Surgical therapy for peri-implantitis management: a systematic review and meta-analysis

Abbreviated running title: Surgical peri-implantitis management

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Abstract

Aim: Peri-implantitis is a common cause of late implant failure. Studies have investigated different treatment strategies. The effectiveness of these modalities, however, remains unclear. This study aimed to evaluate the success of surgical peri-implantitis treatment using clinical and radiographic parameters.

Material and methods: A systematic review of published literature was employed. Key words were selected to conduct an electronic search using four databases for literature on human clinical studies. Meta-analyses were carried out for clinical probing, pocket depth and radiographic bone level.

Results: A total of 16 papers met the inclusion criteria. Four treatment modalities to supplement mechanical debridement were identified: 1) apically-repositioned flap, 2) chemical surface decontamination, 3) implantoplasty and, 4) bone augmentation. Inconsistent results were evident which were dependent on several treatment-independent factors. No clinical benefits were identified for the additional use of surface decontamination, while limited evidence demonstrated improvement of clinical and radiographic outcomes after implantoplasty. The effect of bone augmentation appeared limited to 'filling' radiographic defects.

Conclusions: The outcomes of the currently available surgical interventions for peri-implantitis remain unpredictable. There is no reliable evidence to suggest which methods are the most effective. Further randomised-controlled studies are needed to identify the best treatment methods.

Clinical Relevance

Scientific rationale for study: In the management of patients with peri-implantitis, the treatment of established bony defects around fixtures remains a significant clinical challenge. Principal findings: Whilst a range of surgical treatment modalities have been described, from simple debridement to implantoplasty and attempted guided-tissue regeneration, the individual techniques employed often appear based on operator-preference. Practical implications: This systematic review sought to evaluate the existing evidence to compare the existing surgical treatment modalities, determine their effectiveness and inform the management of these patients, however, the outcomes remain unpredictable. Further studies are required to discover the optimal surgical treatment approach for peri-implantitis.

Introduction

Implants provide a long-term, generally predictable treatment to restore function [1], aesthetics [2], self-esteem [3], and quality of life [4] following tooth-loss. The application and use of dental implants has increased and now represents an indispensable therapeutic option for the replacement of missing teeth.

Peri-implantitis is considered to be the main biological cause of 5-year implant failure [5, 6]. Review studies have estimated that peri-implantitis will affect 28%-56% of patients and 12%–43% of individual implant sites [7, 8]. This variation in prevalence may reflect differences in study design, population size and risk profiles, and the clinical 'definition' of peri-implantitis [7, 9]. There remains a lack of evidence regarding treatment and prognosis of peri-implantitis [8].

The inflammatory destruction of peri-implant tissue is multi-factorial. However, biofilm and bacterial infection are considered to be the major aetiological features in the development of peri-implant disease [8]. Smoking is also a strong predictor of implant failure [10], leading to an increase in prevalence that is 4.7 times greater than is observed in non-smokers [11] . Implant failure is 6 times greater in patients with a history of periodontitis than those who did not have a history of

79 periodontitis [11]. Systemic risk factors such as diabetes, cardiovascular diseases, age, gender, and
80 genetics have been suggested as potential risk factors, although studies are limited [12, 13]. Local risk
81 factors, e.g. excess cement, was associated with signs of peri-implantitis in 100% of patient with a
82 history of periodontal disease and 65% of healthy controls [14].

83 The diagnosis of peri-implantitis depends on the presence of inflammatory signs, bleeding
84 on probing (BOP) or suppuration on probing (SOP) and the degree of bone loss evident
85 radiographically [15]. However, it is important to distinguish this diagnosis of peri-implantitis from
86 bone resorption resulting from bone remodelling which occurs early after implant placement [7].
87 Some authors do not consider peri-implantitis as a differential diagnosis unless the implants have
88 been in place for >12 months [16-18].

