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Efficacy of regenerative therapy in aggressive periodontitis: a systematic review and meta-analysis of randomised controlled clinical trials

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Abstract

Objectives

To analyse evidence regarding the efficacy of periodontal regenerative procedures in intrabony defects in patients treated for aggressive periodontitis (AgP).

Material and Methods

A systematic search of the literature for randomised controlled clinical trials including patients treated for aggressive periodontitis that compared a group treated with regenerative therapy with another group treated with surgical debridement alone was conducted by two independent reviewers.

Results

Six studies were included in the meta-analysis of clinical and/or radiographic parameters at 6 and 12 months. Probing pocket depth was smaller at 6 months in patients treated with regenerative therapies compared with those treated with regular debridement (1.00 mm, $p < 0.001$, 95% CI (0.67, 1.34)). At 12 months this difference was more marked (0.41 mm, $p = 0.12$, 95% CI (−0.10, 0.91)). The distance between the cemento-enamel junction and the alveolar crest at both 6 (1.36 mm, $p < 0.001$, 95% CI (1.03, 1.68)) and 12 months (0.90 mm, $p = 0.01$, 95% CI (0.24, 1.56)) was smaller in the group treated with regeneration.

Conclusions

The use of biomaterials for regenerative therapy in AgP may be more effective than surgical debridement. Better outcomes were observed in terms of probing pocket depth and distance between the cemento-enamel junction and the alveolar crest at 6 months. Regeneration should be considered as a therapy to prevent tooth loss, although more studies with larger sample size and longer follow-up are needed.

Clinical relevance

Periodontal regeneration is effective in the treatment of intrabony defects in patients with AgP, as it leads to better outcomes in clinical and radiographic parameters.

Keywords

Aggressive periodontitis
Periodontal bone loss
Periodontal regeneration
Biomaterials
Meta-analysis

Introduction

Aggressive periodontitis (AgP) was defined by the “1999 International Workshop for a Classification of Periodontal Diseases and Conditions” as a particularly severe form of periodontal disease, characterised by the rapid progression of the periodontal attachment and alveolar bone loss [1]. AgP affects young individuals under 35 years of age with no medical history. Its prevalence ranges from 0.2% for Caucasians to approximately 2.6% for African Americans [2, 3].

However, this classification has turned out to be controversial and, in particular, definition of ‘rapid progression’ is difficult to establish. Recently, the results of the “World Workshop on Periodontal and Peri-Implant Disease Classification” [4] were published, with the aim to update the current classification of periodontal diseases. In this meeting, the terms “chronic” or “aggressive” periodontitis were eliminated, and periodontitis was categorised into necrotizing periodontitis, periodontitis associated with systemic diseases, and other periodontitis (subclassified into stages depending on severity or complexity of clinical management, and into grades depending on the rate of progression). AgP could be included in periodontitis stages III or IV, and in grade C or rapid rate of progression [5].

Fine et al. [6] concluded that the classification of AgP is too broad and has not been reviewed since its inception. They suggest incorporating genetic, host, and microbiological analyses to identify risk groups and improve diagnosis in young individuals.

The treatment of AgP consists of two phases. The first non-surgical phase aims to eliminate the supragingival and subgingival calculus, and plaque, by prophylaxis and scaling and root planning, and controls the risk factors associated with periodontitis [7]. Initial treatment also includes an effective oral hygiene programme. In addition, the study by Guerrero et al. [8] found that a 7-day adjunctive course of systemic metronidazole and amoxicillin significantly improved the short-term clinical outcomes of full-mouth non-surgical periodontal debridement in subjects with generalised AgP.

The second phase of periodontal treatment consists of access flap surgery for open flap debridement (OFD) in the areas where residual periodontal pockets persist after non-surgical treatment. This phase may also incorporate regenerative procedures. Periodontal tissue regeneration techniques include the use of autogenous, allogenic, xenogenic, or alloplastic/synthetic bone grafts; collagen, expanded polytetrafluoroethylene (ePTFE), or polymer guided tissue regeneration (GTR) barriers; and biological agents. Although some of these regenerative procedures are effective in obtaining periodontal regeneration, it remains difficult to achieve a true, complete, and predictable result [9]. Several studies [10, 11, 12, 13, 14] have however demonstrated long-term stability in the results achieved after periodontal treatment in AgP in patients who follow a periodontal maintenance programme.

Vertical bone loss in periodontitis often results in an intrabony defect when the base of the bone defect (and the periodontal pocket) is apical to the alveolar crest and surrounded by one, two, or three bony walls. Several surgical techniques, including OFD, are available to reduce the depth of the periodontal pocket by forming a long junctional epithelium that attaches to the root surface [15]. GTR and biomaterials for periodontal regeneration also aim, in addition to reducing probing pocket depth (PPD), to restore the original architecture of the lost periodontal tissues [16].

Although periodontal regeneration is accepted into clinical practice, a systematic review and meta-analysis of its effectiveness in AgP is important since the procedure is technically complex and costly. The rationale of this study is to conduct a formal meta-analysis to investigate the efficacy of regenerative treatments. Several systematic reviews regarding the outcomes of GTR in chronic periodontitis (CP) have been published. They have shown that GTR results in better outcomes than OFD in terms of clinical attachment level (CAL) and PPD in CP [17, 18, 19, 20]. Corbella et al. [21] recently published a systematic review on the effects of GTR on AgP; however, they focused only on the qualitative analysis of the data and did not conduct a meta-analysis.

The objective of this systematic review and meta-analysis is, therefore, to evaluate the efficacy of regenerative therapies for the treatment of periodontal intrabony defects in AgP compared with conventional OFD, considering both clinical and radiographic treatment outcomes.

Materials and methods

This study has been conducted (in terms of planning and reporting) in accordance with the PRISMA guidelines for systematic reviews and meta-analysis (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [22].

Research question

The purpose of this review was to assess the efficacy of periodontal regenerative therapies in AgP compared with regular surgical debridement. The meta-analysis was conducted to analyse and combine results of the included studies, and to assess the strength of evidence presented on regenerative treatment in AgP. The eventual characteristics not to perform the meta-analysis are different designs, populations, interventions, or variables in the included studies.

