Which reconstructive procedures are effective for treating the periodontal intraosseous defect?

Leonardo Trombelli

Deep intraosseous defects represent a major challenge for the clinician. Sites with intraosseous lesions have been shown to be at higher risk of disease progression in subjects who had not received systematic periodontal therapy (78). Treatments of intrabony defects include scaling and root planing with or without surgical access flap. When the periodontal debridement is surgically performed, additional osseous resective therapy and/or reconstructive therapy by means of the application of membranes, biological agents or grafting biomaterials can be used to correct the bone deformities induced by destructive periodontal disease.

In this respect, reconstructive procedures have been used with varying success during the past decades to accomplish the restitutio ad integrum of lost attachment apparatus in deep intraosseous defects. Although observations from histologic studies in humans (6, 19, 41, 105, 125) and data from controlled clinical trials have demonstrated that some of the available grafting procedures may result in healing that can be termed 'periodontal regeneration', complete and predictable reconstruction of periodontal tissues is still difficult to obtain. Despite the widely accepted effectiveness of the reconstructive procedures previously documented (28, 36, 89), there is a substantial variation in clinical response that can only in part be attributed to the biomaterials/biological agents adopted (54).

Several traditional reviews have previously reported the additional effect of the use of different reconstructive procedures in intraosseous defects (9, 28, 32, 42, 46, 48, 50, 64, 65, 72, 87, 90, 101, 117). Unfortunately, it has been shown that many traditional medical reviews are haphazard and biased, often reflecting the opinion of the review’s authors. In contrast, systematic reviews follow explicit, well-documented, scientific methodology in order to reduce both systematic errors (biases) and random errors (those occurring by chance) and provide a more objective, comprehensive view of the research literature (30). Since all reconstructive procedures are time-consuming, technically demanding and financially costly, in view of the great expense of the reconstructive device/biomaterials and surgical time, systematic reviews are of paramount importance to assess the efficacy of reconstructive procedures in the treatment of periodontal intraosseous defects measured against the current standard of surgical periodontal treatment, access flap surgery.

The aim of this article is to determine the effect of the use of guided tissue regeneration, grafting procedures or the application of enamel matrix proteins in addition to conventional open flap debridement (OFD) in the treatment of deep intraosseous defects. Specifically, the additional efficacy of each reconstructive procedure in comparison to the OFD-only procedure will be evaluated by means of clinical and patient-centered outcome parameters on a short- and long-term basis.

Guided tissue regeneration

Background

One of the most frequently documented reconstructive procedures is guided tissue regeneration (GTR) (28). In this procedure, a biocompatible barrier membrane (either resorbable or nonresorbable) is surgically implanted to isolate and protect the bone defect. If non-resorbable, the barrier is surgically removed 4–6 weeks after implantation. Connective tissue and bone regeneration may then occur within the bony lesion protected by the barrier.
The biological rationale of the procedure is based on prevention of migration of the epithelial periodontal tissues into the osseous defect, allowing time for bone and other attachment tissues to heal. During normal healing, it appears that the epithelial tissues migrate rapidly into the wound, preventing regeneration (47). The placement of a barrier membrane would thus ensure that the detached root surface becomes repopulated with cells from periodontal ligaments capable of forming bone, periodontal ligament and cementum. An alternative explanation is that the membrane provides sufficient space for optimal wound stability, an essential prerequisite for periodontal regeneration to occur (37, 119).

**Results from systematic reviews**

Recently, two systematic reviews have been published aimed at assessing the additional efficacy of GTR in the treatment of periodontal intraosseous defects with respect to OFD (71, 73). The reviews were based on randomized clinical trials of at least 6 (71) or 12 months’ (73) duration. In one systematic review (71) case-control studies as well as cohort studies were included. The literature search was extended up to and including October 2000 in one systematic review (73), and up to January 2002 in the other (71). Quality assessment of GTR systematic reviews is summarized in Table 1.

The study population was limited to patients with a clinical diagnosis of chronic adult periodontitis or periodontitis in subjects aged 21 years or older. The lower age limit was selected to include as many studies as possible, but studies specifically treating early onset forms of disease were excluded.

Short-term clinical outcome was defined as changes in clinical attachment levels, probing depths and gingival recession. Short-term changes in the morphology of the bony lesion were evaluated by means of radiographic assessment and hard tissue probing at surgical re-entry. Long-term clinical outcomes included: disease recurrence (as percentage of sites with 2 mm loss of probing attachment measured from 12 months after treatment), and tooth loss. Ease of maintenance (as percentage of sites with <4 mm probing depth), change in aesthetic appearance, postoperative complications, cost/benefit and patient well-being were considered as patient-centered outcomes.

A weighted treatment effect was calculated and the results were expressed as the weighted mean difference and 95% confidence interval for continuous outcomes and relative risk and 95% CI for dichotomous outcomes. The primary outcome measure was gain in attachment. The significance of discrepancies in the estimates of the treatment effects from the different trials (or heterogeneity) were assessed by means of Cochran’s test for heterogeneity. If any significant heterogeneity ($P < 0.1$) was detected, the significance of the treatment effects was re-assessed by using a random effects model and any heterogeneity was investigated. Subgroup analyses were planned to investigate the effects of factors thought to have the most influence on periodontal outcomes, including smoking status and initial disease severity.

In the two systematic reviews, four types of intervention were considered:

- GTR vs. open flap debridement;
- GTR and bone substitutes combined vs. OFD;
- GTR plus some form of augmentation, usually a particulate bone graft, vs. GTR alone;
- GTR using an expanded polytetrafluoroethylene (ePTFE) barrier membrane vs. GTR using a bioabsorbable barrier device.

**GTR vs. OFD**

The evaluation of clinical attachment level change for GTR alone vs. OFD was based on 10 studies (4, 12, 14, 15, 17, 59, 68, 82, 85, 111) in Needleman et al.’s systematic review (73). The other review (71), using broader inclusion criteria for study selection, found 19 studies comparing GTR vs. OFD (1, 4, 7, 14, 15, 17, 18, 45, 51, 52, 59, 74, 81, 83, 85, 98, 110, 111, 129).

The results from both systematic reviews showed a limited but statistically significantly greater attachment gain for test groups compared with OFD. For GTR, the weighted mean difference between test and control was 1.11 mm (95% CI: 0.63–1.59) in one systematic review (73), and 1.15 mm (range: –0.20–2.90) in the other (71, data not shown) (Table 2). In both systematic reviews, meta-analysis showed a high level of heterogeneity among the results from different studies.