89 The consensus report of the *11th European Workshop on Periodontology* highlights steps to
90 reduce the risk of incidence of peri-implantitis [19]. The indications for appropriate management
91 strategies that appear in clinical studies have resulted in development of the 'cumulative
92 interceptive supportive therapy' [15, 20, 21]. The management of peri-implantitis is based on similar
93 techniques to those of periodontitis [11] which entail the elimination of inflammation and prevention
94 of further bone loss; including non-surgical (conventional) and surgical treatment [22]. Conventional
95 non-surgical treatment can be classified into mechanical, chemical and light-mediated therapies.
96 Reviews and meta-analyses have concluded that there is no reliable non-surgical treatment which
97 results in elimination of the disease [23-25].

98 Surgical treatment allows better access to the implant surface and the surrounding bony
99 defect [26] and is used in conjunction with patient-directed care, and non-surgical therapy to reduce
100 bacterial colonization and local inflammation [21]. Mechanical debridement of the implant surface can
101 be achieved using curettes, ultrasonic scalers, or air-abrasion, in the presence or absence of systemic
102 antibiotics. A 3-month follow-up study has shown that mechanical debridement alone, following
103 surgical access, is effective in reducing clinical/microbial parameters [27]. Whilst adjunctive surface
104 decontamination with antimicrobials such as chlorhexidine (CHX) reduced microbial counts, this had

105 no significant effect on clinical or radiographic parameters [28, 29]. Leonhardt et al. (2003) reported
106 that significant reduction in BOP and PPD (periodontal probing depth) following surgical
107 debridement and decontamination with H_2O_2[30]. Although many clinicians employ topical antibiotics
108 e.g. tetracycline and minocycline, their clinical effect remains unclear [31].
109 Lasers have been shown to have no additional clinical benefit as a potential surface-
110 decontamination agents during surgical therapy when compared with mechanical debridement [32, 33].
111 Photo-dynamic therapy (PDT) was shown to significantly decrease BOP and PPD between test and
112 control subjects in a randomised control trials (RCT), although the bacterial counts showed no
113 difference between the two groups [34].
114 Adjunctive resective surgery using osteoplasty, with or without apically re-positioned flap
115 (ARF) procedures, has been reported to improve clinical sign of peri-implantitis, where PPD ≥ 6 mm
116 were eliminated in 77% of subjects [35]. However, the use of ARF in the aesthetic zone is limited [11].
117 Implantoplasty is directed to reduce surface-roughness of the implant surface to decrease bacterial
118 and biofilm accumulation [36]. However, concerns have been raised regarding the reduction of implant
119 strength [37], deposits of titanium particles in the soft- and hard-tissues [38] and increased marginal
120 tissue recession and exposure of the implant surface [31]. Re-osseointegration using bone
121 augmentation (autogenous bone [39,40] and/or synthetic bone graft materials [41,42] may provide a
122 significant improvement in clinical and radiographic parameters compared to the baseline. Bone
123 graft (autogenous or synthetic), however, cannot be integrated on to a metal surface [43].
124 Furthermore, it has been shown that the use of membrane/s with autogenous or synthetic materials
125 has no additional benefit [40, 44].
126 The aim of this systematic review was to critically evaluate the current literature on the
127 surgical treatment of peri-implantitis and assess the effectiveness of treatment modalities (and
128 adjunctive therapies) on peri-implant and periodontal radiographic outcomes. The objective was to
129 identify the most predictable and reliable treatment modalities by a quantitative comparison of
130 outcomes using meta-analysis.