Using the PICO (patient, intervention, comparison, outcome) framework, the research question was as follows: "Is periodontal regeneration associated with better clinical and radiographical outcomes compared to regular surgical debridement in patients with AgP?"

Eligibility criteria

We applied the following criteria for inclusion in the review:

1. Type of study. Randomised controlled clinical trials (RCT) in humans with a minimum follow-up period of 6 months, with parallel or split-mouth designs. We included international publications published in peer-reviewed journals and also grey literature. Articles written in English, Spanish, or French.

2. Participants. Subjects diagnosed with AgP who require periodontal regeneration.

3. Intervention. Treatment of intrabony defects with periodontal regeneration, such as GTR either alone or in combination with bone grafts, enamel matrix derivative technique, bone grafts and bone substitutes, and cellular growth factors. Studies that analysed at least 15 intrabony defects were included.

4. Comparisons. Regular OFD (surgical phase of the periodontal treatment

which goals include optimum mechanical subgingival root planing and decontamination with direct vision, as well as healing by primary intention following close interdental flap adaptation).

5. Outcomes. Changes in the periodontal intrabony defect assessed by clinical (PPD, gingival recession [REC] and CAL) and/or radiographic parameters (bone defect volume [DV], distance from the cemento-enamel junction to the alveolar crest [CEJ-AC], and distance from the cemento-enamel junction to the base of the intrabony defect [CEJ-BD]). The chosen primary outcome was PPD. Data were collected at 6 and 12 months.

Search strategy

Literature searches were performed in five online databases (PUBMED, Cochrane CENTRAL, ISI Web of Science, Google Scholar, and EMRO) and two databases including doctoral theses and dissertations (PROQUEST and TESEO). Studies were collected between January 1, 1995 and March 28, 2018. The search strategy included the following keywords: "aggressive periodontitis", "regeneration", "guided bone regeneration", "guided tissue regeneration", and "enamel matrix derivative" combined with Boolean operators "AND" and "OR" (Suppl. material search strategy).

The references of all included studies and relevant reviews were manually cross-checked and an additional search was also performed in indexes of relevant dental journals to ensure complete data collection. A reviewer (LD-F) carried out the literature search for potentially eligible studies. In order to minimise the risk of bias, two authors (LD-F and AM-F) independently screened the potentially eligible studies for inclusion in the review. The title and abstract of the studies were scanned and those that met the inclusion criteria for full review were then selected. Disagreements between reviewers were addressed and resolved through discussion with a third supervisor (FM).

Risk of bias assessment in individual studies

To assess the methodological quality of the studies and the risk of bias, the Jadad scale [23] was applied. The analysis to assess risk of bias was based on three main aspects: randomisation, blinding, and account of all patients. These were applied to the included articles by the same independent researchers as described previously.

Statistical analysis

Data were analysed with the statistical package Stata IC (Version 14.2, StataCorp, College Station, TX, USA). For the summary and comparison of included studies, means and standard deviations (SD) were extracted directly from the studies and analysed with a 95% confidence interval (95% CI). The estimates of the pooled mean differences (MD) together with the 95% CI for the different outcomes were calculated by the inverse of variance test. Fixed or random effects models were used based on the presence or absence of heterogeneity. Heterogeneity among studies was assessed by the Q test, considering a p value < 0.10 as statistically significant.

AQ2

Forest plots were created to illustrate the effects of the different studies and the global estimation of the meta-analysis. Statistical significance was defined by a p value ≤ 0.05. Forest plots for each meta-analysis show the MD and 95% CI for each study (shown as lines) and the pooled MD (overall), with the 95% CI, obtained by either the fixed or random effects model as indicated.

Results

Selection of studies

The study selection process is presented in the flow diagram (Fig. 1). The initial search yielded a total of 749 documents (741 from electronic database searches and eight from manual searches), of which 51 were duplicate records. After the title and abstract evaluation process, 17 articles were obtained and analysed in full text. Three were excluded as they did not fit the specified intervention criteria [24, 25, 26], and a further two [27, 28] were excluded because they were case series. Six other articles were excluded because they were not adapted to the intervention [29, 30] or were not RCTs [31, 32, 33, 34]. Finally, six articles (five studies) were included in the quantitative analysis [35, 36, 37, 38, 39, 40]. To show the degree of inter-examiner agreement in the selection of articles, the Kappa index was applied. The result obtained was 0.886 after the complete reading of articles, indicating good agreement ~~(Fig. 2)~~.

Fig. 1

Flow diagram of selection process, eligibility, and reasons for exclusion and inclusion of the final studies

