PROF. LUIGI NIBALI (Orcid ID : 0000-0002-7750-5010)
DR. GEORGE PELEKOS (Orcid ID : 0000-0003-1917-1988)
DR. GUO-HAO LIN (Orcid ID : 0000-0003-1290-9994)

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Periodontal infrabony defects: systematic review of healing by defect morphology following regenerative surgery

Nibali L[1], Sultan D[1], Arena C[2], Pelekos G[3], Lin GH[4], Tonetti MS[3, 5]

[1] Periodontology Unit, Centre for Host-Microbiome Interactions, Dental Institute, King's College London, London, United Kingdom

[2] Universita' di Foggia, Italy

[3] Division of Periodontology and Implant Dentistry, Faculty of Dentistry, The University of Hong Kong, Hong Kong, SAR China

[4] University of California, San Francisco, USA

[5] Department of Oral and Maxillofacial Implantology, Shanghai Key Laboratory of Stomatology, National Clinical Research Centre of Stomatology, Shanghai 9th People Hospital, School of Medicine Shanghai Jiao Tong University, Shanghai, China

Corresponding author:
Luigi Nibali
King's College London Dental Institute
Guy's Hospital
Great Maze Pond, London, United Kingdom

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email: luigi.nibali@kcl.ac.uk

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ABSTRACT

Background: It is thought that infrabony defect morphology affects the outcome of periodontal regenerative surgery. However, this has not been systematically investigated.

Aims: To investigate how well defect morphology is described in papers reporting regenerative therapy of periodontal infrabony defects and to investigate its effect on clinical and radiographic outcomes

Materials and Methods: A search was conducted in 3 electronic databases for publications reporting clinical and radiographic outcomes of periodontal intrabony defects after regenerative therapy, divided by defect morphology.

Results: The initial search resulted in 4487 papers, reduced to 143 after first and second screening. Fifteen of these publications were suitable for a fixed effects meta-analysis. Initial defect depth was found to influence radiographic bone gain 12 months post-surgery, while narrower angles and increased number of walls influenced both radiographic bone gain and clinical attachment level (CAL) gain at 12 months. These associations seemed to occur irrespective of biomaterials used. Risk of bias ranged from low to high.

Conclusion: Deeper defects with narrower angles and increased number of walls exhibit improved CAL and radiographic bone gain at 12 months post-regenerative surgery. More data are needed about other aspects of defect morphology such as extension to buccal/lingual surfaces.

CLINICAL RELEVANCE

Scientific rationale for study: It is important to establish which aspects of infrabony defect morphology influence outcomes of regenerative surgery. **Principal findings:** Defect depth, angle and number of walls appear to influence the healing following regenerative periodontal surgery, irrespective of biomaterials used. **Practical implications**: It is important to consider defect morphology when planning regenerative periodontal surgery. More data about several aspects of defect morphology should be routinely collected and correlated with treatment response, in order to improve the clinician's ability to maximise healing.

INTRODUCTION

Classically, periodontal defects have been differentiated based on bone resorption patterns into 'supraosseous' ('suprabony') and 'infraosseous' ('infrabony') (Goldman & Cohen, 1958). These authors defined suprabony defects as those where the base of the pocket is located coronal to the alveolar crest. On the other hand, infrabony defects are those with apical location of the base of the pocket relative to the bone crest. Goldman and Cohen then classified infrabony defects according to the location and number of osseous walls remaining around the pocket. It has been suggested that the term 'intrabony' means 'within or inside the bone', while 'infrabony' means 'below the crest of bone' (Weinberg & Eskow, 2000). These authors suggested that only 3-wall angular defects should be termed 'intrabony', while all other vertical bony defects should be referred to as 'infrabony'. A large body of clinical and histological evidence accumulated over the last 4-5 decades shows how healing following periodontal surgery of infrabony defects can, with the use of biomaterials, be guided towards the formation of de novo cementum, functionally-oriented periodontal ligament, new alveolar bone and gingiva (Melcher, 1976; Nyman, Lindhe, Karring, Rylander, 1982; Wikesjo & Nilveus, 1990).The emphasis on '3-wall' bony defects was due to their higher chances of successful regeneration (Weinberg & Eskow, 2000). Recent developments in periodontal regenerative techniques and materials have pushed the boundaries of what is considered 'regenerable'(P. Cortellini, Stalpers, Mollo, & Tonetti, 2020). Papapanou & Tonetti differentiated osseous defects into 'suprabony' defects, 'infrabony' and 'interradicular or furcation' defects (Papapanou & Tonetti, 2000). Infrabony defects were further divided into 'intrabony' and 'craters' and the former were sub-divided into '1-, 2- or 3-wall defects' or 'combinations'. The emphasis was placed on differentiating whether or not the defect affected more or less to the same extent the adjacent root surfaces of an interdental space (similar periodontal breakdown along the root surface of two adjacent teeth, i.e. craters) or primarily affected one of the two root surfaces of an interdental space (greater periodontal breakdown on the tooth with the defect and more coronal crest of bone on the adjacent tooth in the same interdental space, i.e. intrabony defect) (Papapanou and Tonetti 2000).

Infrabony defects have been associated with risk of periodontal progression in the absence of the appropriate therapy, but not if included in regular maintenance care programs (Heins, Hartigan, Low, & Chace, 1989; Papapanou & Wennstrom, 1991)(Pontoriero, Nyman, & Lindhe, 1988).

With the currently available regeneration procedures, materials, and technologies, intrabony defects can be successfully regenerated, subject to patient-factors such as plaque control, smoking, medical history, as well as tooth mobility, restorative and endodontic condition (Nibali et al., 2019). Several publications reported on the superiority of periodontal regenerative therapy in the treatment of intrabony defects over the conventional surgeries such as periodontal access flap, known as open flap debridement surgery (OFD), in terms of probing pocket depth (PPD) and clinical attachment loss (CAL) reductions (Castro et al., 2017; Needleman, Worthington, Giedrys-Leeper, & Tucker, 2006; Nibali et al., 2019).

A few studies have also investigated the healing potential of infrabony defects following periodontal regeneration in relation to defect architecture, suggesting that narrower defects surrounded by higher numbers of bony walls have higher regenerative potential (Ellegaard & Loe, 1971; Selvig, Kersten, & Wikesjo, 1993; Tsitoura et al., 2004). However, the effect of defect morphology on treatment outcomes following periodontal surgery has not been investigated systematically, perhaps owing to the lack of a clear classification system for osseous defects. Therefore, the aim of this review is to examine the relationship between intrabony defect morphology and treatment outcomes.