Materials and methods

Search Strategy

In order to achieve the aims of this study, an electronic literature search was conducted using Ovid MEDLINE, EMBASE and EBM Review – Cochrane Central Register of Control Trials and Cochrane Database of Systematic Reviews. The following keywords were combined: '*Tooth Implantation*' OR '*Dental Implants*' OR '*Tooth implants*' OR '*Oral Implants*' OR '*Endosseous implants*' OR '*Osseointegrated implants*' AND '*Periimplantitis*' OR '*Peri-implantitis*' OR '*Peri-implant disease*' OR '*Peri-implant defect*' OR '*Peri-implant infection*' OR '*Peri-implant inflammation*' OR '*Peri-implant bone loss*' AND '*Management*' OR '*Treatment*' OR '*Therapy*' AND '*Surgery*' OR '*Surgical*' OR '*Surgical approach*' OR '*Open flap*' OR '*Access flap*' OR '*Resective*' OR '*Regenerative*' OR '*Bone regeneration*' OR '*Bone augmentation*' (Table 1).

Study Selection Criteria

The criteria for inclusion of specific studies in this review were human studies published in the English language. Studies were selected for randomized controlled trials or prospective cohort studies only with ≥ 10 patients and ≥6 months follow-up (the longest follow up period was chosen in longitudinal studies which were published more than once). Experimental animal or studies *in vitro* were excluded.

Primary and secondary outcomes

The primary outcome for this review study was the reduction of BOP in implants treated surgically for peri-implantitis. The secondary outcomes were the assessment of PPD and RBL (radiographic bone loss).

Qualitative assessment methods (Risk of bias)

The modified 'Critical Appraisal Skills Program' (CASP) checklists was used to assess the quality of the studies [45]. The risks of bias were categorized into; low risk (all the criteria were met), moderate risk (1-2 criteria were missed) or high risk (>2 criteria were missed).

Statistical Analysis

Meta-analyses were conducted separately for the parameters PPD and RBL using computer software (Stata® V13). All data used in meta-analysis were those measurements made at the end of the observation period for both control and intervention arms. Forest plots were produced to represent the standardized mean difference (SMD) between control and test groups. Pooled estimates and associated 95% confidence interval (CI) from meta-analysis for each type of intervention were indicated by 'diamond' symbols in Fig. 5; the center of the diamond (with respect to the x-axis) indicates the pooled point estimate and the edges indicate the pooled 95% CI. I-squared values and a chi-squared test were used to assess the heterogeneity of the studies.[46] Where heterogeneity was not problematic fixed-effects meta-analysis was employed and random-effects meta-analysis was otherwise employed. Although some evidence of an outlier was observed for RBL for some studies [49,50], results for this study were included in Forest plots because it was not used to form any 'pooled' estimates (it was the only study in the 'implantoplasty' group).

Results

Literature on peri-implant disease

Initial results highlighted the increase in published research on peri-implant disease over the last 15 years (Fig. 1a). There were significantly more publications on peri-implantitis and its surgical treatment compared to the numbers of publications regarding peri-implant mucositis and non-surgical treatment (Fig. 1b).

Manuscript selection

The literature search identified 320 studies, and 25 were selected for full-text evaluation following title and abstract screening. A further 9 papers were excluded following careful review (Fig. 2), and the remaining 16 studies included and reviewed for detailed qualitative and quantitative assessment (see Supplementary Information for a summary of the included studies). Selection was based on the 'Preferred Reporting Items for Systematic review and Meta-Analysis' flow chart PRISMA [48]. Of the 16 studies included, 9 were RCTs, 4 were comparative prospective studies, and 3 were single group prospective studies. The CASP checklist revealed that 53% of the included studies have a high risk of bias, 35% have a moderate risk, and the remaining studies (12%) have a low risk of bias. The follow-up periods of the studies that were included in the review ranged from 6 to 60 months. However, the participants were observed for 12 months in most of the studies.

Surgical interventions

The main type of surgical intervention was bone augmentation following mechanical debridement, which was examined in 44% of the studies (Fig. 3a). The effect of mechanical debridement combined with surface decontamination was examined in 38% of the studies. Relatively few studies (12%) considered the effects of mechanical debridement only; 6% of the studies examined mechanical debridement with implantoplasty. Xenograft materials were used for 64% of the bone augmentation cases, whilst autogenous bone was used for 20% of the augmentation studies. CHX was the most common surface decontamination method (57%) and was used in all of the cases (which included debridement plus surface decontamination; Fig. 3b).