The finding of heterogeneity is important as it suggests that the studies within the meta-analysis are too dissimilar to combine meaningfully, i.e. there is a systematic difference in one or more aspects of the studies that is not due to chance. This could be related to the types of patients/defects, the type of treatment or the internal validity of the studies. A more detailed discussion on heterogeneity will be addressed in a separate section. Despite these differences, the most likely conclusion is that GTR provides a greater gain in attachment than the
<table>
<thead>
<tr>
<th>Question (possible categories)</th>
<th>Needleman et al. (73)</th>
<th>Trombelli et al. (115)</th>
<th>Murphy &amp; Gunsolley (71)</th>
<th>Reynolds et al. (88)</th>
<th>Esposito et al. (21)</th>
<th>Giannobile &amp; Somerman (29)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Did the review address a focused question? (yes, no, can’t tell)</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td><strong>B</strong> Did authors look for appropriate papers? (yes, no, can’t tell)</td>
<td>yes</td>
<td>yes</td>
<td>no*</td>
<td>yes</td>
<td>yes</td>
<td>yes**</td>
</tr>
<tr>
<td><strong>C</strong> Do you think authors attempted to identify all relevant studies? (yes, no, can’t tell)</td>
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<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td><strong>D</strong> Search for published and unpublished literature (yes, no, can’t tell)</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes†</td>
</tr>
<tr>
<td><strong>E</strong> Were all languages considered? (yes, no, can’t tell)</td>
<td>yes</td>
<td>no</td>
<td>can’t tell</td>
<td>no</td>
<td>yes</td>
<td>no (English only)</td>
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<tr>
<td><strong>F</strong> Was any hand searching carried out? (yes, no, can’t tell)</td>
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<td>yes</td>
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<td>yes</td>
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<tr>
<td><strong>G</strong> Was it stated that the inclusion criteria were examined by at least two reviewers? (yes, no, can’t tell)</td>
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<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>H</strong> Did reviewers attempt to assess the quality of the included studies? (yes, no)</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
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<tr>
<td><strong>I</strong> If so, did they include this in the analysis? (yes, no, can’t tell, not applicable)</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td><strong>J</strong> Was it stated that the quality assessment was carried out by at least two reviewers? (yes, no, not applicable)</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>K</strong> Are the results given in a narrative or pooled statistical analysis? (narrative, pooled, not applicable)</td>
<td>pooled</td>
<td>pooled</td>
<td>pooled</td>
<td>pooled</td>
<td>pooled</td>
<td>pooled</td>
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<tr>
<td><strong>L</strong> If the results have been combined was it reasonable to do so? (yes, no, can’t tell, not applicable)</td>
<td>yes</td>
<td>yes</td>
<td>can’t tell</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
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<tr>
<td><strong>M</strong> Are the results clearly displayed? (yes, no, not applicable)</td>
<td>yes</td>
<td>yes</td>
<td>no**</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
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<td><strong>N</strong> Was an assessment of heterogeneity made and reasons for variation discussed? (yes, no, not applicable)</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
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<tr>
<td><strong>O</strong> Were the results of the review interpreted appropriately? (yes, no, can’t tell, not applicable)</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

*The systematic review was not limited to randomized clinical trials, but included cohort studies and case-control studies. ** Summary of the effect of the use of a barrier membrane as compared to OFD was not clearly provided. * Did not search for unpublished material. ** The systematic review was not limited to randomized clinical trials, but included cohort studies, case-control studies, case reports and preclinical randomized controlled investigations.
## Table 2. Mean differences (in mm) in clinical outcomes between reconstructive procedure and control (open flap debridement) procedures as assessed in systematic reviews

<table>
<thead>
<tr>
<th>Reconstructive procedure</th>
<th>Systematic reviews</th>
<th>Outcome</th>
<th>No. of studies</th>
<th>Weighted mean difference (mm)</th>
<th>95% CI (SD) [SE]</th>
<th>P-value for difference</th>
<th>P-value for heterogeneity</th>
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<tbody>
<tr>
<td><strong>GTR</strong></td>
<td>Murphy &amp; Gunsolley (71)</td>
<td>CAL change</td>
<td>18</td>
<td>1.15</td>
<td>N/A</td>
<td>&lt;0.0001</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD change</td>
<td>15</td>
<td>1.04</td>
<td>N/A</td>
<td>&lt;0.0001</td>
<td>&lt;0.01</td>
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<td></td>
<td>Needleman et al. (73)</td>
<td>CAL change</td>
<td>10</td>
<td>1.11</td>
<td>0.63, 1.59</td>
<td>*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD change</td>
<td>5</td>
<td>0.80</td>
<td>0.14, 1.46</td>
<td>*</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone gain at re-entry</td>
<td>3</td>
<td>1.39</td>
<td>1.08, 1.71</td>
<td>*</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>GTR + bone substitutes</strong></td>
<td>Needleman et al. (73)</td>
<td>CAL change</td>
<td>2</td>
<td>1.25</td>
<td>0.89, 1.61</td>
<td>*</td>
<td>0.91</td>
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<tr>
<td></td>
<td></td>
<td>PD change</td>
<td>2</td>
<td>1.24</td>
<td>0.89, 1.59</td>
<td>*</td>
<td>0.85</td>
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<td></td>
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<td>Bone gain at re-entry</td>
<td>1</td>
<td>3.37</td>
<td>3.14, 3.61</td>
<td>*</td>
<td>–</td>
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<tr>
<td><strong>Autogenous bone graft</strong></td>
<td>Trombelli et al. (115)</td>
<td>CAL change</td>
<td>1</td>
<td>1.20</td>
<td>[0.39]</td>
<td>&gt;0.20</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Reynolds et al. (88)</td>
<td>CAL change</td>
<td>3</td>
<td>0.72</td>
<td>(1.82)</td>
<td>0.030</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD change</td>
<td>1</td>
<td>0.60</td>
<td>(1.35)</td>
<td>0.062</td>
<td>–</td>
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<tr>
<td></td>
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<td>Bone fill</td>
<td>2</td>
<td>1.62</td>
<td>(1.53)</td>
<td>0.058</td>
<td>≤0.004</td>
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<td><strong>Bone allograft</strong></td>
<td>Trombelli et al. (115)</td>
<td>CAL change</td>
<td>6</td>
<td>0.36</td>
<td>–0.16, 0.87</td>
<td>0.174</td>
<td>0.013</td>
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<td></td>
<td>Reynolds et al. (88)</td>
<td>CAL change</td>
<td>11</td>
<td>0.44</td>
<td>(2.25)</td>
<td>0.008</td>
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<tr>
<td></td>
<td></td>
<td>PD change</td>
<td>9</td>
<td>0.43</td>
<td>(2.25)</td>
<td>0.032</td>
<td>NS</td>
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<tr>
<td></td>
<td></td>
<td>Bone fill</td>
<td>12</td>
<td>1.06</td>
<td>(1.97)</td>
<td>&lt;0.0001</td>
<td>NS</td>
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<tr>
<td><strong>Dentin allograft</strong></td>
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<td>CAL change</td>
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<td>0.80</td>
<td>[0.38]</td>
<td>&gt;0.50</td>
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<tr>
<td><strong>Coralline calcium carbonate</strong></td>
<td>Trombelli et al. (115)</td>
<td>CAL change</td>
<td>4</td>
<td>0.90</td>
<td>0.53, 1.27</td>
<td>&lt;0.001</td>
<td>0.104</td>
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<td></td>
<td>Reynolds et al. (88)</td>
<td>CAL change</td>
<td>4</td>
<td>0.91</td>
<td>(1.94)</td>
<td>0.004</td>
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<td></td>
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<td>PD change</td>
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<td>(2.16)</td>
<td>0.886</td>
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<td>Bone fill</td>
<td>3</td>
<td>2.21</td>
<td>(1.82)</td>
<td>&lt;0.0001</td>
<td>NS</td>
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<tr>
<td><strong>Bioactive glass</strong></td>
<td>Trombelli et al. (115)</td>
<td>CAL change</td>
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<td>1.04</td>
<td>0.31, 1.76</td>
<td>0.005</td>
<td>0.024</td>
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<tr>
<td></td>
<td>Reynolds et al. (88)</td>
<td>CAL change</td>
<td>4</td>
<td>1.05</td>
<td>(1.89)</td>
<td>0.022</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD change</td>
<td>4</td>
<td>0.71</td>
<td>(2.22)</td>
<td>0.018</td>
<td>NS</td>
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<tr>
<td></td>
<td></td>
<td>Bone fill</td>
<td>4</td>
<td>1.61</td>
<td>(1.47)</td>
<td>0.086</td>
<td>0.006</td>
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<tr>
<td><strong>Porous/nonporous hydroxyapatite</strong></td>
<td>Trombelli et al. (115)</td>
<td>CAL change</td>
<td>4</td>
<td>1.40</td>
<td>0.64, 2.16</td>
<td>&lt;0.001</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>Reynolds et al. (88)</td>
<td>CAL change</td>
<td>4</td>
<td>1.20</td>
<td>(2.22)</td>
<td>0.003</td>
<td>NS</td>
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<td></td>
<td></td>
<td>PD change</td>
<td>6</td>
<td>0.74</td>
<td>(2.12)</td>
<td>0.030</td>
<td>NS</td>
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<tr>
<td></td>
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<td>Bone fill</td>
<td>5</td>
<td>1.58</td>
<td>(1.77)</td>
<td>&lt;0.0001</td>
<td>≤0.04</td>
</tr>
</tbody>
</table>
control treatment, although the size of this superiority is unclear.