MATERIALS AND METHODS

A systematic review protocol was written in the planning stages and the PRISMA statement (Moher, Liberati, Tetzlaff, Altman, & Group, 2009) was followed both in the planning and reporting of the review (checklist attached as Supplemental Material 1). The protocol was registered on 26/03/2020 with PROSPERO (available from ID: 176697).

Focused questions

The present review aimed to answer two focused questions:

- How often and how well is defect morphology described in papers reporting regenerative therapy of periodontal infrabony defects (defect depth, number of walls, extension of the defect, defect angle)?
- How does defect morphology predict the outcomes of regenerative therapy of periodontal infrabony defects?

Eligibility criteria

In brief, the **PECOS** method was the following:

- **(P)** Participants: Adult human patients with periodontitis who have completed a cycle of non-surgical periodontal therapy and present with residual pockets and infrabony defects.
- **(E)** Exposure: Defect morphology (depth, angle, number of walls) in defects undergoing mucoperiosteal surgery including regenerative surgery with Guided Tissue Regeneration (GTR), Enamel Matrix Derivative (EMD), bone fillers or substitutes, growth factors (GF) or combination.
- **(C)** Comparisons: Different types of intrabony defect morphology and different types of biomaterials used.
- **(O)** Outcomes: CAL gain, PPD reduction and radiographic bone gain
- **(S)** Studies: Randomized controlled trials (RCTs), cohort studies or case series

The following additional criteria were considered:

Inclusion criteria: i) Definition of periodontal infrabony defects at least 3mm deep; ii) with at least 12-months follow-up, iii) only studies published in English. Exclusion criteria: i) animal studies, ii) reviews, iii) including less than 20 patients; iv) studies including patients with diabetes or immunocompromised.

Information sources and Search

Papers were searched on MEDLINE, Cochrane Database and Scopus databases (search details are reported in supplemental material 2).

Study characteristics

This systematic review focused specifically on intrabony defect morphology and on its impact on regenerative treatment outcomes. Data extraction was performed in duplicate (authors DS and CA) including description of the infrabony defect and treatment outcomes by defect depth, defect angle and defect type (1- wall, 2-wall, 3-wall or more description if available).

The exposure 'defect morphology' was assessed as:

- Description of defect depth and width/angle

- Description of number of defect walls, divided into craters, 1-wall, 2-wall, 3-wall or combination
- Description of extension of defect to buccal and/or lingual walls, for example following the definition of trench (Karn, Shockett, Moffitt, & Gray, 1984) or circumferential defects or 'moats'(Karn et al., 1984)
- Description of materials used
- Description of study outcomes (clinical, radiographic, patient-reported) divided by defect type and materials used

Risk of bias analysis

In order to assess the quality of the included studies, Risk of Bias was assessed using the Cochrane Collaborations Tool for assessing risk of bias for RCTs, the Newcastle Ottawa Tool for cohort studies and the The Modified Delphi Tool for case series. Assessment across all key domain was summarized in order to draw a conclusion of the overall risk of bias within and across trials. This judgment was made independently by two reviewers (DS, CA); any discrepancies were resolved by discussion.

Summary measures and planned method of analysis

Studies were initially divided by reporting of defect morphology (based on criteria above). Among publications reporting defect morphology (even if just one aspect of defect morphology was reported), study outcomes were investigated and compared with type of regenerative materials used (when possible) and by defect morphology reported. A meta-analysis was considered appropriate and was performed in the presence of at least two studies with the same follow-up and reporting the same data. The outcomes of interest were CAL gain, PPD reduction and radiographic bone gain. The impact of initial defect depth, defect walls, and defect angle on bone gain and CAL gain were pooled and weighted mean difference (WMD) were estimated using a computer program [Review Manager (RevMan). Version 5.0. Copenhagen; The Nordic Cochrane Centre, The Cochrane Collaboration, 2008]. In addition, the coefficient estimates and the standard errors of the investigated variables, including defect depth, defect angle, and number of walls, from each publication were also pooled to assess the odds ratio (OR) and 95% confidence interval (CI) of the primary and secondary outcomes. The contribution of each article was weighed. Forest plots were produced to graphically represent the difference in outcomes. A p value= 0.05 was used as the

level of significance. Heterogeneity was assessed with p value for chi-square test. Random effects meta-analyses of the selected studies were applied if the p value for chi-square test was > 0.05. Fixed effects meta-analyses were applied if the p value for chi-square test was ≤ 0.05 to avoid any bias being caused by methodological differences among studies. In addition, the funnel plot was used to assess the presence of the publication bias. The reporting of these meta-analyses adhered to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (Liberati et al., 2009).

Evaluation of the strength of evidence

Evidence provided by RTCs was rated using different levels of methodological strength modified from GRADE (grading of recommendations assessments development and evaluation) (Guyatt et al., 2008). Three different strength of evidence were considered:

- **High**: At least 3 RCTs at low risk of bias and low heterogeneity ($I^2 < 30\%$).
- **Moderate**: More than 1 RCT and at least 1 RCT at low risk of bias, low heterogeneity.
- **Low**: Lack of RCTs or RCTs at high risk of bias or high heterogeneity.

RESULTS

Supplemental material 3 presents the flow chart from initial search to included papers. The initial search generated 4487 articles from Medline, Cochrane Library Database and Scopus combined. After screening the titles and abstracts, 404 articles were considered potentially suitable by at least one reviewer and qualified for full text screening. Following full text reading, 143 articles (from 136 original publications) met the defined inclusion criteria, while 261 were excluded. The reasons for exclusion are detailed in supplemental material 3. A total of 117 RCTs, 20 cohort studies and 6 case series were included. The publication year ranged from 1992 to 2019. The Cohen's kappa value for inter reviewer agreement was 0.57 at title and abstract screening level (94.7% agreement) and 0.87 at second screening (94.3% agreement). Every effort was made to retrieve original data from authors when needed. Data from 15 publications were available for meta-analyses. One study data (Cosyn, Cleymaet, Hanselaer, & De Bruyn, 2012) were retrieved from the study team but excluded from the meta-analysis due to high heterogeneity detected through subgroup analysis (CAL gain and bone gain data had opposite directions of association

based on defect morphology). Therefore, only 14 publications were included for quantitative analyses as detailed below for the different analyses.