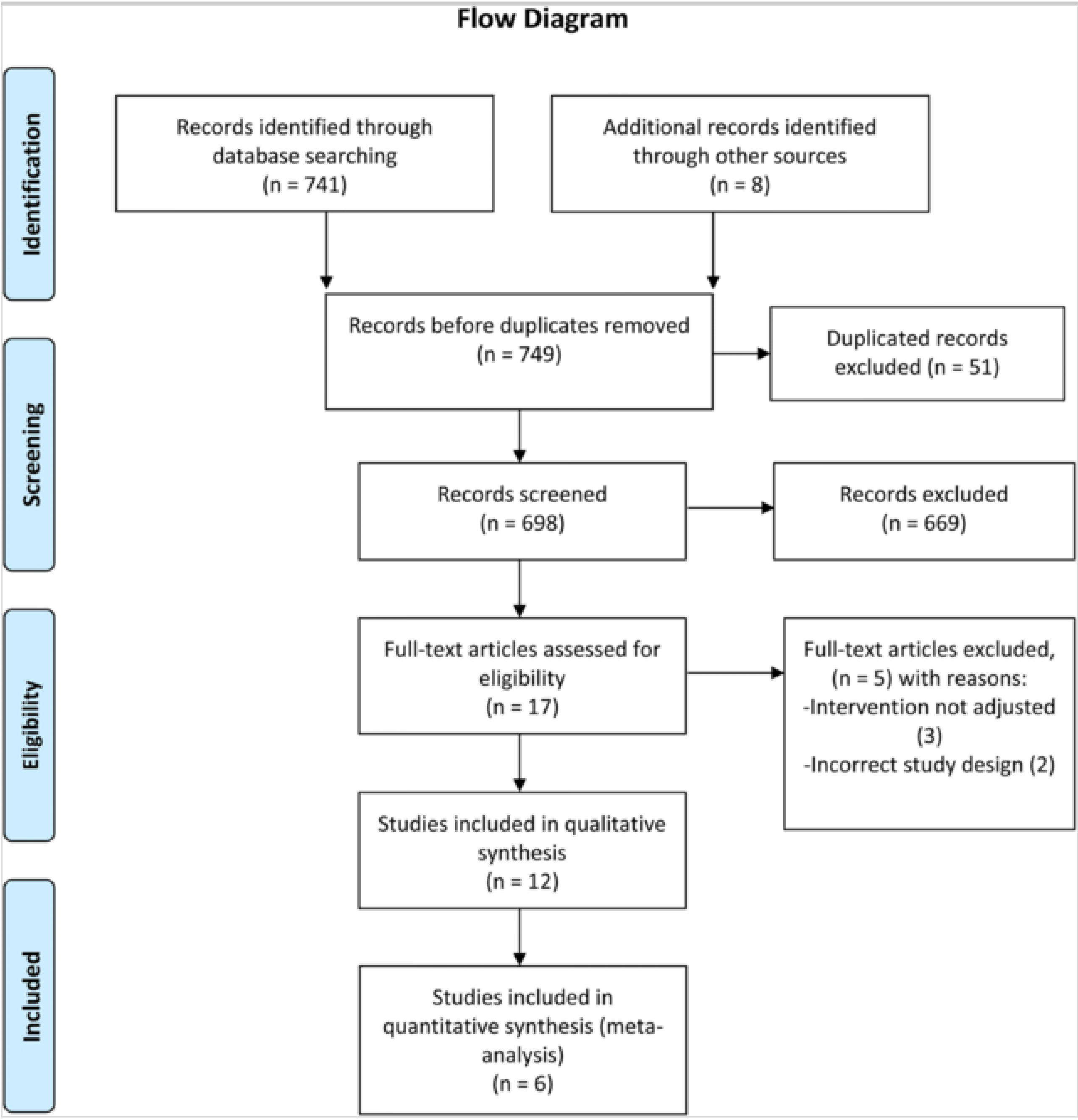
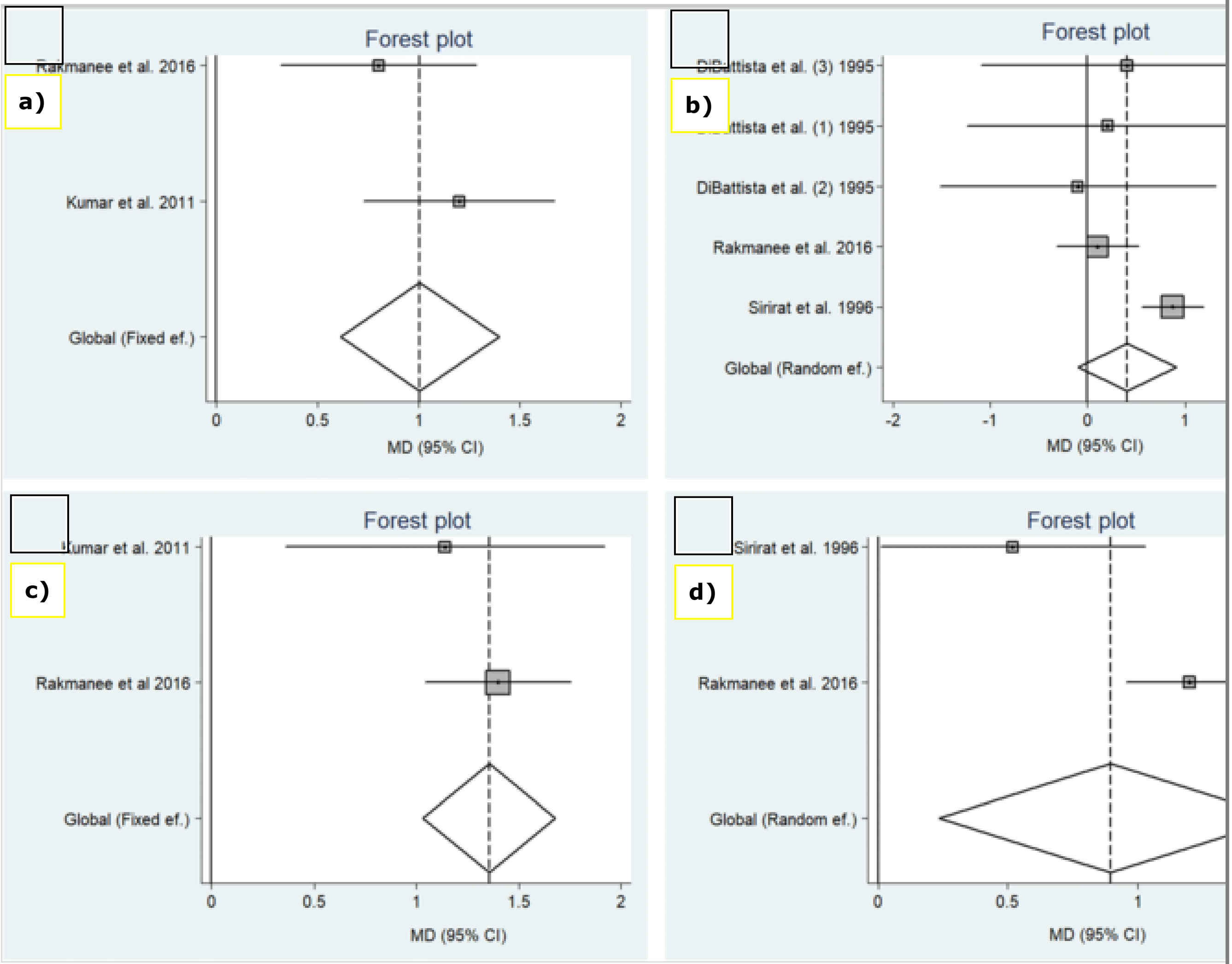


Fig 2

Forest plots. **a)** PPD 6 months. **b)** PPD 12 months. **c)** CEJ-AC 6 months. **d)** CEJ-AC 12 months.