When considering the number of sites gaining less than 2 mm of attachment (73), again a significant benefit was shown for GTR [relative risk 0.58 (95% CI: 0.38–0.88, chi-square for heterogeneity 5.72 (3 df), \( P = 0.13 \)] (20, 21, 80). The number needed to treat with GTR to achieve one extra site gaining 2 mm or more attachment over OFD was therefore 8 (95% CI: 4–33), based on an incidence of 32% of sites in the control group failing to gain 2 mm or more of attachment.

For change in probing depth, five studies were found for GTR alone including change in probing depth as an outcome (4, 17, 59, 68, 85) in one systematic review (73), and 18 studies (1, 4, 7, 14, 15, 17, 18, 45, 51, 52, 59, 74, 81, 83, 99, 110, 111, 129) in the other (71). The results demonstrated a small but significantly greater probing depth reduction for GTR. Weighted mean difference ranged from 1.04 mm (range: 0.05–2.66 (71, data not shown) to 0.80 mm (95% CI: 0.14–1.46) (73) (Table 2). Again, a significant heterogeneity among studies was observed in both systematic reviews.

The only study (59) containing the radiographic data in one systematic review (73) showed a 0.6 mm gain in bone from the base of the defect in both test and control groups. The other systematic review (71) included only one study (51) that demonstrated a difference in gain of bone height of 0.90 mm, favoring GTR over OFD.

A statistically significantly greater gain in hard tissue probing was found for GTR compared with open flap debridement. This amounted to a weighted mean difference of 1.39 mm [95% CI: 1.08–1.71, chi-square for heterogeneity 0.85 (2 df), \( P = 0.65 \)] (Table 2) (73). In Murphy & Gunsolley’s systematic review (71), the additional bone gain provided by GTR at re-entry varied from 0.20 mm to 1.16 mm, with one of the selected studies favoring OFD.

### Table 2. Continued

<table>
<thead>
<tr>
<th>Reconstructive procedure</th>
<th>Systematic reviews</th>
<th>Outcome</th>
<th>No. of studies</th>
<th>Weighted mean difference (mm)</th>
<th>95% CI (SD) [SE]</th>
<th>( P )-value for difference</th>
<th>( P )-value for heterogeneity</th>
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</thead>
<tbody>
<tr>
<td><strong>PMMA-PHEMA</strong></td>
<td>Trombelli et al. (115)</td>
<td>CAL change</td>
<td>1</td>
<td>0.90</td>
<td>[0.22]</td>
<td>0.001</td>
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<td></td>
<td>PD change</td>
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<td>0.90</td>
<td>N/A</td>
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<td>Reynolds et al. (88)</td>
<td>Bone fill</td>
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<td>1.26</td>
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<td><strong>Polylactic acid granules</strong></td>
<td>Trombelli et al. (115)</td>
<td>CAL change</td>
<td>1</td>
<td>−1.45</td>
<td>N/A</td>
<td>N/A</td>
<td>–</td>
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<td>PD change</td>
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<td>−1.60</td>
<td>(0.55)</td>
<td>N/A</td>
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<td>Reynolds et al. (88)</td>
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<td>−0.28</td>
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<td><strong>Enamel matrix proteins</strong></td>
<td>Trombelli et al. (115)</td>
<td>CAL change</td>
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<td>1.33</td>
<td>0.78, 1.88</td>
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<tr>
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<td>PD change</td>
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<td>1.60</td>
<td>0.59, 2.62</td>
<td>0.002</td>
<td>&lt;0.001</td>
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<td>Esposito et al. (21)</td>
<td>CAL change</td>
<td>8</td>
<td>1.31</td>
<td>0.84, 1.78</td>
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<td>PD change</td>
<td>8</td>
<td>0.96</td>
<td>0.50, 1.41</td>
<td>&lt;0.001</td>
<td>0.002</td>
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<td></td>
<td>Radiographic bone level</td>
<td>1</td>
<td>2.0</td>
<td>0.88, 3.12</td>
<td>&lt;0.001</td>
<td>–</td>
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</table>

*P*-values are not given for Needleman et al. (73) because the 95% confidence interval was reported.

CAL, clinical attachment level. CI, confidence interval. GTR, guided tissue regeneration. PD, probing depth. PMMA-PHEMA, polymethylmethacrylate and polyhydroxyethylmethacrylate. SD, standard deviation. SE, standard error. NS, not significant.