Effect of defect morphology on regenerative outcomes

Defect depth: 114 papers reported average or range of defect depth measured radiographically and/or intra-surgically (often subdivided by study arm). Sixteen papers (from 15 publications) presented separate results for defects of different depth (see Table 1). Figure 1 reports forest plots for meta-analysis of defect depth data. Meta-analysis was carried out for the effect of initial defect depth > 4 mm vs. ≤ 4 mm on radiographic bone gain (in mm) at 12 months, including 3 papers (125 sites). A statistically significant association was found between defect depth > 4 mm and increased bone gain (-0.75 mm, 95% CI -1.12, -0.38) with moderate heterogeneity (I^2=57%) (Fig.1 A, categorical analysis with 4 mm threshold). Six publications (including 314 sites) were included in meta-analysis of the regression estimates for the effect of initial defect depth on radiographic bone gain at 12 months, showing a statistically significant association between deeper defect depth and increased bone gain (OR=1.32, 95% CI= 1.19, 1.47, I^2=0) (Fig.1 B, continuous analysis). Subgroup analysis by studies using GTR or EMD (with or without adjuncts) showed a significant association between deeper defect depth and increased bone gain of similar magnitude for both (see supplemental material 4). Four studies (n= 292 sites) were included in meta-analysis of the regression estimates for the effect of initial depth on CAL gain at 12 months, showing no statistically significant associations (Fig. 1 C).

Defect angle: 36 papers reported data on defect width/angle. Ten papers reported treatment outcomes by defect angle (see Table 2). However, these studies could not be meta-analysed together, owing to heterogeneity in reporting data. Figure 2 reports forest plots for meta-analysis of defect angle data. Two studies (n=91 sites) were included in meta-analysis of the regression estimates for the effect of initial defect angle on radiographic bone gain at 12 months. A statistically significant association was found between defect angle < 37° and increased bone gain (0.94 mm, 95% CI 0.48, 1.39) with moderate heterogeneity (I^2= 50%) (Fig. 2 A, categorical analysis with 37° threshold). Three studies (n=201 sites) were included in meta-analysis of the regression estimates for the effect of initial defect angle on radiographic bone gain at 12 months, showing no statistically significant associations (Fig. 2 B, continuous analysis). Four studies (n=274 sites) were included in meta-analysis of the regression estimates for the effect of initial

defect angle on CAL gain at 12 months, showing a statistically significant association between narrower angles and increased CAL gain (OR=0.97, 95% CI= 0.95, 0.98) with low-moderate heterogeneity (I^2= 33%) (Fig. 2 C).

Number of walls: 122 papers reported defect morphology as described below (see supplemental material 5):

- 1-, 2- and 3-walled defects or combinations: 78 papers
- 1- or 2- walled defects or combinations only: 14 papers
- 1-, 2- walled, combined 1-2 or circumferential defects: 5 papers
- 2-walled defects only: 1 paper
- 2- or 3-walled defects or combinations: 19 papers
- 3-walled defects only: 1 paper
- 1-walled defects only (or mainly 1-walled): 4 papers

Out of 122 papers reporting defect morphology 87 reported breakdowns of different types of defects included (based on defect morphology details above), while 35 did not. Out of 87 papers reporting breakdowns of different defects by number of walls, only 17 reported treatment outcomes for defects divided by baseline defect morphology. However, in 3 cases (Briguglio, Briguglio, Briguglio, Cafiero, & Isola, 2013; Crea, Dassatti, Hoffmann, Zafiropoulos, & Deli, 2008; Xu et al., 2019) only 1 type of defect was included in the study, so no comparison across different types of defects was possible. The remaining 14 papers are reported in Table 3.

Figure 3 reports forest plots for meta-analysis of number of walls data. Three publications (n= 150 sites) reported data on bone gain after regenerative treatment between 1-wall and 2-wall defects and showed significant radiographic bone gain at 12 months favoring 2-wall defects (-0.57 mm, 95% CI= -0.93, -0.21) with low heterogeneity (I^2=0%) (Fig. 3 A). Two publications (n= 108 sites) reported data on radiographic bone gain 12 months after regenerative treatment between 2-wall and 3-wall defects and showed significant bone gain favoring 3-wall defects (-0.39 mm, 95% CI= -0.78, -0.01) with moderate heterogeneity (I^2=54%) (Fig. 3 B). In addition, only one publication (Cortellini et al. 1993) reported data on radiographic bone gain 12 months after regenerative treatment between 1-wall and 3-wall defects and reported a significant bone gain favoring 3-wall defects (-1.18 mm, 95% CI= -1.66, -0.71).

Meta-analysis of regression estimates for radiographic bone gain at 12 months including two studies (n=101 sites) revealed a statistically significant association (OR= 3.43, 95% CI= 1.09, 10.85) with low heterogeneity (I^2=0%) (Fig. 3 C). Meta-analysis of regression estimates for CAL gain at 12 months including five papers (n=431 sites) revealed a statistically significant association between more bone walls and increased CAL gain (OR=1.42, 95% CI= 1.14, 1.77) with high heterogeneity (I^2=80%) (Fig. 3 D). Results of meta-analyses including Cosyn et al. 2012 are reported in supplemental material 6.

Not enough publications were available to analyze the outcome PPD.

Overall summary of results for defect depth, angle and number of walls, with associated level of evidence, is reported in table 4.

Risk of bias analysis

Supplemental materials 7, 8 and 9 report risk of bias analysis for RCT, cohort studies and case series. Risk of bias score for RCTs ranged from 0 to 10. A total of 75 papers were defined as 'good quality', 27 as 'fair' and 15 as 'poor' quality. Aspects which recorded highest risk of bias scores were allocation concealment bias and performance bias, while the area that according to our scoring showed lowest score was reporting bias. Risk of bias scores for cohort studies ranged from 5 to 8 stars, with the item 'comparability' often scored as 0. Eleven papers were identified as 'good quality' and the remaining 9 as 'poor quality'. Risk of bias scores for case series ranged from 11 to 16 out of 18. The item 'study population' was often scored low.

DISCUSSION

This systematic review investigated the effect of infrabony defect morphology on outcomes of periodontal regenerative therapy. The effect of baseline defect depth, defect angle and number of walls on radiographic bone and CAL gain was investigated. This review produced probably the largest body of systematically assessed evidence to suggest that deeper, narrower defects and defects with more walls are associated with improved clinical and radiographic outcomes 12 months post-regenerative surgery.

High strength of evidence suggests that deeper defects are associated with more radiographic bone gain at 12 months (both continuous and categorical analyses). The magnitude of additional radiographic bone gain was approximately 0.7 mm for defects initially deeper than 4 mm compared with those 3-4 mm deep. It is interesting to notice that the association between defect depth and bone gain seems to occur irrespective of biomaterials used and was of the same magnitude for EMD (including studies with or without adjunctive bone replacement grafts) or GTR. On the other hand, the more clinically meaningful CAL outcome was not associated with baseline defect depth.