AQ3

Characteristics of the studies

Data were extracted from the studies and entered into a spreadsheet (LibreOffice v. 5.4.4.2 The Document Foundation) according to the general characteristics of the study (authors and year of publication), characteristics of the population (number of participants, age, sex, smoking history), and outcome measures (follow-up, PPD, REC, CAL, DV, CEJ-AC, and CEJ-BD. These clinical measurements were taken after non-surgical therapy. No study included antibiotic use prior to surgery; however, all studies with the exception of Rakmanee et al. [39, 40] included the used of 500 mg amoxicillin every 6–8 h for 5–7 days post-surgically.

Four of the six included papers (Table 1) were “split-mouth” designs [35, 36, 39, 40]. All included articles were written in English, took place in a university setting, and were not commercially funded. The follow-up period varied from 6 to 12 months. One study was conducted in Thailand [35], two studies in India [36, 37], one in OH, USA [38, ,], and the other one in the UK [39, 40].

Table 1

Characteristics of included studies

Author	Year	Participants (*N*)	Age (years)	Characteristics of the participants	Intrabony defects (*N*)	Character of the intrabo defect
DiBattista et al. [38]	1995	7	14–18	5 women, 2 men with LAgP	26	Presence o AA. Molar with intrab defects wit CAL > 5 m
Sirirat et al. [35]	1996	6	24–30	4 women, 2 men. Split-mouth design	15	
Kumar et al. [36]	2011	10	17–35	6 women, 4 men. Non-smokers. Split-mouth design	20	Bilateral interproxin intrabony ≥ 4 mm (as evidenced X-ray) in molars and ≥ 5 mm
Rakmanee et al. (A) [39]	2016	18	15–39	14 women, 4 men. Split-mouth design. 8 Caucasians, 8 African Americans, 1 Hispanic, 1 Asian. 3 smokers ≤ 10 cigarettes/day	36	Bilateral intrabony ≥ 3 mm an PPD ≥ 5 m One-wall d (3 control/ test), two-w defect (10 control/6 te three-wall defect (5 control/7 te Defect dep 3 mm (3 control/5 te 4 mm (5 control/6 te 5 mm (10 control/7 te

Data from Rakmanee et al. (A) and (B) are results from the same sample of patients

Author	Year	Participants (*N*)	Age (years)	Characteristics of the participants	Intrabony defects (*N*)	Character of the intrabo defect
Rakmanee et al. (B) [40]	2016	18	15–39	14 women, 4 men. Split-mouth design: 8 Caucasians, 8 African Americans, 1 Hispanic, 1 Asian. 3 smokers ≤ 10 cigarettes/day	36	Bilateral intrabony ≥ 3 mm an PPD ≥ 5 m One-wall d (3 control/ test), two- defect (10 control/6 t three-wall defect (5 control/7 t Defect dep 3 mm (3 control/5 t 4 mm (5 control/6 t 5 mm (10 control/7 t
Bajaj et al. [37]	2017	19	20–30	9 women, 10 men. Non-smokers	54	3-wall interproxin intrabony
Data from Rakmanee et al. (A) and (B) are results from the same sample of patients						

Bajaj et al. [37] performed power calculations before the study was initiated to achieve 85% power and detect mean difference of 1 mm in CAL between the 2 groups. Also, Rakmanee et al. (A) [39] made power calculations in order to have an 80% power to detect a difference in means of 0.75 mm of probing measurement. As Rakmanee et al. (B) [40] is part of the same study, subjects and power calculation are the same.

In total, 60 subjects and 172 periodontal intrabony defects were analysed. With regard to the type of intrabony defects analysed, DiBattista et al. [38] studied defects in the mesial surface of molars with CAL > 5 mm, and Sirirat et al. [35] and Kumar et al. [36] analysed interproximal intrabony paired defects although Kumar et al. focused on molars with bone loss of > 4 mm as evidenced on intraoral periapical X-rays with PPD > 5 mm. Bajaj et al. [37] analysed 3-wall interproximal intrabony defects. Rakmanee et al. [39, 40] studied one-, two,-, or three-wall intrabony defects with 3, 4, or 5 mm of depth.

The age of subjects ranged from 14 to 39 years. Thirty-eight of the subjects were female and 22 were male. One study included three smokers on ≤ 10 cigarettes per day [39, 40]. One study was restricted to localised aggressive periodontitis

(LAgP) [38], whereas the remaining studies included both localised and generalised aggressive periodontitis (GAgP).

CAL was the primary outcome in Sirirat et al. [35], CAL and PPD in Rakmanee et al. (A) [39], linear radiographic bone fill was the primary outcome in Bajaj et al. [37] and Rakmanee et al. (B) [40], and volumetric bone fill in DiBattista et al. [38] and Kumar et al. [36]. Rakmanee et al. (A, B) [39, 40] are considered as one study, although it was published in two papers.

OFD was conducted using a simplified papillae preservation flap technique [41] in Rakmanee et al. [39, 40] and using a modified Widman flap [42] in the other studies [35, 36, 37, 38]. With regard to the biomaterial used for regeneration, two studies used non-resorbable membrane ePTFE (expanded polytetrafluoroethylene) alone [35] or in combination with a demineralized freeze-dried bone allograft (DFDBA) [38]. The latter study divided the test group into three subgroups, which were included separately in the meta-analysis. The first one consisted of ePTFE alone ($n = 7$); the second consisted of ePTFE with previous conditioning of the root surface with a solution of doxycycline ($n = 7$); and the third consisted of ePTFE, doxycycline, and DFDBA ($n = 7$). Other studies [36] used an allograft (Bonelike, Medmat Innovation. Portugal), composed mainly of hydroxyapatite (HA), tricalcium phosphate (TCP), and bioactive glass (BAG) without any membrane. Bajaj et al. [37] used autologous platelet-rich fibrin (PRF). Rakmanee et al. [39, 40] used a resorbable membrane (RESOLUT XT®, WL Gore & Associates Ltd., Flagstaff, AZ, USA). All the studies compared results to a control group of OFD.

