 direct composite materials (FS, TEC) and for one indirect (E) but 95% A for 1 indirect (TATL) and one direct (AA) at 5 years. The meta-analysis of Pallesen & Qvist and Cetin trials [18,19], indicated no statistically significant differences in the risk ratio of color match between the two techniques (RR: 0.62; 95%CI: 0.26, 1.47; $p = 0.28$), (Fig. 6) after five to eleven years. A decreased, but insignificant frequency of perfect color match has been reported for both techniques in studies with an observation period up to 10 years [16,35].

Another parameter than has been evaluated is that of marginal discoloration. Pallesen and Qvist [18], reported discoloration of the margin for 50% of indirect inlays and 26% of direct. The least marginal discoloration was found in BD and EP direct materials, although no statistical significant difference was observed. ISO material for direct and indirect inlays was found at the highest frequency of marginal discoloration with 45% and 67% respectively. Same results concerning ISO inlay material have been reported by Hannig in 1996 after 7 years [36]. In the Cetin et al. study [19], marginal discoloration was scored as Alpha for both direct and indirect composite restorations but there were statistically significant differences between two direct materials (AA 64%: AELITE Bisco, Schaumburg, IL, USA and TEC 95% Tetric Evo Ceram/Ivoclar). The overall marginal discoloration risk ratio was statistically in favor of direct inlays (RR: 0.41; 95% CI: 0.17, 0.96; $p = 0.04$), (Fig. 6) after five to eleven years. A major reason of marginal discoloration of indirect inlays was the loss of cement due to wear

[32,37]. Contrary, a higher rate of marginal discoloration in favor of direct composite inlays has been reported from other studies [16,30,34], but with insufficient significant differences. However, it is not surprising to see controversial results between studies as the materials and techniques used from authors varied. Nevertheless, it has to be noted that inadequate blinding of outcome assessment has much higher risk for introducing bias, in parameters like marginal discoloration which may considered a subjective outcome [37].

Many studies have verified that main reasons for failure of composite inlays include secondary caries and postoperative sensitivity [11,16,18,38]. In the present review, secondary caries was the principal reason of failure. In the Pallesen and Qvist study, two direct restorations (4%) had been detected with secondary caries in the proximal gingival area at 5 and 9,2 years and four indirect inlays (6%) in four teeth were diagnosed with secondary caries at 6.5, 6, 8 and 8.8 years. Cetin et al. in their RCT [19] required replacement of only one direct composite restoration (member of TEC group) due to secondary caries, after three years. The low incidence of secondary caries at Cetin et al. trial may be explained by the newer generation bonding agents in combination with all-enamel margins restorations included in the study. The meta-analysis indicated no statistically significant differences in the risk ratio between direct versus indirect composite inlays (RR: 0.93; 95% CI: 0.21, 4.04; $p = 0.92$), (Fig. 3) in this aspect, after five to eleven years. However in Pallesen and Qvist study [18] it is mentioned that the actual study population showed low to moderate caries activity and in Cetin et al. trial that the restorations were carried out by excellent clinicians under optimal conditions, while patients were specifically selected for good compliance. Thus, these parameters are likely to have an important impact on our confidence in the estimate effect and may change the estimate in 'real-life' circumstances.

In the evaluation of the criterion hypersensitivity, Pallesen and Qvist trial [18] showed better results for direct (7%) than indirect (10%) inlays while Cetin et al. [19] reported sensitivity for five teeth at baseline and one indirect inlay that required canal treatment; Meta-analysis on clusters (RR: 0.60, 95% CI: 0.19, 1.90; $p = 0.38$), (Fig. 4) suggested that there is insignificant difference between the two methods after five to eleven years, although results were in favor of direct inlays. Postoperative hypersensitivity is usually an early complication of dental restorations, often encountered after the luting of the adhesive restoration [33,39]. The high incidence of post-operative sensitivity at the Pallesen and Qvist study [18] compared to Cetin et al. [19] can be attributed to the older bonding agents and resin cements available at that time. Lastly, the isolation method of the operative field (cotton rolls but no rubber dam used in any of the studies) was found not to influence the failure rate. That was in agreement with the study of Raskin et al., where in a ten-year evaluation of posterior composite restorations, no significant differences were observed between these two isolation methods [40].