Low level of evidence suggests that narrower angles are associated with more radiographic bone gain (only at categorical analysis with 37° threshold) and with more CAL gain (magnitude approximately 1 mm more CAL gain for angle < 37°). Furthermore, more walls are associated with more radiographic bone gain and CAL gain (magnitude approximately 0.5 mm per extra wall from 1 to 2 to 3). The increased chance of favorable treatment outcomes following periodontal surgery by number of residual walls has also been widely reported in publications not included in this review (Rosling, Nyman, Lindhe, & Jern, 1976). When categorizing infrabony defects by number of walls, we should not forget that often defects are categorized as 'combinations' and relative proportions of 1-, 2- or 3-wall components of the defects are reported (P. Cortellini et al., 2008). The prevalence of 'combination' defects in some GTR studies was as high as 31% to 56% (Christgau et al., 2002; Falk, Laurell, Ravald, Teiwik, & Persson, 1997). Furthermore, a 1-wall component may be present in the majority of sites (P. Cortellini & Tonetti, 2011). A gradient effect on percentage of defect fill has been shown from the 3-wall component of the defects (95 ± 6.2%) to the 2-wall component (82 ± 18.7%) and the 1-wall component (39 ± 62.4%) in a study using GTR (Cortellini et al., 1993). In contrast, other researchers reported limited influence of the defect's characteristics on the clinical outcome as defect characteristics showed weak or no correlations to defect fill (Polson & Heijl, 1978; Renvert, Garrett, Nilveus, Chamberlain, & Egelberg, 1985). It is clear that defect depth, narrow angle and increased number of walls are correlated, since usually the deepest part of the defect has increased walls and it is narrower. Therefore, it might be difficult to disentangle the relative contribution of each of these morphology aspects on regenerative surgery outcomes. It is also important to highlight that these observations, based on studies inclusion, were specific to defects with at least 3 mm radiographic infrabony component. These findings are further confounded by the fact that, in combination

defects, the subcomponents with a lower number of walls are the more superficial ones, which may be negatively affected by the oral environment and the wound healing process.

Another important finding of this review is that, although most publications reported some description of the study defects, only a minority of publications did report outcomes based on defect morphology. This is somehow surprising, since it has long been suspected that regeneration of intraosseous defects is thought to depend on uninterrupted maturation of the fibrin clot, favoured by stability of the wound and good soft tissue coverage of the defect (Hiatt, Stallard, Butler, & Badgett, 1968; Wikesjo & Nilveus, 1990). As such, intraosseous defect morphology is believed a crucial factor to facilitate predictable regeneration by influencing stability of the blood clot. These initial theories are supported by observations in animal models, showing that bone and cementum regeneration was positively correlated to the number of bone walls limiting the infrabony periodontal defects (Kim et al., 2004). Interestingly, the description of defect morphology in the included papers was limited to depth, angle and number of residual walls in the interproximal area and not to whether the defects extended to buccal and/or lingual walls, with the exception of a few studies including circumferential defects (Al Machot, Hoffmann, Lorenz, Khalili, & Noack, 2014; Hoffmann, Al-Machot, Meyle, Jervoe-Storm, & Jepsen, 2016; Meyle et al., 2011). Such extension is often pivotal for decision making on biomaterials to be used and on flap design (for example MIST vs. M-MIST or single-flap approach). No mention of 'craters' was found in the reviewed papers, although other papers not included in this review have described attempted regeneration of this type of defects (Falk et al., 1997). Therefore, no meaningful conclusion can be drawn on the regenerative potential of craters and on the potential effect of defect extension on outcomes of regenerative therapy.

Different types of regenerative materials can be adapted to the defect morphology: some materials are supportive and space-maintaining, like non-resorbable membranes, bone grafts, and combination of resorbable membrane and bone grafts, and others are non-supportive and non-space maintaining materials, like resorbable membranes alone, enamel matrix proteins, and growth factors (Pierpaolo Cortellini & Tonetti, 2015). Some publications have suggested that supportive biomaterials may overcome the negative effect of defect morphology and improve the outcomes of regeneration in non-space maintaining defects as they have the ability to create and maintain space

for regeneration and provide increased stability to the blood clot (Palmer, Cortellini, & Group, 2008; Reynolds, Aichelmann-Reidy, Branch-Mays, & Gunsolley, 2003; Slotte, Asklow, Sultan, & Norderyd, 2012; Tonetti et al., 2004; Tonetti et al., 1993; Tonetti, Prato, et al., 1996; Trombelli & Farina, 2008). On the other hand, for non-supportive biomaterials, such as EMD, their added benefit is thought to be greater in defects with a predominantly 3-wall anatomy compared with one-wall defect (Tonetti et al., 2002). However, these concepts are in constant evolution together with developments in the surgical procedure itself, specifically flap design and suturing technique. The most common complications of periodontal regeneration procedures were dehiscence of interdental tissues, graft exfoliation, membrane collapse and/or exposure, with the subsequent bacterial contamination which negatively affects the outcomes of regeneration, such as CAL gain and bone gain (P. Cortellini et al., 1993; P. Cortellini et al., 2001; Selvig, Kersten, Chamberlain, Wikesjo, & Nilveus, 1992). Therefore, new surgical techniques were developed with the aim of soft tissue preservation in order to achieve tension-free primary closure over the defect and the regenerative materials, and to ensure wound stability and blood clot stability during the early healing phase. It has been shown that stable flap designs, such as achieved by minimally-invasive surgical therapy (MIST) can lead to such favorable regenerative outcomes that the use of regenerative materials may not offer any additional benefits (Liu, Hu, Zhang, Li, & Song, 2016). No clear effect of biomaterials (supportive or not) on these results, although the only factor where this could be formally analyzed was defect depth.

A recent systematic review has concluded that EMD and GTR with resorbable membranes appear to be the gold standard for the surgical treatment of deep (≥ 3mm) infrabony defects which have not resolved following completion of non-surgical therapy and that among the possible replacement biomaterials, Deproteinized Bovine Bone Mineral (DBBM) improved clinical outcomes of both EMD and resorbable GTR compared with OFD and it should be considered a viable treatment option especially in non-supporting defects (Nibali et al., 2019). These authors also suggested that papillary preservation flaps may improve the clinical outcomes and should be considered a surgical pre-requisite when performing any regeneration procedure (Nibali et al., 2019). These observations are the basis for the recently published EFP S3 clinical guidelines (Sanz et al., 2020). The topic of periodontal regeneration of periodontal infraosseous defects is developing quickly with other biologically active agents such as growth factors (Smith, Martínez,

Cáceres, & Martínez, 2015) and bone morphogenetic proteins (Larsson et al., 2016). Therefore, the frontier of what is 'regenerable' is quickly moving and the 'bar' is being raised.