Uneventful healing was demonstrated in all studies except Rakmanee et al. [39, 40]. In Rakmanee et al.'s studies, 13 subjects presented membrane exposure at test sites [39, 40]. Two subjects experienced major exposure (diameter of the area ≥ 4 mm bucco-lingually) resulting in membrane removal at 1 and 4 weeks postoperatively. Eleven subjects had minor exposure (diameter of the area ≤ 3 mm bucco-lingually), and two of them presented with slight suppuration at 1 and 4 weeks after surgery. In these cases, the infection was controlled following a course of antibiotics (i.e. metronidazole; 400 mg three times/day for 2 weeks). Eighteen subjects were initially enrolled but only 16 were followed up at 6 and 12 months.

Synthesis of results

The results of the meta-analyses are shown in Table 2.

Table 2

Results of meta-analysis

Variable	Pooled mean difference (mm)	95% CI	Heterogeneity	
			Q	*p*
PPD 6 months	1	0.67–1.34	1.34[a]	0.25
PPD 12 months	0.41	− 0.10–0.91	2.13[b]	0.71
REC 6 months	− 0.34	− 1.23–0.54	1[b]	0.32
REC 12 months	− 0.32	− 1.23–0.59	1[b]	0.32
CAL 6 months	0.66	− 0.61–1.94	1[b]	0.32
CAL 12 months	0.18	− 1.55–1.90	1[b]	0.32
CEJ-AC 6 months	1.36	1.03–1.68	0.35[a]	0.55
CEJ-AC 12 months	0.9	0.24–1.56	1[b]	0.32
CEJ-BD 6 months	1.19	− 0.66–3.04	1[b]	0.32

[a]Fixed-effects model

[b]Random effects model

In terms of PPD reduction, there was a statistically significant increase at 6 months in subjects treated with regenerative therapies compared with those treated with OFD (1.00 mm, $p < 0.001$, 95% CI [0.67, 1.34]; $Q = 1.34$, $p = 0.25$). The weighted mean difference for the PPD variable at 12 months also shows an increase in the reduction, however this does not reach statistical significance (0.41 mm, $p = 0.12$, 95% CI [− 0.10, 0.91], $Q = 2.13$, $p = 0.71$). Only three studies however reported PPD at 12 months. In one of these studies [38], subjects were divided into three treatment subgroups as different biomaterials were used for regeneration. (Fig. 2 a, b).

There was a reduction in REC after 6 months in subjects treated with regenerative therapies compared with those treated with OFD (− 0.34 mm, $p = 0.45$, 95% CI [− 1.23, 0.54], $Q = 1$, $p = 0.32$), however this was not statistically significant. The reduction in REC at 12 months was 0.32 mm and also did not reach statistical significance (− 0.32 mm, $p = 0.49$, 95% CI [− 1.23, 0.59], $Q = 1$, $p = 0.32$).

A greater increase in CAL at 6 months was observed in subjects treated with regeneration techniques compared with OFD (0.66 mm, $p = 0.31$, 95% CI (− 0.61, 1.94), Q = 1, $p = 0.32$), however the results were not statistically significant. Similar results were observed at 12 months, albeit with less increase (0.18 mm, $p = 0.31$, 95% CI [− 1.55, 1.90], $Q = 1$, $p = 0.32$).

Radiographically, the distance between CEJ and AC at both 6 and 12 months was significantly lower in the group treated with GTR. A significantly lower CEJ-AC was observed at 6 months (1.36 mm, $p < 0.001$, 95% CI [1.03, 1.68], $Q = 0.35$, $p = 0.55$) and at 12 months (0.90 mm, $p = 0.01$, 95% CI [0.24, 1.56], $Q = 1$, $p = 0.32$). There was also a greater reduction in the distance between the CEJ-BD at 6 months for regeneration techniques (1.19 mm, $p = 0.21$, 95% CI [− 0.66, 3.04], $Q = 1$, $p = 0.32$), however this was not statistically significant. The variables VD and CEJ-BD at 12 months were not included in the analysis due to lack of data from the included studies. No tooth loss or adverse effects were reported in the studies (Fig. 2 c, d).

Results of the analysis of the risk of bias

The results of the application of the Jadad scale to the six included studies are summarised in Table 3. Two studies obtained a low score (2), and only two could be described as high-quality studies obtaining the maximum score of 5.

Table 3

Jadad scale for randomised controlled trials

Author	Randomisation (0–2)	Blinding (0–2)	Account of all patients (0–1)	Total
DiBattista et al. [38]	1	0	1	2
Sirirat et al. [35]	1	0	1	2
Kumar et al. [36]	2	2	1	5
Rakmanee et al. (A) [39]	2	0	1	3
Rakmanee et al. (B) [40]	2	0	1	3
Bajaj et al. [37]	2	2	1	5

Discussion

The present meta-analysis was carried out to estimate the effect of regenerative therapy on patients affected by AgP. This study was carried out between 2016 and 2018, before the results of the "World Workshop on Periodontal and Peri-Implant Disease Classification" [4] were published.

It is difficult to extrapolate data from the included studies on AgP to the recent classification of periodontal diseases [4], as we lack the specific patient characteristics in each study. We could say AgP is a stage either III or IV, and grade C periodontitis. However, we still find this meta-analysis relevant due to the complexity of clinical management regarding the aggressive nature of the disease, the specific bacteria of its subgingival biofilm, and the immune responsiveness that could influence the disease manifestation and progression.