Study outcomes

The parameters used in clinical measurement of peri-implantitis were BOP, PPD, and RBL. The majority of studies used both clinical and radiographic outcomes (69%), and the remaining studies

208 employed clinical parameters only (31%). Three studies [28, 29, 49] measured change in outcome
209 measurements with time (3, 6, and 12 months follow-up) and they showed that the mean BOP was
210 significantly decreased ($P < 0.05$) after 3 and 6 months followed by a gradual increase from 6 to 12
211 months (Fig. 4a). The mean PPD was also decreased significantly ($P < 0.05$) at 3-month follow-up
212 then remained relatively constant during the remaining periods (Fig. 4b). By contrast, RBL had not
213 increased significantly ($P > 0.05$) after 3 months.
214
215 **Meta-analysis**
216 The meta-analysis was conducted using 8 RCTs [28, 29, 32, 34, 50-53] and 2 controlled prospective cohort
217 studies [40, 44] as they reported mean reductions (and standard deviations) for PPD and RBL. The forest
218 plots for PPD and RBL are represented by the four methods for surgical peri-implantitis treatment
219 identified: 1) surface decontamination, 2) implantoplasty, 3) bone augmentation, and 4) additional
220 use of membranes in bone regeneration. Few studies have published data relating to BOP, and so no
221 meta-analysis could be conducted for this parameter.
222 Meta-analysis demonstrated that implants treated with surface decontamination had SMD of -0.21
223 (95% CI: -1.70 to 1.27) for PPD reduction. Only one study [50, 51] reported the effect of implantoplasty
224 on PPD reduction which shows a significant SMD of -3.33 (95% CI: -4.37 mm to -2.28 mm). Bone
225 augmentation with grafting materials and the additional use of membrane resulted in SMD of 0.15
226 mm (95% CI: -0.55 to 0.84 mm) and 0.30 mm (95% CI: -0.31 to 0.91 mm) respectively (Fig. 5a). In
227 terms of RBL changes, the use of surface decontamination methods resulted in SMD of 0.54 mm
228 (95% CI: -0.20 to 1.28 mm). Whereas implant treated with implantoplasty, had SMD of -3.38 (95% CI:
229 -4.43 to -2.33 mm). The SMD for RBL changes after the use of bone augmentation was -1.50 (95% CI:
230 -0.80 to -0.31 mm). However, the additional use of membrane has SMD of -0.16 (95% CI: -0.56 to
231 0.24 mm) (Fig. 5b). Whilst implantoplasty and bone augmentation resulted in significant
232 improvement in RBL, the use of surface decontamination or additional membrane application failed
233 to significantly affect observed treatment outcomes.

Heterogeneity was found to be small or moderate for the additional membrane subgroup (i.e.: RBL, I-squared = 0.0%, P = 0.64; PPD, I-squared = 52.1%, P = 0.152) and so random-effects meta-analysis should provide a reasonable pooled estimates in this case. Heterogeneity was found to be high for the surface decontamination subgroup (i.e.: RBL, I-squared = 88.6%, P < 0.001; PPD, I-squared = 97.1%, P < 0.001). A sensitivity analysis for RBL and for the additional membrane subgroup could not be carried out for due to the small number of studies in this case. A sensitivity analysis could be carried out for PPD for this subgroup, where removal of the study with the smallest sample size of seventeen subjects in total (namely, Schwartz et al., 2013) did not affect pooled results very greatly (i.e., SMD = -0.253 and 95% CI = -2.001 to 1.494), whereas removal of the only "outlying" study that indicated a positive mean difference (namely, de Waal et al., 2015) did affect pooled results (i.e., SMD = -0.866 and 95% CI = -1.663 to -0.069). This result indicates a significant reduction in PPD for surface decontamination subgroup in this circumstance, although caution should still be exercised due to the small number of studies and heterogeneity. Again, funnel plots are likely to yield limited information only due to the small number of the studies included in the analysis.