Strengths of this review are the analysis of a large body of literature and the relatively low heterogeneity, leading to moderate to high strength of evidence for most meta-analyses. The exclusion of one paper (Cosyn et al., 2012) significantly reduced heterogeneity for the radiographic bone gain outcomes. Risk of bias revealed that only a minority of papers were defined as 'poor quality' across all study designs, with 'reporting bias' for RCT and 'comparability' for cohort studies resulting as areas requiring improvement. The main limitation of this review is that despite the inclusion of more than a hundred papers, only 15 papers could be included in meta-analyses, due to limited or heterogeneous data reporting.

From these data, it emerges clearly how infrabony defect morphology has an important influence on outcomes of regenerative periodontal surgery. Baseline defect depth seems to positively influence radiographic bone gain 12 months post-surgery, while narrower angles and increased number of walls positively influence both bone and CAL gain. A good description and definition of the infraosseous defects can help in planning the most appropriate treatment option. Such specific definition can only really be obtained intra-surgically or perhaps through CBCT scan, although combined accurate assessment of probing pocket depths and periapical radiographs has good value (Wolf, von Bethlenfalvy, Hassfeld, Staehle, & Eickholz, 2001) and should be sufficient for treatment planning of most cases. A detailed classification system for infraosseous defects, which takes into account also other aspects of defect morphology, such as extension to buccal-lingual walls, should be used widely to improve our understanding of regenerative potential and of appropriate biomaterials for different types of defects.

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TABLES

Author	Study characteristics	Results by intrabony defect depth
Sanz et al. 2004	EMD vs. GTR (Guidor)	Intrabony defect depth did not influence significantly CAL gain. Estimate= -0.4 ± 0.2, P-value= 0.07
Meyle et al. 2011	EMD/synthetic bone graft vs. EMD	Deeper intrabony defect depth was associated with more defect fill (estimate= 3.068, P-value= 0.003)
Loos et al. 2002	GTR (Guidor)/Antibiotic vs. GTR alone vs. OFD/Antibiotic vs. OFD alone	Intrabony defect depth did not significantly influence bone gain (P-value= 0.38)
Grusovin & Esposito 2009	EMD vs. Placebo	Initial intrabony defect depth didn't significantly influence CAL gain and radiographic bone gain at 1 year. P-value= 0.41 and 0.81 respectively
Ehmke et al 2003	GTR (Guidor)	Intrabony defect depth significantly influenced alveolar bone gain (b-weight ± SD= 0.32 ± 0.15, P-value= 0.045)
Tonetti et al 1996	GTR Titanium ePTFE vs. GTR ePTFE vs. OFD	Borderline significance for initial intabony defect depth on CAL gain at 1 year (P-value= 0.055)
Klein et al. 2001	GTR (ePTFE/bioabsorbable)	Statistically significant positive influence of baseline intrabony depth on bone gain (P-value= <0.0001). More bone fill for initially deep intrabony defects (≥3 mm) but no association with CAL gain
Eickholz et al. 2004	GTR (ePTFE/bioabsorbable)	Deep (≥4 mm) infrabony defects exhibited statistically significantly more favorable bony fill than defects <4 mm (bone fill 2.50 ± 1.99 and -0.57 ± 2.16 respectively). Intrabony defect depth had statistically significant positive influence on bone fill (estimate= 0.314, P-value= 0.033)
Eickholz et al. 2014	EMD/Doxycycline vs. EMD/Placebo	Baseline intrabony defect depth influenced bone gain positively (P-value= 0.04)
Francetti et al. 2005	EMD vs. OFD	Statistically significant difference in bone gain between the EMD and OFD groups only at 12 months in the ≤6-mm subgroup (P-value= 0.05, in favor to EMD)
Bratthall et al. 2001	ready-to-use EMD-gel vs. marketed EMD	Higher CAL gain in sites with deeper baseline defects. Defects gaining >4 mm had deeper bony defects at baseline compared to the other group which gained ≤4 mm (baseline defect depth 6.1 ± 1.27 and 5.3 ±

		1.33 respectively)
Tonetti et al 2004	GTR (Bio-Guide)/Bio-oss vs. OFD	Depth of the intrabony component did not have a significant impact on CAL gain (estimate= 0.01 ± 0.09, P-value= 0.8751)
Zucchelli et al. 2003	EMP/bovine porous bone mineral vs. EMP	Intrabony defect depth significantly influenced CAL gain (more CAL gain in cases with deeper intrabony component, F-ratio= 19.62, P-value= 0.00001)
Zucchelli et al 2002	EMD vs. GTR (ePTFE) vs. OFD	Intrabony defect depth did not influence significantly CAL gain. F-ratio= 2.01, P-value= 0.1603
Linares et al. 2006 (same clinical study as Tonetti et al. 2004)	GTR (collagen membrane)/Deproteinized Bovine Bone Mineral vs. OFD	Initial radiographic intrabony defect depth was a significant covariate (p-value= 0.0001) to predict bone gain after 1 year
Ilgenli et al. 2007	Demineralized freeze-dried bone allograft/PRP vs. PRP	Initial defect depth was positively correlated to the bony fill (p-value= 0.047

Table 1. Details of papers reporting treatment outcomes divided by baseline defect depth.

Author	Study characteristics	Results by intrabony defect width/angle
Losada et al. 2017	EMD/Biphasic calcium phosphate vs. EMD	Probability of gaining ≥3mm of attachment diminished as the angulation score increased (OR=2.57 higher if the treatment was performed in an angle <24.75 than in wider angles, but not statistically significant)
Cortellini et al. 2008	EMD	CAL gain significantly associated with the baseline radiographic defect angle (estimate= -0.05, SE= 0.02, P-value= 0.0038)
Loos et al 2002	GTR (Guidor)/Antibiotic vs. GTR alone vs. OFD/Antibiotic vs. OFD alone	Radiographic defect angle did not influence significantly bone gain (P-value= 0.20)
Ilgenli et al. 2007	Demineralized freeze-dried bone allograft/PRP	No significant differences between narrow and wide defects in the PRP-alone therapy group (P-value= 0.89 for CAL gain & 0.90 for defect bone fill). More CAL gain and defect bone fill