4.1. Quality of the evidence

The present systematic review is not free of limitations. The number of the studies included (2 RCTs for inlays and one RCT for onlays) and the sample size (157 patients with 176 restorations for direct/indirect onlays and 82 patients with 248 restorations for direct/indirect inlays) may be regarded as relatively small. The included studies, moreover, were found to be at unclear or high risk of bias. Additionally, included trials concerning inlays, had some methodological issues: although both trials [18,19] presented low heterogeneity regarding the cavity size, tooth type was different; only molars were restored in Cetin et al. study [19], whereas molars and premolars were restored in Pallesen and Qvist study [18]. Finally, the observation time differed between the studies (5 versus 11 years) and the composite restorative materials utilized were various. Nevertheless, the statistical analysis, tried to minimize these imbalances, and, indeed, was performed at a great extent in a homogeneous sample and materials assessing common outcomes at common time-points, taking clustering into consideration, as well.

4.2. Implications for research

The control of multiple variables necessary for such RCTs makes the designing of new studies difficult. Moreover, the strict inclusion criteria needed and the lack of patients with specific characteristics willing to participate in a study make it difficult to achieve a proper sample size. These reasons, as well as the long follow-up observation period that is often required for such studies, may explain the scarcity of research in the field.

Consequently, greater attention to the design and reporting of studies should be given in order to improve the quality of clinical trials on composite inlays/onlays. In our review, the minimum follow-up period accepted was 3 years for the analysis of the long-term behavior of those techniques, as this may represent better the patients' interests. Thus, more long-term RCTs are required.

5. Conclusions

Overall, there is insufficient evidence to make strict recommendations in favor of direct over indirect technique. The results of our review and meta-analysis derive from studies with unclear and high risk of bias. Certainly, further well-designed long-term studies should be undertaken in order to make more meaningful comparisons or recommendations about both techniques.

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Conflict of interest

The authors declare no conflict of interest on relevant composite resin materials.

Appendix A.

Medline via Pubmed, search date: 14.12.2015.

#1	dental inlay	3828
#2	dental onlay	3762
#3	(dental onlay) OR dental inlay	4151
#4	(((dental onlay) OR dental inlay)) AND indirect[Title/Abstract]	450
#5	(((dental onlay) OR dental inlay)) AND direct[Title/Abstract]	350
#6	((((((dental onlay) OR dental inlay)) AND direct[Title/Abstract])) OR ((((dental onlay) OR dental inlay)) AND indirect[Title/Abstract])	608
#7	((((((dental onlay) OR dental inlay)) AND direct[Title/Abstract])) OR ((((dental onlay) OR dental inlay)) AND indirect[Title/Abstract]) Filters: Randomized Controlled Trial	33
#8	((posterior[Title/Abstract]) AND restoration*[Title/Abstract]) AND (direct[Title/Abstract] OR indirect[Title/Abstract])	521
#9	((posterior[Title/Abstract]) AND restoration*[Title/Abstract]) AND (direct[Title/Abstract] OR indirect[Title/Abstract]) Filters: Randomized Controlled Trial	29
#10	(((((((dental onlay) OR dental inlay)) AND direct[Title/Abstract])) OR ((((dental onlay) OR dental inlay)) AND indirect[Title/Abstract]))) AND (failure OR success) Filters: Randomized Controlled Trial	14
#11	(((((((dental onlay) OR dental inlay)) AND direct[Title/Abstract])) OR ((((dental onlay) OR dental inlay))	1

(*Continued*)

#1	dental inlay	3828
	AND indirect[Title/Abstract]))) AND survival Filters: Randomized Controlled Trial	
#12	(((((posterior[Title/Abstract]) AND restoration*[Title/Abstract]) AND (direct[Title/Abstract] OR indirect[Title/Abstract])) AND Randomized Controlled Trial[ptyp])) AND survival	3
#13	(((((posterior[Title/Abstract]) AND restoration*[Title/Abstract]) AND (direct[Title/Abstract] OR indirect[Title/Abstract])) AND Randomized Controlled Trial[ptyp])) AND (failure OR success)	17
#14	(dental restoration failure[MeSH Terms]) AND (direct OR indirect) Filters: Randomized Controlled Trial	53
#15	((dental restoration failure[MeSH Terms]) AND direct) AND indirect Filters: Randomized Controlled Trial	9
#16	((dental onlays[MeSH Terms]) AND direct) AND indirect Filters: Randomized Controlled Trial	10
#17	((dental inlays[MeSH Terms]) AND direct) AND indirect Filters: Randomized Controlled Trial	10
#18	((composite resins[MeSH Terms]) AND restoration) AND (direct[Title/Abstract] OR indirect[Title/Abstract]) Filters: Randomized Controlled Trial	111
#19	(((((composite resins[MeSH Terms]) AND restoration) AND (direct[Title/Abstract] OR indirect[Title/Abstract])) AND Randomized Controlled Trial[ptyp])) AND survival	13
#20	(((((composite resins[MeSH Terms]) AND restoration) AND (direct[Title/Abstract] OR indirect[Title/Abstract])) AND Randomized Controlled Trial[ptyp])) AND (failure OR success)	51

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