Discussion

This systematic review and meta-analysis was conducted to explore the literature relating to the surgical management of peri-implantitis. It was evident that the patient selection criteria for entry into the studies (and the definition of 'peri-implantitis') varied considerably between the included studies. For example, one study defined peri-implantitis by implants with RBL indicating >50% of bone loss [40], whereas other studies defined peri-implantitis as affecting implants that exhibited PPD >6mm with radiographically visible bony defects [32, 54, 55].

Radiographic interpretation of results was found to be inconsistent. Defect configuration needs to be taken into account, and this is particularly evident where bone regeneration is to be attempted using guided bone regeneration [55]. Roccuzzo et al. (2016) went on to show that the circumferential defects showed better bone regeneration compared with the other types of defect.

However, another four-year study which included combined surgical therapy, surface decontamination, and implantoplasty revealed that the outcomes were not directly affected by the defect configuration [32].

Plaque control is pivotally important in peri-implant disease and response to treatment [15]. Adequate oral hygiene maintaining plaque scores at lower levels (PI ≤ 1) was important for reducing the incidence of BOP [56]. The severity of peri-implantitis at the commencement of treatment (as measured by the PPD and RBL) may clearly influence treatment outcomes [35, 57]. Other important plaque-retentive factors, e.g. surface roughness are an important consideration when conducting comparative studies [49, 53, 54]. A history of both smoking and periodontitis has been shown to have an adverse effect on the treatment of peri-implantitis [44, 52, 58]. Due to the small numbers of patients, variation in tobacco usage, and incomplete assessment of the severity of the previous periodontal disease in the papers included within this study, this correlation could not be linked to the outcomes of surgical peri-implantitis treatment.

The definition of a successful treatment also varied between studies. In marked contrast, some studies [49] simply considered the survival of the affected implants following treatment to represent success. Other studies [28, 29, 53, 57] have considered no further bone loss and presence of PPD ≤ 5mm, with no BOP, to be a successful treatment. Inter- and intra-examiner bias may also lead to variable in outcome measures, for example, force of probing [59]. Furthermore, PPD alone is considered as an invalid marker for the progression of the disease as the reduction in PPD post-treatment may simply reflect gingival recession and/or the surgical technique e.g. apically-repositioned flap procedures [52, 60]. Although radiographic assessment is the only truly non-invasive method for measuring marginal bone levels [52] it can only indicate 'defect-fill' but not the actual re-osseointegration [44] and represents the mesial and distal bone levels only [61]. More recently, cone-beam CT has been used to detect the levels of buccal and lingual bones, although concerns have been raised regarding both radiation exposure and their validity due to a radiolucent halo that may occur around the implant [51].

The rationale behind the use of adjunctive systemic antibiotics in the management of peri-implantitis was considered in three studies [40, 49, 58]. There is a lack of evidence to support the prescription of antibiotics in peri-implantitis treatment, which appears operator-dependent. An RCT investigating the effectiveness on systemic antibiotics failed to demonstrate any effect on local microbiological parameters within the defect [53].

The most popular surface decontaminant was CHX, which has been tested extensively and approved to have a broad-spectrum anti-bacterial activity [62]. Variation occurred in the CHX concentrations used in two studies (0.12% CHX Vs placebo[29] or 2% CHX Vs 0.12% [28]). Although both studies reported reduced microbial loads when compared to control groups, this did not translate into demonstrable clinical effects on peri-implantitis. Although other chemical antimicrobial treatments were employed e.g. H_2O_2, H_3PO_4, and EDTA, no studies compared their effects to other adjunctive treatments (or placebo-treated control groups). A 4-year review revealed that curette and saline mechanical debridement showed better results than those treated with Er:YAG laser [32], although one study indicates that the Er:YAG laser gave better outcomes at 2-year follow-up [63]. Meta-analysis failed to detect any significant difference in the use of surface decontamination (via CHX or Laser) on PPD and RBL. Previous studies have indicated that treatment results are independent of decontamination method and that other risk factors such as oral hygiene, defect configuration are better predictors of treatment success [33, 55].