	vs. PRP	in favor of the narrow defects (P-value was 0.03 for both) in the DFDBA + PRP group
Eickholz et al. 2004	GTR (ePTFE/bioabsorbable)	Initially narrow (angle <37°) defects exhibited statistically significantly more favorable bony fill than did wide defects (bone fill 2.30 ± 1.88 mm and -0.72 ± 2.49 mm respectively). Baseline defect angle had statistically significant positive influence on bone fill. Estimate= -0.064, P-value= 0.003
Zucchelli et al. 2003	EMP/bovine porous bone mineral vs. EMP	Defect angle did not influence significantly CAL gain (F-ratio= 2.20, P-value= 0.1439)
Tonetti et al. 1993	GTR (GoreTex)	Defect angle significantly affected CAL gain and bone gain (estimate= -0.05/P-value= 0.0026, and estimate= -0.05/P-value= 0.0031 respectively)
Tsitoura et al. 2004	EMD vs. OFD	Radiographic defect angle statistically significantly associated with CAL gain (p-value= 0.0477). The probability of obtaining CAL gain >3mm was 2.464 times higher (with a 95% confidence interval: 1.017– 5.970) when the radiographic defect angle was ≤ 22°, than when the radio- graphic defect angle was ≥36°
Klein et al. 2001	GTR (ePTFE/bioabsorbable)	Initially narrow (angle < 26°) infrabony defects exhibited more favorable CAL gain than wide defects (not statistically significant) and statistically significantly more favorable bony gain (P <0.05)
Linares et al. 2006	GTR (collagen membrane)/Deproteinized Bovine Bone Mineral vs. OFD	Radiographic defect angle did not have a statistically significant effect on CAL gain (p-value= 0.8138). Radiographic defect angle did not have statistically significant effect on bone gain either (p-value= 0.6179)

Table 2. Details of papers reporting treatment outcomes divided by baseline defect width/angle.

AUTHORS	DEFECTS INCLUDED	REGENERATIVE TREATMENT PROVIDED	COMPARISON RESULT BY DEFECT TYPE
Cortellini et al. 2008	1-, 2-, 3-wall, and combined	MIST+EMD	No statistically significant association for CAL change at multilevel regression analysis for 3-wall vs. other defects at 12 months (p=0.135)
Cortellini et al. 1993	1-, 2-, 3-wall, and combined	Gore-Tex	Bone gain at 12 months: 3-wall=2.7 ±2.2, 2-wall=1.6±1.6, 1-wall=0.4±1.6 (Bone fill: 95 ±6.2%, 82 ±18.7% and 39 ±62.4% for 3- , 2- and 1-wall components respectively)
Cosyn et al. 2012	1-, 2-, 3-wall, and combined	M-MIST vs. MIST+Bio-oss	Association between 1-wall defects and both failure (CAL gain < 2mm at 12 months, OR=10.4 for 1-wall vs. 2-wall defects) and increased buccal recession (OR=58.8 for 1- vs. 2-wall defects)
Crea et al. 2014	2-, 3-wall, or combined	OFD+ Intramarrow Penetration IMP vs. OFD	Radiographic defect depth change: 2-wall OFD (n=4):1.00 ± 1.82, OFD+IMP (n=13): 3.14 ± 1.36, 3-wall OFD (n=9): 2.00 ± 1.12, OFD+IMP (n=15): 3.00 ± 1.76. CAL change: 2-wall OFD (n=4):1.75 ± 3.33, OFD+IMP (n=13): 3.00 ± 1.62, 3-wall OFD (n=9): 1.78 ± 2.63, OFD+IMP (n=15): 3.14 ± 1.85
Loos et al. 2002	1-, 2- or 3-wall	Bioresorbable membrane or not (with or without systemic antibiotics)	No statistically significant association between number of walls and CAL gain
Losada et al. 2017	1-2 wall, or combined	EMD+BC vs. EMD	Probability of gaining ≥3 mm CAL: 2.57 (0.36-18.33) times higher for narrow defect angles (<24.75°) and 0.55 (0.16-1.92) for 1-wall vs. 2-wall
Meyle et al. 2011	1-, 2-, combined 1- and 2-wall, circumferential	EMD + synthetic bone graft vs. EMD	Tukey's plot showing bone fill in each defect type
Silvestri et al. 2003	2-, 3-wall	EMD vs. GTR	CAL gain: 3-wall= 5.02±1.86 mm, 2-wall= 4.25± 2.34 mm
Stavropoulos et al. 2003	1-, 2-, combined 1- and 2-wall	GTR (resorbable membrane) vs. resorbable membrane + Bio-Oss impregnated with saline vs. resorbable membrane + with Bio-	Estimated differences for 1-wall vs. 2-wall: PPD gain (0.40 mm, CI= -0.32;1.12, p=0.26), CAL gain (0.44 mm, CI= 1.68; 0.74, p=0.44), bone gain (1.33 mm, CI= 0.14; 2.53, p=0.03)

		Oss impregnated with gentamicin vs. flap surgery	
Tonetti et al. 2002	1-, 2- and 3-wall	Papilla preservation flap with EMD vs. no regenerative material	OR of CAL gain ≥3mm: 3-wall vs. 1-wall: 2.69 (CI=1.1-7.5)
Tonetti et al. 2004	1-, 2- and 3-wall	Papilla preservation flap with GTR vs. no regenerative material	Estimated difference in CAL gain in 1- vs. 3-wall= -0.5 ± 0.04
Yukna et al. 1994	1-, 2-, 3-wall, and combined	Calcium carbonate graft vs. OFD	Relative Defect Fill number (≥90%, ≥50%, <50%, <10%of defect) presented for each defect type
Tonetti et al. 1996	1-, 2-, 3-wall, and combined	GTR Titanium ePTFE vs. GTR ePTFE vs. OFD	General linear model showing lack of significance of depth of 1-, 2- or 3-wall on 1-year CAL gain (p-value= 0.664, 0.24, 0.19 respectively)
Nevins et al. 2013	1,2 wall, combined or circumferential	β-TCP + sodium acetate (SA) vs. β-TCP + SA + 0.3 mg/mL rhPDGF-BB vs. β-TCP + SA + 1.0 mg/mL rhPDGF-BB	Graph showing the influence of defect type on CAL gain with time

Table 3. Details of papers reporting treatment outcomes divided by baseline defect morphology.