GTR + bone substitutes vs. OFD

In one systematic review (73) two studies were selected to evaluate the adjunctive benefit of GTR + bone substitutes vs. OFD (4, 53). GTR + bone substitutes resulted in an additional clinical attachment level gain of 1.25 mm [95% CI: 0.89–1.61, chi-square for heterogeneity 0.01 (1 df), \( P = 0.91 \)] (Table 2). For change in probing depth, the results demonstrated a small but significantly greater probing depth reduction for GTR + bone substitutes vs. OFD.
substitutes [weighted mean difference 1.24 mm (95% CI: 0.89–1.59, chi-square for heterogeneity 0.03 (1 df), \( P = 0.85 \)] (Table 2). Data stemming from one study (4) showed a difference in hard tissue probing of 3.37 mm (95% CI: 3.14–3.61).

**GTR with ePTFE membrane vs. GTR with bioabsorbable membrane**

In one systematic review (71) three studies were included which directly compared the efficacy of a bioabsorbable barrier (polylactic acid or polylactic acid 910) with that of an ePTFE membrane (11, 20, 118). Meta-analysis failed to demonstrate a significant difference in clinical attachment level gain and probing depth reduction between bioabsorbable and non-resorbable membranes.

**GTR + bone substitutes vs. GTR alone**

The efficacy of the addition of a bone substitute (mainly demineralized freeze-dried bone allograft) under a membrane device was investigated in one systematic review (71). Meta-analysis of the seven selected studies (3, 10, 31, 33, 62, 77, 112) did not reveal any adjunctive effect on either clinical attachment level gain or probing depth reduction. There was significant heterogeneity among the studies when clinical attachment level gain was considered (\( P < 0.03 \)).

**Long-term and patient-centered outcomes**

Interestingly, no data were found on either long-term clinical outcomes or patient-centered outcomes. Therefore, no statements can be made regarding the efficacy of periodontal therapy using various GTR procedures to enhance tooth retention.

**Heterogeneity**

When considering the additional effect of GTR with or without bone substitutes with respect to OFD, meta-analysis showed a statistically significant heterogeneity of results from different studies, implying that the differences between the outcomes of included studies are greater than would occur by chance. The studies appear too dissimilar (some studies favor GTR, some studies show no difference between treatments) in certain respects to be sensibly combined and overall summary values should be interpreted with caution.

How confident can we be that GTR is of greater benefit than OFD? The most likely threat to this conclusion is bias. Several possible sources of bias have been investigated in one systematic review, including publication bias, concealment of group allocation and blinding of examiner and surgeon (73).

Publication bias is the preferential publication of studies with positive outcomes over studies with negative results. Investigation of this showed that it was unlikely to contribute to the results of the meta-analysis (73). However, tests for publication bias have a low power of detection. Since study quality has been shown to have a direct impact on the size of the effect of treatment (67, 93), Needleman et al. (73) explored this effect with sensitivity analyses including a compound quality scale (44) and the individual parameters of allocation concealment, examiner and therapist blinding. The results of these analyses did not help to explain the differences between studies, as heterogeneity was not eliminated despite the reduced number of included studies. In view of the limitations in study design, we should be aware that bias could be contributing to these results.

A possible explanation for the heterogeneity might be variability between studies in prognostic factors that have been documented to affect the outcome of regenerative surgery. Factors affecting GTR outcome have been extensively explored in the past 15 years. It has been suggested that the primary factors that influence the successful management of intraosseous defects when treated by barrier membranes include, but are not limited to, bacterial contamination, innate wound healing potential, local site characteristics, and surgical procedures (54). Evaluation of the relative impact exerted by these factors may help to explain the variability in outcome variables in studies selected for meta-analysis (high level of heterogeneity). Variability of results is clearly an important issue when considering the relevance of a treatment to clinical practice. In their systematic review, Needleman and coworkers (73) have attempted to explore some of the possible causes of the heterogeneity that emerged from the results across studies (sensitivity analysis).

A longitudinal study on the GTR procedure for the treatment of intraosseous defects has clearly demonstrated that the stability of the regenerative outcome is strictly dependent on a regular recall program including supra- and subgingival plaque control (13). To investigate the robustness of the results with respect to the very frequent maintenance, which may be impractical to provide in many
clinics (more often than every 3 months), a sensitivity analysis was conducted from which studies with very frequent follow-up were excluded. This eliminated heterogeneity and showed a small reduction in the weighted mean difference in clinical attachment level gain favoring GTR vs. OFD (0.9 mm, 95% CI: 0.6–1.1).

The benefits of plaque control on the short- and long-term response to periodontal therapy are well established. In contrast, smoking habit is associated with adverse healing after therapy and, particularly, less favorable regeneration (15, 109, 113). When approaching a sensitivity analysis regarding plaque and smoking, it was apparent that substantial differences in the way that both factors are reported between studies prevented sensible comparisons (73). The effect of smoking on reducing the gain in attachment following surgery is reported in only one subgroup analysis of a randomized clinical trial (59). This highlights the need for more research into prognostic factors to help explain heterogeneity.

One factor of paramount importance in explaining the study differences is the surgical technique used, with particular emphasis on preservation of the interdental tissues and/or coronal positioning to ensure primary closure and prevent/limit membrane exposure. In Needleman et al.’s review (73), two studies from the same group (14, 15) reported an attachment gain approximately twice that of the total group estimate. The authors also observed that when this same treatment approach was examined in a multicenter trial, although with less frequent maintenance (11 different clinicians), the clinical attachment level gain was highly variable between centers, showing a smaller overall benefit of GTR compared to OFD (111). They conclude that although the efficacy of GTR has been demonstrated in some studies, the effectiveness and external validity of such a technique may be questioned.

Concluding remarks

Data stemming from the two available systematic reviews on the effect of GTR for intraosseous defects indicate that:

- GTR most likely provides an additional benefit, in terms of clinical attachment level gain, probing depth reduction and defect fill, when compared to OFD in the treatment of deep intraosseous defects.
- A limited number of studies showed that the additional effect of the combination treatment (i.e. GTR + bone substitutes) is similar to GTR alone when compared to OFD with respect to attachment gain, but results in slightly more probing depth reduction and greater gain in hard tissue probing at re-entry surgery.
- There is no evidence for a difference between bioabsorbable and non-resorbable (ePTFE) membranes in producing clinical attachment level gain and probing depth reduction.
- The addition of a bone substitute to a membrane device does not seem to produce any adjunctive effect compared to the use of a membrane device alone.
- Long-term clinical outcomes or patient-centered outcomes could not be determined due to the lack of available data.
- A substantial variation was observed in the results from the included studies. In both systematic reviews, the attachment gain varied greatly following both GTR and OFD. The mean difference between GTR and OFD surgery varied from 0.02 to 2.60 mm between studies in one systematic review (73), and from –0.20 mm and 2.90 in the other (71). The heterogeneity was large and unexplained. The role of bias could not be eliminated.