Implantoplasty reduces the macro-surface texture (threads) of the implants. The authors feel that the procedure is effective, partly as it is associated with complete elimination of the primary aetiological factor in peri-implantitis- namely the biofilm. Barbour et al. (2007) reports that it may increase the micro-surface roughness leading to biofilm retention. Furthermore, it may alter implant strength [37, 64] and increase the temperature of the implants surface [65], leading to adverse effects on bone cellularity [66]. The significant improvement of clinical and radiographic parameters following implantoplasty was only based on one study [50, 51] and further research regarding this method is needed.

Bone augmentation is limited due to the biological principle of bone regeneration which needs a blood supply to provide nutrition, inflammatory cells to induce bone formation (osseoinduction), and collagen matrix for osseoconduction [43]. The significant effect of bone augmentation on RBL relates to the bone grafts material occluding the defect; no effect on clinical outcome (PPD) is evident [52]. Autogenous bone particles ± membranes in multi-walled defects resulted in significant improvement in PPD and RBL at 36 months [40]. In contrast, Aghazadeh et al. (2012) demonstrated that bovine-derived xenograft (BDX) was more effective than autogenous particulate bone [58]. Khoury and Buchmann (2001) and Roos-Jansåker et al. (2014) were unable to demonstrate any additional benefits in comparison to defects treated with graft material alone [40,44].

There are several limitations of this current study due to the inclusion of English language papers only, as well as considerable variability between the different studies included in this review relating to the inclusion/ exclusion criteria. Furthermore, there were only a small number of studies included for each type of surgical intervention, with most studies consisting of relatively small sample sizes and high risk of selection bias in patient inclusion. The high degree of heterogeneity between studies prevents quantitative comparison between the groups [47]. Therefore, neither the differences between the groups nor the overall results were calculated. Furthermore, the meta-analyses should be interpreted cautiously because of the small number of the included studies in each group and the high degree of heterogeneity between them.

This current review concludes that a need exists for a long-term, double blind RCT with large sample size and split-mouth technique are required to eliminate patient-related bias. In addition, all potential confounders should be taken into account. Finally, it would be helpful if the definition, diagnosis and the outcomes of the disease were standardised, to be able to conduct more precise reviews, meta-analyses and the evidence-based surgical treatment of these patients.

Conclusion

This systematic review shows that a surgical approach to mechanical debridement alone may result in improved clinical outcomes, with no evidence to show the benefits of apically-repositioned flap procedures. No additional clinical benefits were found from the use of surface decontaminants (chemicals or lasers) or additional systemic antibiotics. A single study demonstrated a significant improvement following implantoplasty. Bone augmentation improved radiographic bone levels; the use of additional membrane/s, however, did not result in any additional benefit. The high degree of heterogeneity and the small number of controlled studies make it difficult to identify which procedure is superior to any other.

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Conflict of Interest

The authors confirm that there are no conflicts of interest to declare.

Ethical approval

None required

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513 **Table 1** Keywords used for the electronic search

Dental Implantology	Peri-implant disease	Procedure	Technique
Tooth Implantation	Periimplantitis	Management	Surgery
Dental Implants	Peri-implantitis	Treatment	Surgical
Tooth implants	Peri-implant disease	Therapy	Surgical approach
Oral Implants	Peri-implant defect		Open flap
Endosseous implants	Peri-implant infection		Access flap
Osseointegrated implants	Peri-implant inflammation		Resective
	Peri-implant bone loss		Regenerative
			Bone regeneration
			Bone augmentation

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Figure legends:

Figure 1 Publishing rate of papers on (a) peri-implant disease and (b) peri-implantitis treatment in the period 2001-2015.

Figure 2 PRISMA flow chart for study selection.