Our results suggest that regeneration treatment is effective in these patients in terms of PPD and distance between CEJ-AC. The quality of evidence provided by the included studies is limited, and we must draw conclusions with caution.

The studies evaluated the effects of a series of different biomaterials for periodontal regeneration, including bone substitute materials such as HA, BAG, and DFDBA. These biomaterials were used alone or in combination with resorbable or non-resorbable membranes following a GTR treatment protocol. Nevertheless, Bajaj et al. [37] used PRF alone as a biological agent for regeneration. The combination of different regeneration techniques might have resulted in greater variability in the results.

Previous studies have reported that variability in clinical outcomes may also reflect differences in defect characteristics, including preoperative attachment level and probing depth, intrabony wall components, and defect depth and angle [43, 44, 45]. In addition, Cortellini and Tonetti showed that ΔCAL was associated with the depth of the three-wall intrabony components of the defect [46].

The clinical and radiographic results in Rakmanee et al. [39, 40] showed substantial comparability between the two groups, likely as the planned surgical approach for the control site (papilla preservation flap [41]) guaranteed adequate stability of the blood clot, even without a barrier membrane [47, 48]. We must bear in mind however, that the ΔCAL was reduced at the sites with membrane exposure compared with those with the non-exposed membrane.

This meta-analysis has shown that outcomes at 6 months appear more promising than those at 12 months. The reduction of PPD at 6 months is 1 mm higher for regenerative therapy; while at 12 months, it decreases to 0.41 mm. Similar observations are seen in the CAL assessment, although results at both 6 and 12 months were not statistically significant. An attachment gain of 0.66 mm at 6 months was reduced to 0.18 mm at 12 months. This could also be related to poor compliance of periodontal supportive therapy. A similar pattern is evident for radiographical variables, where the greater CEJ-AC reduction seen for regenerative therapy decreases from 1.36 mm at 6 months to 0.90 mm at 12 months. A slight reabsorption of the alveolar crest following 1 year of treatment may occur in these cases. We also have to bear in mind that some biomaterials such as DFDBA or hydroxyapatite give an initially denser radiographic image than that seen for other biomaterials such as platelet-rich fibrin or perhaps even GTR. The REC, on the other hand, remains stable throughout this period of time and no changes are observed. Therefore, based on the data obtained, regeneration techniques do not seem to be clearly superior to OFD in terms of clinical outcomes.

To our knowledge, this is the first meta-analysis on the efficacy of regenerative therapy for intrabony defects in AgP. The most similar evidence already available comes from the meta-analysis by Needleman et al. [17], who assessed GTR in CP for 12 months. We noted that both PPD and CAL values were not similar compared with our results. In our meta-analysis, observed PPD reduction was 0.41 mm, compared with 1.21 mm reported by Needleman. Similarly, CAL increased by only 0.18 mm in our study compared with 1.22 mm reported by Needleman. This difference may result from a poorer response to treatment in AgP compared with CP. Also, the study of Needleman presented higher baseline PPD values than those in our study, and hence the effect of the treatment would be greater. However, the results regarding REC are similar; an increased gain of 0.26 mm in the subgroup of split-mouth studies and 0.33 mm in the subgroup membrane and bone graft were observed compared with controls, whereas in our study the observed REC gain was 0.32 mm. Regarding radiographic variables, the results between the studies are not comparable as Needleman et al. only present CEJ-BD results at 12 months, and in our study the analysis of this variable could not be performed.

In 2002, Trombelli et al. [9] also performed a meta-analysis comparing use of graft materials and biological agents with OFD for periodontal intrabony defects in CP. The duration of the included RCTs ranged from 6 months to 5 years. The CAL change significantly improved after treatment with coralline calcium carbonate (0.90 mm; 95% CI 0.53–1.27), bioactive glass (1.04 mm; 95% CI 0.31–1.76), hydroxyapatite (1.40 mm, 95% CI 0.64–2.16), and enamel matrix proteins (1.33 mm, 95% CI 0.78–1.88). In our meta-analysis, the CAL change improved by 0.66 mm at 6 months and 0.18 mm at 12 months compared with OFD, however the results were not significant. This difference could be caused by the fact that the low evidence in AgP did not allow to stratify the analysis by the type of biomaterial used, as Trombelli et al. [9].

A further systematic review and meta-analysis by Murphy et al. [19] compared GTR with OFD in CP and included a maximum follow-up of 5 years. They reported a mean CAL gain of 0.81 mm ($p < 0.001$) and a reduction in PPD of 0.78 mm ($p < 0.001$), both favourable to GTR. The results of REC were not statistically significant (0.17 mm, $p = 0.27$). These results are similar to those obtained in our study, although this must be interpreted with caution as the follow-up period and the clinical entities assessed are different between the two studies.

The present study has some limitations. Firstly, none of the included studies tested for normality in the distribution of the data. This limitation should be taken into consideration when interpreting the meta-analysis results. In addition, the number of RCTs found on AgP was limited as was the quality. Thus, there was a high-moderate risk of bias according to the assessment used. We were not able to perform quantitative analysis of some variables such as VD and CEJ-BD at 12 months due to heterogeneity in these variables. More RCTs with a larger sample size and longer follow-up, as well standardisation of outcome reporting, are needed to enable more reliable conclusions to be made.

Conclusions

The use of biomaterials for regenerative therapy was more effective than OFD in terms of PPD and distance between the CEJ and the alveolar crest at 6 months. The improvement in these parameters does not appear stable, as PPD and CEJ-AC deteriorated between 6 and 12 months.

Regeneration is effective for the treatment of intrabony defects in patients with AgP, as it leads to better outcomes with regard to clinical and radiographic parameters. Although the number and strength of the reviewed studies might not necessarily conclude that regeneration should be considered over OFD, as the improvements in clinical and radiographic parameters do not clearly justify the additional time and cost of the procedure. Regeneration should be considered as a therapy to prevent tooth loss, although more studies with larger sample size and longer follow-up are needed.