Morphology parameter		**Radiographic bone gain**			**CAL gain**			**Strength of evidence**
		Effect size if statistically significant	**Heterogeneity (I^2)**	**Number of studies with low RoB**	**Effect size if statistically significant**	**Heterogeneity (I^2)**	**Number of studies with low RoB**	
Defect depth	Threshold (<4mm)	-0.75 mm	52%	3	No data	-	-	LOW
	Regression analysis	OR 1.32	0%	6	NS	4%	4	HIGH
Defect angle	Threshold (< 37°)	0.94 mm	50%	2	-	-	-	LOW
	Regression analysis	NS	80%	2	OR 0.97	33%	2	LOW-MODERATE
Number	1 vs. 2	-0.57 mm	0%	2	No data	-	-	MODERATE

of walls	2 vs. 3	-0.39 mm	54%	1	No data	-	-	LOW
	1 vs. 3	-1.18 mm	-	0	No data	-	-	-
	Regression analysis	OR 3.43	0%	2	OR 1.42	80%	3	MODERATE-LOW

Table 4. Summary of all meta-analyses findings. OR= Odds Ratio, NS= not statistically significant, RoB= Risk of Bias. Regression analyses were carried out having outcomes (bone gain, CAL gain) as continuous variables.

FIGURE LEGENDS

Fig. 1. Forest plots of meta-analysis of effect of defect depth on healing following regenerative surgery: categorical analysis for the effect of defect depth > 4mm on radiographic bone gain at 12 months (1A), regression estimates for the effect of initial defect depth on radiographic bone gain at 12 months (1B), regression estimates for the effect of initial depth on CAL gain at 12 months (1C).

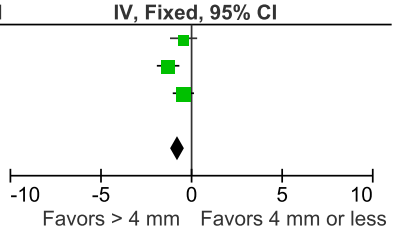
Fig. 2. Forest plots of meta-analysis of effect of defect angle on healing following regenerative surgery: categorical analysis for the effect of initial defect angle < 37° on radiographic bone gain at 12 months (2A), regression estimates for the effect of initial defect angle on radiographic bone gain at 12 months (2B), regression estimates for the effect of defect angle on CAL gain at 12 months (2C).

Fig. 3. Forest plots of meta-analysis of effect of number of walls on healing following regenerative surgery: categorical analysis for the effect of 1-wall vs. 2-wall defects on radiographic bone gain at 12 months (3A), categorical analysis for the effect of 2-wall vs. 3-wall on radiographic bone gain at 12 months (3B), regression estimates for the effect of number of walls on radiographic bone gain at 12 months (3C), regression estimates for the effect of number of walls on CAL gain at 12 months (3D).

1A

Study or Subgroup	Defect depth 4 mm or less Mean	SD	Total	Defect depth > 4 mm Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Ehmke et al. 2003	1.3	1	12	1.9	1.5	17	24.5%	-0.44 [-1.19, 0.31]
Eickholz et al. 2004	-0.92	1.92	21	1.87	2.25	29	35.6%	-1.30 [-1.92, -0.68]
Losada et al. 2017	2.227	1.27	22	3.167	2.548	24	39.9%	-0.45 [-1.04, 0.13]
Total (95% CI)			**55**			**70**	**100.0%**	**-0.75 [-1.12, -0.38]**

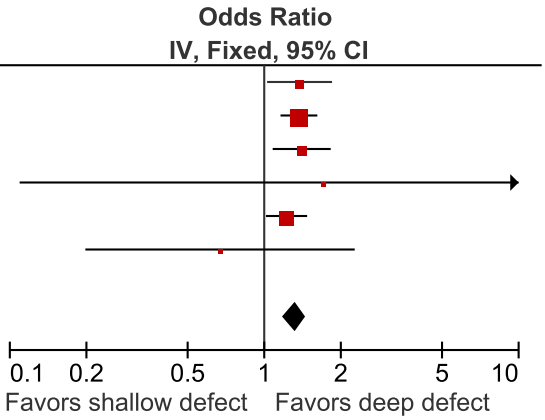
Heterogeneity: Chi² = 4.61, df = 2 (P = 0.10); I² = 57%
Test for overall effect: Z = 3.97 (P < 0.0001)



1B

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Ehmke et al. 2003	0.32	0.15	12.6%	1.38 [1.03, 1.85]
Eickholz et al. 2004	0.314	0.085	39.3%	1.37 [1.16, 1.62]
Eickholz et al. 2014	0.339	0.134	15.8%	1.40 [1.08, 1.83]
Losada et al. 2017	0.534	1.402	0.1%	1.71 [0.11, 26.63]
Meyle et al. 2011	0.202	0.095	31.4%	1.22 [1.02, 1.47]
Stavropoulos et al. 2003	-0.4	0.622	0.7%	0.67 [0.20, 2.27]
Total (95% CI)			**100.0%**	**1.32 [1.19, 1.47]**

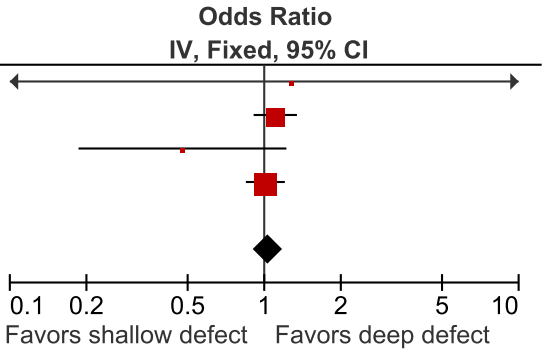
Heterogeneity: Chi² = 2.33, df = 5 (P = 0.80); I² = 0%
Test for overall effect: Z = 5.23 (P < 0.00001)



1C

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Losada et al. 2017	0.244	1.608	0.2%	1.28 [0.05, 29.83]
Sanz et al. 2004	0.1	0.1	43.8%	1.11 [0.91, 1.34]
Stavropoulos et al. 2003	-0.74	0.48	1.9%	0.48 [0.19, 1.22]
Tonetti et al. 2004	0.01	0.09	54.1%	1.01 [0.85, 1.20]
Total (95% CI)			**100.0%**	**1.04 [0.91, 1.18]**

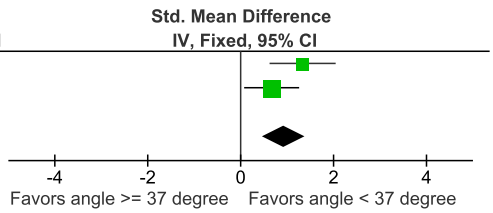
Heterogeneity: Chi² = 3.12, df = 3 (P = 0.37); I² = 4%
Test for overall effect: Z = 0.54 (P = 0.59)



2A

Study or Subgroup	defect angle < 37 degree Mean	SD	Total	defect angle >= 37 degree Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Eickholz et al. 2004	1.72	2.19	18	-1.13	2	20	40.9%	1.33 [0.62, 2.05]
Losada et al. 2017	3	2.204	36	1.7	1.059	17	59.1%	0.67 [0.08, 1.26]
Total (95% CI)			**54**			**37**	**100.0%**	**0.94 [0.48, 1.39]**