### Grafting procedures

#### Background

One of the most investigated methods used to achieve the reconstruction of intraosseous defects is to combine access surgery with placement of bone grafts or implant biomaterials into the debrided bony lesion in order to regenerate the lost periodontal tissues. Grafting biomaterials include autogenous grafts, allogenic grafts, xenogenic grafts and alloplastic materials. The assumption behind the clinical use of grafting procedures is that the complete regeneration of the attachment apparatus (including new bone formation and new connective tissue attachment) would be enhanced by the various biomaterials due to their osteogenetic potential (if the graft contained viable bone-forming cells), osteoinductive capacities (exerted by the release of bone-inducing substances), or osteoconductive properties (i.e. the possibility to create a scaffold to support bone formation). Observational and controlled trials have generally reported an additional benefit in terms of soft and hard tissue improvements following the use of grafting procedures. However, due to the large variety of graft biomaterials on the market, the magnitude of such improvements as well as the consistency of the advantage achieved when grafting
procedures are compared to an access flap procedure remains to be determined.

Results from systematic reviews

Data to assess the effect of the use of grafting procedures in the treatment of intraosseous defects were derived from two recent systematic reviews (88, 115). Our estimation was limited to assessing the additional efficacy of different bone substitutes, either alone or in combination, when compared to OFD. In both systematic reviews, all studies grouped for the meta-analysis were identified as randomized clinical trials. The literature search was extended up to and including June 2001 in one systematic review (115), and up to October 2002 in the other (88). The characteristics of the two systematic reviews are summarized in Table 1.

The therapeutic endpoints examined included short-term (as evaluated 12 months after intervention) and long-term (as evaluated 13 months or more after intervention) changes in clinical attachment level, probing depth, and bone level (defect fill). The incidence of disease recurrence and incidence of tooth loss were also considered outcome variables. Data synthesis and analysis were similar to those reported for GTR. In one systematic review (115), only studies where the patient, not the defect/site, was regarded as the statistical unit were selected. In Reynolds et al.’s systematic review (88), multiple defect sites from the same subject were averaged to provide a ‘pooled’ estimate of the true outcome variable for the individual. Moreover, the primary outcome measures were clinical attachment level gain in our systematic review (115), and change in bone level in the other (88). Our review (115) was based on 21 studies (2, 4, 5, 22, 26, 27, 49, 52, 55, 58, 60, 69, 70, 76, 80, 91, 92, 122–124, 126), while the other (88) was based on 27 studies (2, 4, 5, 8, 22, 25, 26, 49, 51, 52, 55, 57, 58, 60, 61, 63, 69, 76, 80, 84, 86, 91, 92, 120, 122–124). Differences in the inclusion criteria for study eligibility may partly explain the discrepancy in the number of selected studies between the two systematic reviews.

In one systematic review (115), grafting procedures agents were separately analyzed as the following: autogenous bone, bone allograft, dentin allograft, coralline calcium carbonate, bioactive glass, hydroxyapatite, calcium-layered composite of polymethylmethacrylate and polyhydroxyethylmethacrylate (PMMA-PHEMA), and polyactic acid granules. In the other systematic review (88), graft materials were categorized on an a priori basis into one of the following categories: autogenous bone, bone allograft, porous/nonporous hydroxyapatite (calcium phosphate ceramic), bioactive glass, and other (including coralline calcium carbonate; polyactic acid; PMMA, PHEMA and calcium hydroxide polymer; hydroxyapatite cement; hydroxyapatite-glycosaminoglycan).

Autogenous bone

Only one parallel-arm trial (70) comparing the autogenous bone to the OFD procedure was selected in our systematic review (115). The results indicated a greater clinical attachment level gain for the grafted group (clinical attachment level gain: 3.2 mm, SD 0.5) than for controls (clinical attachment level gain: 2.0 mm, SD 0.8). However, the difference in clinical attachment level gain between groups (1.20 mm, SE 0.39) was not statistically significant (Table 2). In the systematic review by Reynolds et al. (88) autogenous bone treatment resulted in significantly greater clinical attachment level gain (weighted mean difference: 0.72 mm, SD 1.82) and bone fill (weighted mean difference: 1.62 mm, SD 1.53) for autogenous bone compared to OFD (Table 2).

Bone allograft

Six studies (2, 4, 5, 22, 58, 124) met the inclusion criteria for comparing bone allograft to OFD in one systematic review (115) and 12 studies (2, 4, 5, 8, 22, 57, 58, 60, 63, 69, 92, 124) met the criteria in the other (88). Meta-analysis showed a greater clinical attachment level gain for the grafted group with respect to OFD (Table 2). Weighted mean difference between graft and control ranged from 0.36 mm (95% CI: −0.16–0.87; P = 0.174) (115), to 0.44 mm (SD 2.25) (88). Significant heterogeneity [Q-test for heterogeneity: 14.40 (5 df), P = 0.01] was found between studies in one systematic review (115), but not in the other (88).

Adjunctive defect fill amounted to 1.06 mm (SD 1.97) with the use of bone allograft (88). In both systematic reviews, a significantly greater probing depth reduction was reported for bone allograft treatment [0.41 mm, 95% CI: 0.16–0.66 (115); 0.43 mm, SD 2.25 (88)] compared to OFD (Table 2). These results were consistent among the different studies (heterogeneity not significant).

Dentin allograft

Clinical attachment level gain following treatment with dentin allograft was evaluated in one trial (70). Clinical attachment level gain amounted to 2.8 mm
(SD 0.7) for grafted patients and 2.0 mm (SD 0.8) for controls. The difference in clinical attachment level gain between groups (0.80 mm, SE 0.38) was not statistically significant (Table 2).

**Coralline calcium carbonate**

Meta-analysis of four selected studies (52, 69, 94, 123) resulted in a consistent and statistically significant difference in clinical attachment level gain between groups. Weighted mean difference 0.90 mm (95% CI: 0.53–1.27; Q-test for heterogeneity: 6.16 (3 df), $P = 0.10$) (115) (Table 2). Reynolds et al. (88) consistently reported a weighted mean difference in clinical attachment level gain of 0.91 mm (SD 1.94) (Table 2). When changes in bone level were considered, the analysis from three studies (52, 69, 123) suggested that coralline calcium carbonate produces a significant ($P = 0.001$) and consistent (heterogeneity not significant) treatment effect (gain in bone fill: 2.21 mm, SD 1.82) (88). In contrast, treatment with coralline calcium carbonate did not produce any significant improvement in probing depth reduction [weighted mean difference: 0.04 mm (115), and 0.09 mm (88)] (Table 2).