Publisher’s note

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

References

1. Armitage GC (1999) Development of a classification system for periodontal diseases and conditions. Ann Periodontol 4:1–6. https://doi.org/10.1902/annals.1999.4.1.1

2. Loe H, Brown LJ (1991) Early onset periodontitis in the United States of America. J Periodontol 62:608–616. https://doi.org/10.1902/jop.1991.62.10.608

3. Albandar JM, Tinoco EM (2002) Global epidemiology of periodontal diseases in children and young persons. Periodontol 2000(29):153–176

4. Caton JG, Armitage G, Berglundh T, Chapple ILC, Jepsen S, Kornman KS, Mealey BL, Papapanou PN, Sanz M, Tonetti MS (2018) A new classification scheme for periodontal and peri-implant diseases and conditions - introduction and key changes from the 1999 classification. J Clin Periodontol 45(Suppl 20):S1–S8. https://doi.org/10.1111/jcpe.12935

5. Tonetti MS, Greenwell H, Kornman KS (2018) Staging and grading of periodontitis: framework and proposal of a new classification and case definition. J Clin Periodontol 45(Suppl 20):S149–S161. https://doi.org/10.1111/jcpe.12945

6. Fine DH, Patil AG, Loos BG (2018) Classification and diagnosis of aggressive periodontitis. J Periodontol 89(Suppl 1):S103–S119. https://doi.org/10.1002/JPER.16-0712

7. Teughels W, Dhondt R, Dekeyser C, Quirynen M (2014) Treatment of aggressive periodontitis. Periodontol 2000 65:107–133. https://doi.org/10.1111/prd.12020

8. Guerrero A, Griffiths GS, Nibali L, Suvan J, Moles DR, Laurell L, Tonetti MS (2005) Adjunctive benefits of systemic amoxicillin and metronidazole in non-surgical treatment of generalized aggressive periodontitis: a randomized

placebo-controlled clinical trial. J Clin Periodontol 32:1096–1107. https://doi.org/10.1111/j.1600-051X.2005.00814.x

9. Trombelli L, Heitz-Mayfield LJ, Needleman I, Moles D, Scabbia A (2002) A systematic review of graft materials and biological agents for periodontal intraosseous defects. J Clin Periodontol 29(Suppl 3):117–135 discussion 160-2

10. Baumer A, Pretzl B, Cosgarea R, Kim TS, Reitmeir P, Eickholz P, Dannewitz B (2011) Tooth loss in aggressive periodontitis after active periodontal therapy: patient-related and tooth-related prognostic factors. J Clin Periodontol 38:644–651. https://doi.org/10.1111/j.1600-051X.2011.01733.x

11. Graetz C, Dorfer CE, Kahl M, Kocher T, Fawzy El-Sayed K, Wiebe JF, Gomer K, Ruhling A (2011) Retention of questionable and hopeless teeth in compliant patients treated for aggressive periodontitis. J Clin Periodontol 38:707–714. https://doi.org/10.1111/j.1600-051X.2011.01743.x

12. Nibali L, Farias BC, Vajgel A, Tu YK, Donos N (2013) Tooth loss in aggressive periodontitis: a systematic review. J Dent Res 92:868–875. https://doi.org/10.1177/0022034513501878

13. Diaz-Faes L, Guerrero A, Magan-Fernandez A, Bravo M, Mesa F (2016) Tooth loss and alveolar bone crest loss during supportive periodontal therapy in patients with generalized aggressive periodontitis: retrospective study with follow-up of 8 to 15 years. J Clin Periodontol 43:1109–1115. https://doi.org/10.1111/jcpe.12596

14. Graetz C, Salzer S, Plaumann A, Schlattmann P, Kahl M, Springer C, Dorfer C, Schwendicke F (2017) Tooth loss in generalized aggressive periodontitis: prognostic factors after 17 years of supportive periodontal treatment. J Clin Periodontol 44:612–619. https://doi.org/10.1111/jcpe.12725

15. Caton J, Nyman S, Zander H (1980) Histometric evaluation of periodontal surgery. II Connective tissue attachment levels after four regenerative procedures. J Clin Periodontol 7:224–231

16. Karring T, Nyman S, Gottlow J, Laurell L (1993) Development of the biological concept of guided tissue regeneration--animal and human studies. Periodontol 2000 1:26–35

17. Needleman I, Tucker R, Giedrys-Leeper E, Worthington H (2002) A systematic review of guided tissue regeneration for periodontal infrabony defects. J Periodontal Res 37:380–388

18. Needleman IG, Worthington HV, Giedrys-Leeper E, Tucker RJ (2006) Guided tissue regeneration for periodontal infra-bony defects. Cochrane Database Syst Rev CD001724. https://doi.org/10.1002/14651858.CD001724.pub2

19. Murphy KG, Gunsolley JC (2003) Guided tissue regeneration for the treatment of periodontal intrabony and furcation defects. A systematic review. Ann Periodontol 8:266–302. https://doi.org/10.1902/annals.2003.8.1.266

20. Aichelmann-Reidy ME, Reynolds MA (2008) Predictability of clinical outcomes following regenerative therapy in intrabony defects. J Periodontol 79:387–393. https://doi.org/10.1902/jop.2008.060521

21. Corbella S, Weinstein R, Francetti L, Taschieri S, Del Fabbro M (2017) Periodontal regeneration in aggressive periodontitis patients: a systematic review of the literature. J Investig Clin Dent 8. https://doi.org/10.1111/jicd.12245

22. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 62:1006–1012. https://doi.org/10.1016/j.jclinepi.2009.06.005

23. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17:1–12

24. Buchmann R, Nunn ME, Van Dyke TE, Lange DE (2002) Aggressive periodontitis: 5-year follow-up of treatment. J Periodontol 73:675–683. https://doi.org/10.1902/jop.2002.73.6.675

25. Machtei EE, Oettinger-Barak O, Peled M (2003) Guided tissue regeneration in smokers: effect of aggressive anti-infective therapy in class II furcation defects. J Periodontol 74:579–584. https://doi.org/10.1902/jop.2003.74.5.579

26. Schincaglia GP, Hebert E, Farina R, Simonelli A, Trombelli L (2015) Single versus double flap approach in periodontal regenerative treatment. J