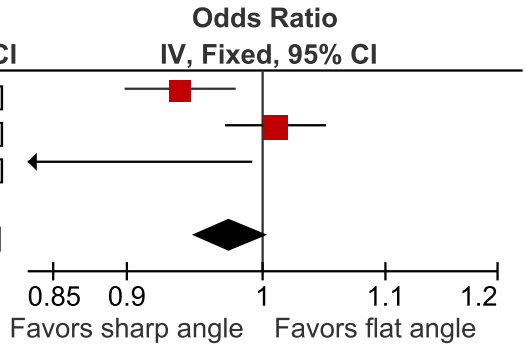
Heterogeneity: Chi² = 1.99, df = 1 (P = 0.16); I² = 50%
Test for overall effect: Z = 4.05 (P < 0.0001)



2B

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Eickholz et al. 2004	-0.064	0.022	45.1%	0.94 [0.90, 0.98]
Linares et al. 2006	0.01	0.02	54.6%	1.01 [0.97, 1.05]
Losada et al. 2017	-0.502	0.252	0.3%	0.61 [0.37, 0.99]
Total (95% CI)			**100.0%**	**0.98 [0.95, 1.00]**

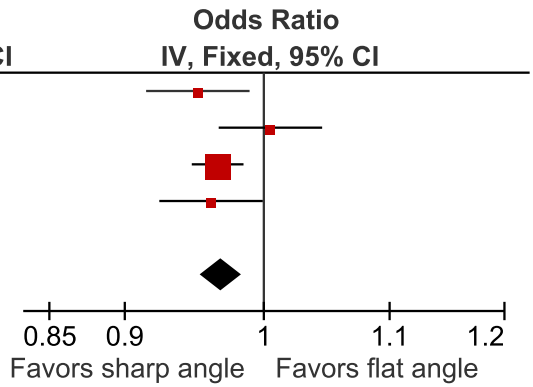
Heterogeneity: Chi² = 9.79, df = 2 (P = 0.007); I² = 80%
Test for overall effect: Z = 1.70 (P = 0.09)



2C

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Cortellini et al. 2008	-0.05	0.02	14.3%	0.95 [0.91, 0.99]
Linares et al. 2006	0.005	0.02	14.3%	1.01 [0.97, 1.05]
Losada et al. 2017	-0.035	0.01	57.1%	0.97 [0.95, 0.98]
Tsitoura et al. 2004	-0.04	0.02	14.3%	0.96 [0.92, 1.00]
Total (95% CI)			**100.0%**	**0.97 [0.95, 0.98]**

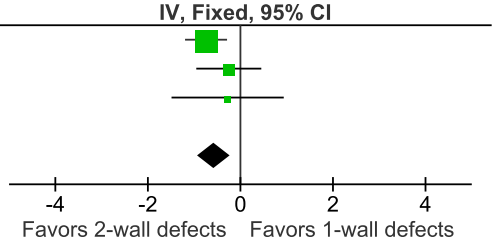
Heterogeneity: Chi² = 4.48, df = 3 (P = 0.21); I² = 33%
Test for overall effect: Z = 4.25 (P < 0.0001)



3A

Study or Subgroup	1-wall defects Mean	SD	Total	2-wall defects Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Cortellini et al. 1993	0.4	1.6	40	1.6	1.6	40	64.2%	-0.74 [-1.20, -0.29]
Losada et al. 2017	2.3	1.703	10	2.833	2.171	36	26.8%	-0.25 [-0.95, 0.45]
Meyle et al. 2011	2	1	3	2.45	1.619	21	9.0%	-0.28 [-1.49, 0.94]
Total (95% CI)			**53**			**97**	**100.0%**	**-0.57 [-0.93, -0.21]**

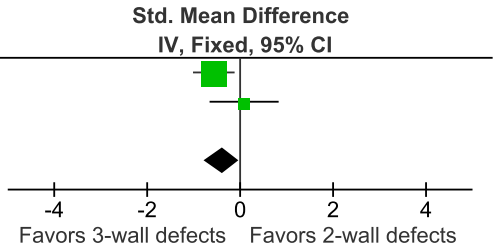
Heterogeneity: Chi² = 1.57, df = 2 (P = 0.46); I² = 0%
Test for overall effect: Z = 3.07 (P = 0.002)



3B

Study or Subgroup	2-wall defects Mean	SD	Total	3-wall defects Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Cortellini et al. 1993	1.6	1.6	40	2.7	2.2	40	73.4%	-0.57 [-1.01, -0.12]
Crea et al. 2014	3.14	1.36	13	3	1.76	15	26.6%	0.09 [-0.66, 0.83]
Total (95% CI)			**53**			**55**	**100.0%**	**-0.39 [-0.78, -0.01]**

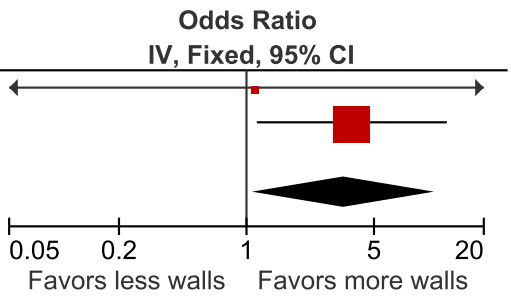
Heterogeneity: Chi² = 2.17, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 2.01 (P = 0.04)



3C

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Losada et al. 2017	0.107	2.084	7.9%	1.11 [0.02, 66.13]
Stavropoulos et al. 2003	1.33	0.612	92.1%	3.78 [1.14, 12.55]
Total (95% CI)			**100.0%**	**3.43 [1.09, 10.85]**

Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 2.10 (P = 0.04)



3D

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Cortellini et al. 2008	0.13	0.08	27.4%	1.14 [0.97, 1.33]
Losada et al. 2017	0.55	0.199	15.9%	1.73 [1.17, 2.56]
Stavropoulos et al. 2003	-0.47	0.617	3.0%	0.63 [0.19, 2.09]
Tonetti et al. 2002	0.372	0.122	23.1%	1.45 [1.14, 1.84]
Tonetti et al. 2004	0.5	0.04	30.6%	1.65 [1.52, 1.78]
Total (95% CI)			**100.0%**	**1.42 [1.14, 1.77]**

Heterogeneity: Tau² = 0.04; Chi² = 19.80, df = 4 (P = 0.0005); I² = 80%

Test for overall effect: Z = 3.09 (P = 0.002)