**Bioactive glass**

Treatment of intraosseous defects by means of bioactive glass resulted in an improvement of the bony lesion when compared to the OFD procedure. Weighted mean difference in clinical attachment level gain between bioactive glass and OFD was 1.04 mm [95% CI: 0.31–1.76; Q-test for heterogeneity: 9.44 (3 df), $P = 0.02$] in one systematic review (115), and 1.05 mm (SD 1.89) in the other (88) (Table 2). Meta-analysis of change in bone fill revealed a greater, although not significant, increase (1.61 mm, SD 1.47) for bioactive glass than for OFD (Table 2). Significant heterogeneity was found across the studies ($P = 0.006$), the inconsistency being attributable to one study (76) that reported a more favorable change in bone fill following an OFD procedure (88). Meta-analysis also showed that bioactive glass resulted in significantly greater probing depth reduction than the OFD procedure [weighted mean difference: 0.60 mm, 95% CI: 0.20–1.00 (115); 0.71 mm, SD 2.22 (88)] (Table 2).

**Porous/nonporous hydroxyapatite**

Various forms of hydroxyapatite resulted in significantly greater clinical attachment level gain compared with the OFD [weighted mean difference: 1.40 mm, 95% CI: 0.64–2.16 (115); 1.20 mm, SD 2.22 (88)] (Table 2). However, meta-analysis from one systematic review (115) revealed that there was highly significant evidence of heterogeneity among studies [Q-test for heterogeneity: 10.72 (3 df), $P = 0.01$].

Weighted mean difference in bone fill between hydroxyapatite and OFD was 1.58 mm (SD 1.77), the difference being statistically significant (88) (Table 2). Again, significant heterogeneity was found in the studies ($P = 0.04$). Meta-analysis showed that hydroxyapatite resulted in significantly greater probing depth reduction than the OFD procedure (Table 2). Weighted mean difference ranged from 0.98 mm (95% CI: 0.67–1.29) in one systematic review (115) to 0.74 mm (SD 2.12) in the other (88). Significant heterogeneity in studies was found in one systematic review (115), but not in the other (88).

**Polymethylmethacrylate and polyhydroxylethylmethacrylate**

Meta-analysis was not possible for this group since the SE of the difference could not be imputed in one (100) of the two selected studies (100, 123). One study showed a clinical attachment level gain of 3.43 mm in the test group, and 2.73 mm in the control group, difference 0.70 mm (100). In the other systematic review (115) a clinical attachment level gain of 1.9 mm (SD 1.1) in the test group, and 1.0 mm (SD 0.9) in the control group was found. The difference between treatments (0.90 mm, SE 0.22) was statistically significant ($P < 0.001$) (Table 2). Polymethylmethacrylate and polyhydroxylethylmethacrylate was also found to improve bone levels and result in a statistically significant probing depth reduction relative to OFD (122).

**Polylactic acid granules**

One trial (60) evaluated the adjunctive effect of polylactic acid plus OFD compared to OFD only. Clinical attachment level gain was 0.50 mm for polylactic acid treatment and 1.95 mm for the OFD procedure (difference −1.45 mm) (Table 2).

**Long-term outcomes**

Most of the studies did not provide information about long-term outcomes of the grafting procedure, in terms of either disease recurrence or incidence of tooth loss during follow-up. In one study (22) 6-month vs. 36-month clinical attachment level recordings were compared. A 0.12 mm gain in
clinical attachment level was observed for the test procedure and a 0.43 mm decrease for the control procedure from 6 to 36 months postsurgery. In another study (27) the 48-month clinical attachment level was assessed. When compared to the 12-month clinical attachment level, a 0.27 mm decrease for the grafted group and a 0.14 mm gain for the OFD group were observed. A long-term evaluation of a hydroxyapatite graft compared to OFD showed that 40% of the OFD defects lost attachment over the 5-year follow-up, whereas two thirds of the hydroxyapatite defects gained attachment over the same interval (121).

Patient-centered outcomes

There are insufficient and inconsistent data to enable analytic comparisons among different grafting procedures to be made with respect to OFD related to patient-centered outcomes. In most of the studies, no systemic or local adverse effects in grafted patients were observed. Adverse effects included pebbled surface texture of grafted site (76), transient slight gingival inflammation (5), delayed soft tissue healing (70), and exfoliation/shedding of implanted biomaterial (27, 55, 122). The information available revealed the absence of patient-related differences in frequency of complaints, level of comfort, and need for analgesia (122, 124, 125). Patient-centered outcomes where no data were found were ease of maintenance, change in aesthetic appearance, estimation of patient well-being derived from additional use of grafting biomaterials/biologicals, and cost/benefit ratio.

Heterogeneity

In both systematic reviews (88, 115), different grafting procedures have been crudely grouped and separately analyzed with respect to their nature or physicochemical characteristics. This may have resulted in pooling graft materials with different biologic potential in enhancing periodontal regeneration and, consequently, clinically assessed outcomes. However, the heterogeneity in clinical attachment level gain or bone fill reported between different studies dealing with the same bone substitute seems to suggest that other factors may significantly influence the variability in clinical response. It should be also pointed out that for some grafting procedures (such as bone allograft and bioactive glass) the heterogeneity was due to studies which reported a more favorable change in bone fill following an OFD procedure along with studies favoring the grafting procedure, thus calling into question the clinical validity of the graft biomaterial. In contrast, for hydroxyapatite-derived biomaterials, heterogeneity was associated with a generally positive treatment effect across studies. In this case only the magnitude of benefit for grafting procedures over OFD needs to be determined.

Due to limited sample sizes for each treatment modality, sensitivity analysis including individual components of quality assessment could not be performed. The limited number of studies in the analyses also prevented formal testing for publication bias. It was therefore not possible to determine the effect of publication bias on the results. Nevertheless, the possibility that publication bias may have exaggerated the treatment effects should be considered when interpreting the results of the review.

Among patient characteristics, supragingival plaque accumulation and smoking status have been reported to be negatively correlated with treatment outcome associated with the use of reconstructive procedures (54). In the studies considered in our systematic review, differences in methods for plaque assessment between studies (full-mouth plaque scores, full-mouth plaque index, plaque index at the experimental sites only) prevented exploration of the relevance of this potential prognostic factor on outcome variability. It should, however, be pointed out that in all selected studies, the surgical phase was always preceded by multiple sessions of cause-related therapy and followed by a stringent maintenance program. This may have limited the detrimental impact of plaque on healing response. Regarding the effect of smoking status, no studies reported a separate analysis of outcome variables in smokers and nonsmokers, thus impeding any evaluation of this predictor.