Clin Periodontol 42:557–566. https://doi.org/10.1111/jcpe.12409

27. Zucchelli G, Brini C, De Sanctis M (2002) GTR treatment of intrabony defects in patients with early-onset and chronic adult periodontitis. Int J Periodontics Restorative Dent 22:323–333

28. Sant'Ana AC, Passanezi E, Todescan SM, de Rezende ML, Greghi SL, Ribeiro MG (2009) A combined regenerative approach for the treatment of aggressive periodontitis: long-term follow-up of a familial case. Int J Periodontics Restorative Dent 29:69–79

29. Vandana KL, Shah K, Prakash S (2004) Clinical and radiographic evaluation of emdogain as a regenerative material in the treatment of interproximal vertical defects in chronic and aggressive periodontitis patients. Int J Periodont Rest 24:185–191

30. Gupta G (2014) Clinical and radiographic evaluation of intra-bony defects in localized aggressive periodontitis patients with platelet rich plasma/hydroxyapatite graft: a comparative controlled clinical trial. Contemp Clin Dent 5:445–451. https://doi.org/10.4103/0976-237X.142806

31. Evans GH, Yukna RA, Sepe WW, Mabry TW, Mayer ET (1989) Effect of various graft materials with tetracycline in localized juvenile periodontitis. J Periodontol 60:491–497. https://doi.org/10.1902/jop.1989.60.9.491

32. Mengel R, Soffner M, Flores-de-Jacoby L (2003) Bioabsorbable membrane and bioactive glass in the treatment of intrabony defects in patients with generalized aggressive periodontitis: results of a 12-month clinical and radiological study. J Periodontol 74:899–908. https://doi.org/10.1902/jop.2003.74.6.899

33. Queiroz AC, Nobrega PB, Oliveira FS, Novaes AB Jr, Taba M Jr, Palioto DB, Grisi MF, Souza SL (2013) Treatment of intrabony defects with anorganic bone matrix/p-15 or guided tissue regeneration in patients with aggressive periodontitis. Braz Dent J 24:204–212. https://doi.org/10.1590/0103-6440201302169

34. Artzi Z, Tal H, Platner O, Wasersprung N, Weinberg E, Slutzkey S, Gozali N, Carmeli G, Herzberg R, Kozlovsky A (2015) Deproteinized bovine bone in association with guided tissue regeneration or enamel matrix derivatives procedures in aggressive periodontitis patients: a 1-year

retrospective study. J Clin Periodontol 42:547–556. https://doi.org/10.1111/jcpe.12413

35. Sirirat M, Kasetsuwan J, Jeffcoat MK (1996) Comparison between 2 surgical techniques for the treatment of early-onset periodontitis. J Periodontol 67:603–607. https://doi.org/10.1902/jop.1996.67.6.603

36. Kumar PG, Kumar JA, Anumala N, Reddy KP, Avula H, Hussain SN (2011) Volumetric analysis of intrabony defects in aggressive periodontitis patients following use of a novel composite alloplast: a pilot study. Quintessence Int 42:375–384

37. Bajaj P, Agarwal E, Rao NS, Naik SB, Pradeep AR, Kalra N, Priyanka N, Kumari M (2017) Autologous platelet-rich fibrin in the treatment of 3-wall intrabony defects in aggressive periodontitis: a randomized controlled clinical trial. J Periodontol 88:1186–1191. https://doi.org/10.1902/jop.2017.120661

38. DiBattista P, Bissada NF, Ricchetti PA (1995) Comparative effectiveness of various regenerative modalities for the treatment of localized juvenile periodontitis. J Periodontol 66:673–678. https://doi.org/10.1902/jop.1995.66.8.673

39. Rakmanee T, Griffiths GS, Auplish G, Darbar U, Petrie A, Olsen I, Donos N (2016) Radiographic outcomes following treatment of intrabony defect with guided tissue regeneration in aggressive periodontitis. Clin Oral Investig 20:1227–1235. https://doi.org/10.1007/s00784-015-1609-y

40. Rakmanee T, Griffiths GS, Auplish G, Darbar U, Petrie A, Olsen I, Donos N (2016) Treatment of intrabony defects with guided tissue regeneration in aggressive periodontitis: clinical outcomes at 6 and 12 months. Clin Oral Investig 20:1217–1225. https://doi.org/10.1007/s00784-015-1608-z

41. Cortellini P, Prato GP, Tonetti MS (1999) The simplified papilla preservation flap. A novel surgical approach for the management of soft tissues in regenerative procedures. Int J Periodontics Restorative Dent 19:589–599

42. Ramfjord SP, Nissle RR (1974) The modified Widman flap. J Periodontol 45:601–607. https://doi.org/10.1902/jop.1974.45.8.2.601

43. Kornman KS, Robertson PB (2000) Fundamental principles affecting the outcomes of therapy for osseous lesions. Periodontol 2000(22):22–43

44. Tonetti MS, Prato GP, Cortellini P (1996) Factors affecting the healing response of intrabony defects following guided tissue regeneration and access flap surgery. J Clin Periodontol 23:548–556

45. Tonetti MS, Pini-Prato G, Cortellini P (1993) Periodontal regeneration of human intrabony defects. IV. Determinants of healing response. J Periodontol 64:934–940. https://doi.org/10.1902/jop.1993.64.10.934

46. Cortellini P, Tonetti MS (2000) Focus on intrabony defects: guided tissue regeneration. Periodontol 2000(22):104–132

47. Cortellini P, Tonetti MS (2009) Improved wound stability with a modified minimally invasive surgical technique in the regenerative treatment of isolated interdental intrabony defects. J Clin Periodontol 36:157–163. https://doi.org/10.1111/j.1600-051X.2008.01352

48. Rasperini G, Acunzo R, Barnett A, Pagni G (2013) The soft tissue wall technique for the regenerative treatment of non-contained infrabony defects. Int J Periodontics Restorative Dent 33:e79–e87. https://doi.org/10.11607/prd.1628