Previous studies reported that variability in clinical outcome may reflect variability in defect characteristics, including preoperative attachment level and probing depth, intrabony wall components, and defect depth and angle (54, 56). In particular, the magnitude of the differences in outcome parameters, such as clinical attachment level gain or bone fill, seems to parallel initial differences in average pretreatment depth of the intrabony component of the defect (56). It was not possible with the data available to perform a sensitivity analysis to explore the relevance of these factors in determining the heterogeneity.

Periodontal reconstructive surgery for intraosseous defects is a technique-sensitive procedure. Selection of a specific flap design, in relation to anatomic characteristics of interdental space and location/morphology of bony lesion, and proper suturing technique may significantly contribute to soft and
hard tissue changes following surgery (115). This is partly confirmed by a significant center-related effect on treatment outcome observed when a specific bone substitute has been evaluated in a multicenter trial (124). Further studies are therefore needed to determine how and to what extent surgical variables may influence treatment outcome when a regenerative procedure is performed in association with grafting procedures.

Study quality has been shown to have a direct impact on the size of the effect of treatment (67, 93), thus potentially contributing to heterogeneity between studies. However, due to limited sample sizes for each treatment modality, sensitivity analysis including individual components of quality assessment could not be performed. The limited number of studies in the analyses also prevented formal testing for publication bias. It was therefore not possible to determine the effect of publication bias on the results. Again, this effect should be considered when interpreting the results of these systematic reviews.

Concluding remarks

In conclusion, the results from the two available systematic reviews on the effect of grafting procedures for the treatment of intraosseous defects indicate the following:

• Apart from polylactic acid, the use of grafting procedures produces a greater clinical attachment level gain and bone fill when compared to the OFD procedure. A greater probing depth reduction is also generally observed with graft biomaterials.

• However, differences in clinical attachment level gain and bone fill between grafting procedures and OFD procedures varied greatly with respect to different graft biomaterials.

• A marked variability in hard and soft tissue improvements among studies dealing with the same bone substitute (heterogeneity) was also observed. This variability prevents a formal estimation of how great a difference will result from treatment.

• Due to limited information on long-term outcome, it is unclear whether stability of periodontal support and tooth survival are affected by application of grafting procedures.

• Variations in grafting biomaterials and procedures as well as lack of objective standardized data did not allow for a meaningful summary of treatment-related adverse effects as well as evaluation of cost/benefit ratio.

Enamel matrix proteins

Background

Enamel matrix proteins (Emdogain®, Biora AB, Malmö, Sweden) constitute a commercially available compound consisting mainly of amelogenin and related proteins derived from porcine tooth buds. During fetal life, these enamel matrix proteins are secreted and temporarily deposited on the root surface by the cells of Hertwig’s epithelial root sheath, being essential for the formation of acellular cementum and development of associated periodontal ligament and alveolar bone (34, 43, 106, 107). It is believed that enamel matrix proteins used in periodontal lesions mimic the development of the tooth-supporting apparatus during tooth formation (34). Recently, enamel matrix proteins have been shown to be effective in regenerating the periodontal attachment apparatus both in animals (35, 97) and in humans (39, 40, 66, 95, 96, 116, 125), and in improving the clinical attachment level in deep intrabony defects (38–40, 79, 81, 95, 96, 103).

Results from systematic reviews

Three systematic reviews have been recently published with the purpose to determine the additional efficacy of enamel matrix proteins in the treatment of periodontal intraosseous defects with respect to either OFD (21, 29, 115) or GTR (21). Two systematic reviews were based on randomized clinical trials (115) or quasi-randomized clinical trials (29) of at least 6–8 months’ duration, and one systematic review included only randomized clinical trials with a 1-year follow-up (21). The literature search was extended up to and including June 2001 for Trombelli et al.’s systematic review (115), up to April 2002 for Giannobile & Somerman systematic review (29), and up to January 2003 for Esposito et al.’s systematic review (21). Search strategy and inclusion criteria resulted in the selection of five studies (24, 75, 81, 103, 108) for Trombelli et al.’s (115), eight studies for Giannobile & Somerman (24, 40, 75, 81, 99, 103, 108, 127), and 10 studies (23, 40, 75, 81, 98, 99, 103, 104, 108, 128) for Esposito et al. (21). Quality assessment of systematic reviews of enamel matrix proteins is summarized in Table 1.

The study population was extended to patients affected by periodontitis with intraosseous defects to be treated. The clinical attachment level change was regarded as the primary outcome measure. Changes
in probing depth, gingival recession and radiographic bone level were also considered. Evaluation of long-term benefits included ease of maintenance based on residual probing depth, incidence of relapsing or recurrent disease, and tooth loss. Changes in aesthetic appearance, postoperative complications (infection, soft tissue dehiscences), pain, tooth hypersensitivity, cost/benefit and patient well-being were considered as patient-centered outcomes.

In data pooling, a weighted treatment effect was calculated and the results were expressed as weighted mean differences (and 95% CI) for continuous outcomes using both fixed and random models (115) or a random model only (21). In one systematic review (21) the significance of any discrepancies in the estimates of the treatment effects from the different trials was assessed by means of Cochran’s test for heterogeneity and any heterogeneity was investigated. In Trombelli et al. (115) if any significant heterogeneity ($P < 0.05$) was detected, meta regression was performed to explore heterogeneity.

### Enamel matrix proteins vs. OFD

Overall, the results derived from the systematic reviews indicate that there were significant differences between enamel matrix proteins and the OFD for the three outcomes measured as change from the baseline values: clinical attachment level, probing depth, and radiographic marginal bone levels. There was a significant gain in mean clinical attachment level for enamel matrix proteins compared to OFD defects, with weighted mean difference of 1.33 mm (95% CI: 1.01–1.42; $Q$-test for heterogeneity: 24.27 (4 df), $P < 0.001$) in one systematic review (115), and 1.31 mm (95% CI: 0.84–1.78, chi-square = 32.9, 7 df, $P < 0.001$) in another (21) (Table 2). However, in both systematic reviews the analysis contained statistically significant heterogeneity in the results among studies. In one systematic review (29), the additional clinical attachment level gain achieved with enamel matrix proteins with respect to OFD was not explicitly reported.

A significant reduction in probing depth was also observed, with a weighted mean difference ranging from 0.96 mm (95% CI: 0.50–1.41; $P = 0.002$) (21) to 1.60 mm (95% CI: 0.59–2.62; $P < 0.001$) (115) (Table 2). No data regarding the adjunctive probing depth reduction with enamel matrix proteins was reported in one systematic review (29). The significant increase in marginal bone levels favoring enamel matrix proteins was only based on one trial in one systematic review (21) with weighted mean difference 2.0 mm (95% CI: 0.88–3.12) (Table 2). There was no statistically significant difference in gingival recession between Emdogain and OFD (21). No postoperative infections or other adverse events were reported.

### Enamel matrix proteins vs. GTR

Six trials from one systematic review (21) provided data for this comparison between enamel matrix proteins and GTR. A significantly greater reduction in probing depth was found for GTR compared to enamel matrix proteins (weighted mean difference: 0.58 mm, 95% CI: 0.08–1.07; chi-square = 8.9, 5 df, $P = 0.11$). There was also a significant increase in change in gingival recession for GTR with a weighted mean difference of 0.47 mm (95% CI: 0.17–0.76; chi-square = 1.5, 4 df, $P = 0.82$). No statistically significant differences for clinical attachment level and postoperative infections were observed between treatments.

### Heterogeneity

Systematic reviews have shown that the use of enamel matrix proteins resulted in a statistically significant improvement in average clinical attachment level and probing depth over control flap surgery when used in intrabony defects. Although all studies generally showed an additional benefit with the use of enamel matrix proteins, a high degree of heterogeneity was found in the included trials.

In one systematic review (21) random effects meta regression analysis was used to investigate which factors might, at least in part, explain the heterogeneity in the comparisons between enamel matrix proteins and OFD. Factors included antibiotics given, surgical technique used in control group, funding by manufacturer, risk of bias, baseline depth of intrabony defects and trial location. Only one of the random effects meta regressions was significant, where manufacturer-funded studies found less recession than the unfunded studies. Apart from this, Esposito et al. (21) were unable to explain the heterogeneity found between the studies. In their systematic review, a planned subgroup for maintenance was not possible as all studies were categorized as providing very high levels of maintenance.

In our systematic review (115) we have attempted to explore the effect of preoperative defect depth on difference in clinical attachment level and probing depth change as recorded in patients treated with enamel matrix proteins compared to OFD. Meta regression failed to detect an effect of initial defect...
depth on the difference in clinical attachment level gain and probing depth reduction between test and control procedures. The lack of significant correlation may be partly explained by limited variability in mean defect depth, as reported in different studies, since a threshold for defect severity represented a consistent inclusion criterion for most of the studies.

In all systematic reviews the relevance of publication bias on heterogeneity was not tested, therefore preventing the exploration of the effect of publication bias on the results. Again, the possible impact of publication bias in exaggerating the size of the treatment effect should be considered when interpreting the results of the review.

One of the potential drawbacks inherent in enamel matrix protein treatment is its gel-like consistency after reconstitution. This limits the space-making potential of the preparation when used in intrabony defects (66). Moreover, if primary closure is not properly ensured over the interdental space, displacement or contamination of the material may take place, thus jeopardizing the regenerative potential. As a consequence, provision of a secluded space by means of adequate interdental tissue management may allow enamel matrix protein-induced healing process to occur undisturbed, maximizing the clinical outcome. Adequate preservation of interdental soft tissues may also limit the collapse of the flap into the bone defect, thus optimizing available space for regeneration (102, 114). These observations suggest that the surgical application of enamel matrix proteins is a technique-sensitive procedure. Although the exploratory sensitivity analysis was not able to detect any significant difference with respect to the surgical procedures used (traditional modified Widman flap or new papilla preservation flaps) (21), differences in flap management with respect to the physical properties of enamel matrix proteins may in part explain the great variability in clinical attachment level gain reported in the systematic reviews. In this respect, results from a large multicenter randomized clinical trial comparing enamel matrix proteins to OFD (108), which involved eight expert clinicians, showed that the difference in clinical attachment level gain between the center performing best and the center performing worst was more than 4-fold higher than the additional effect achieved by the application of enamel matrix proteins.

Concluding remarks

Data from the three systematic reviews seem to suggest the following:

- Application of enamel matrix proteins resulted in statistically significant improvements in attachment levels (additional clinical attachment level gain of 1.3 mm) and probing depth reduction (ranging from 1.0 mm to 1.6 mm) in comparison with OFD.
- General conclusions about the clinical relevance (i.e. magnitude of the additional effect) of enamel matrix proteins are limited by the high level of heterogeneity found across the studies.
- No evidence of major differences between enamel matrix derivative and guided tissue regeneration could be found with the exception of slightly more probing depth reduction (0.6 mm) due to increased gingival recession (0.5 mm) in GTR-treated sites.
- Because of insufficient information on long-term outcome, it was not possible to confirm the efficacy of enamel matrix proteins on the stability of periodontal support and tooth survival.

Conclusions

The aim of this article was to determine the effect of GTR, grafting procedures or the application of enamel matrix proteins in addition to OFD in the treatment of deep intraosseous defects. Overall, data resulting from systematic reviews indicate that all reconstructive treatment modalities produce comparable and more favorable clinical improvements in hard and soft tissue parameters of healing response (i.e. clinical attachment gain, pocket reduction and bone fill) compared to conventional OFD procedures. Although the biomaterial-supplemented reconstructive procedures are associated with a generally positive treatment effects with respect to OFD, a significant heterogeneity was found among studies in the different reconstructive procedures. This limits the possibility of drawing general conclusions about the clinical relevance (in particular, the magnitude of the adjunctive effect) of the additional use of GTR, grafting procedures or enamel matrix proteins for the treatment of intraosseous defects. Some of the possible causes of heterogeneity have been explored; however, the limited number of studies currently available did not permit definite conclusions about which factors account for the variability in treatment outcome. More research is therefore needed to identify patient, site, choice of material and technique factors associated with the successful outcome of treatment of intraosseous defects.
This review indicates that different reconstructive procedures support comparable clinical outcomes. It should, however, be considered that similar improvements in clinical parameters do not necessarily imply similar wound healing processes on a histologic level. Whereas the use of some reconstructive procedures, such as GTR and enamel matrix proteins, has been demonstrated to result in a ‘true’ and complete periodontal regeneration, for some of the graft biomaterials the effect on the formation of a new attachment apparatus, including bone, cementum and periodontal ligament, rather than periodontal repair, is still a matter of debate.

Due to limited information on long-term outcomes, it is unclear whether the stability of periodontal support and tooth survival are affected by the additional application of reconstructive devices/biomaterials. While the improvements in probing recordings may be reasonably considered surrogate measurements related to a better long-term tooth prognosis, we recommend that more clinical studies should examine whether and to what extent more compromised teeth could be saved using a reconstructive procedure.

There are at present insufficient data to permit analytic comparisons among different reconstructive procedures with OFD with respect to patient-centered outcomes. When considering the adjunctive effect of reconstructive procedures, evaluation of adverse effects related to the additional use of biomaterials/biological agents, postoperative complications, ease of maintenance, change in aesthetic appearance, estimation of patient well-being, and cost/benefit ratio (including estimation of additional treatment time and costs for implant/placement of biomaterials/biological agents) should be carried out. Studies including patient-centered outcomes will be critical, as well as long-term follow-up cohorts to examine the effect of a reconstructive biomaterial/device on true therapeutic endpoints.

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