Figure 3 Proportion of (a) surgical intervention investigated and (b) surface decontamination methods used in the included studies.

Figure 4 The relationship between observed outcomes and time for (a) BOP and (b) PPD [28, 29, 49].

Figure 5 Forest plot for (a) probing pocket depth (PPD) reductions and (b) radiographic bone level (RBL) changes.

537 Figure 1:

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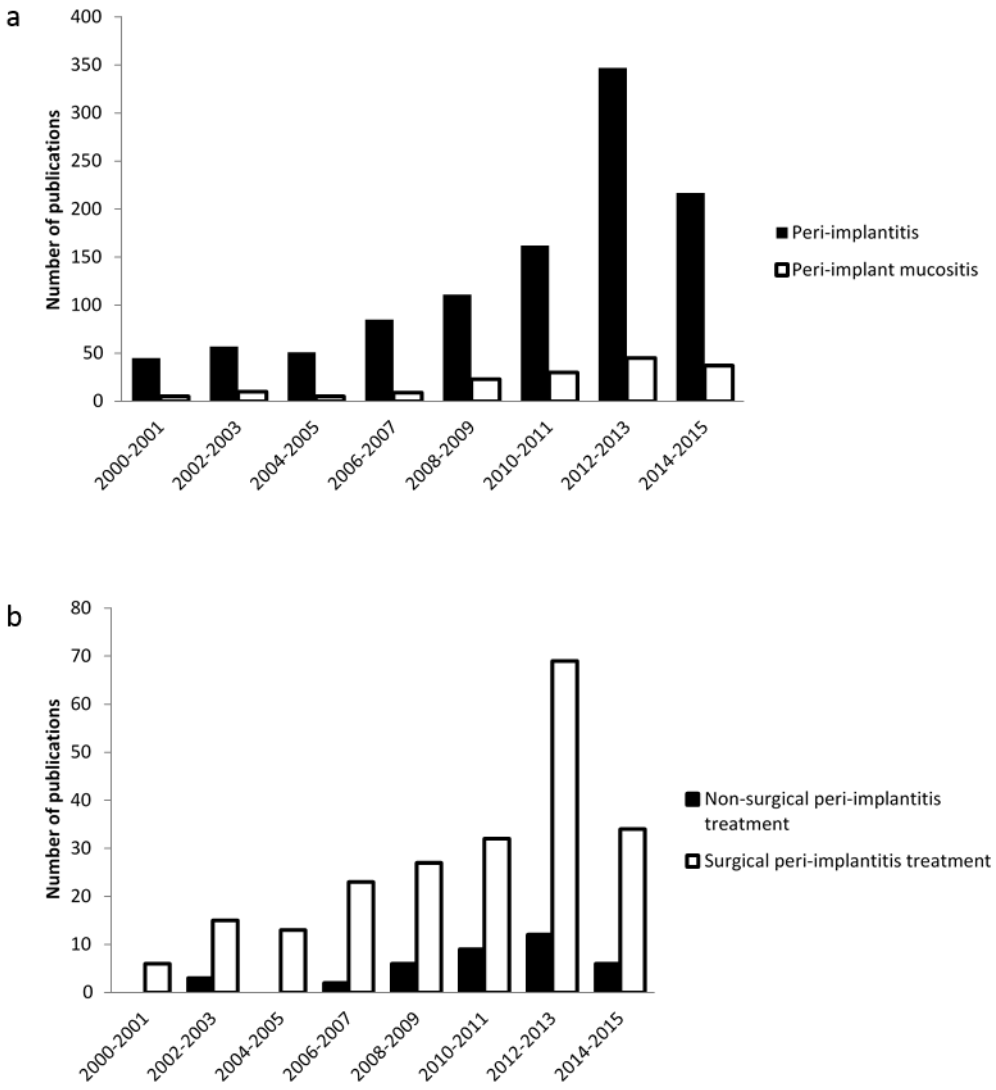

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544 Figure 2:

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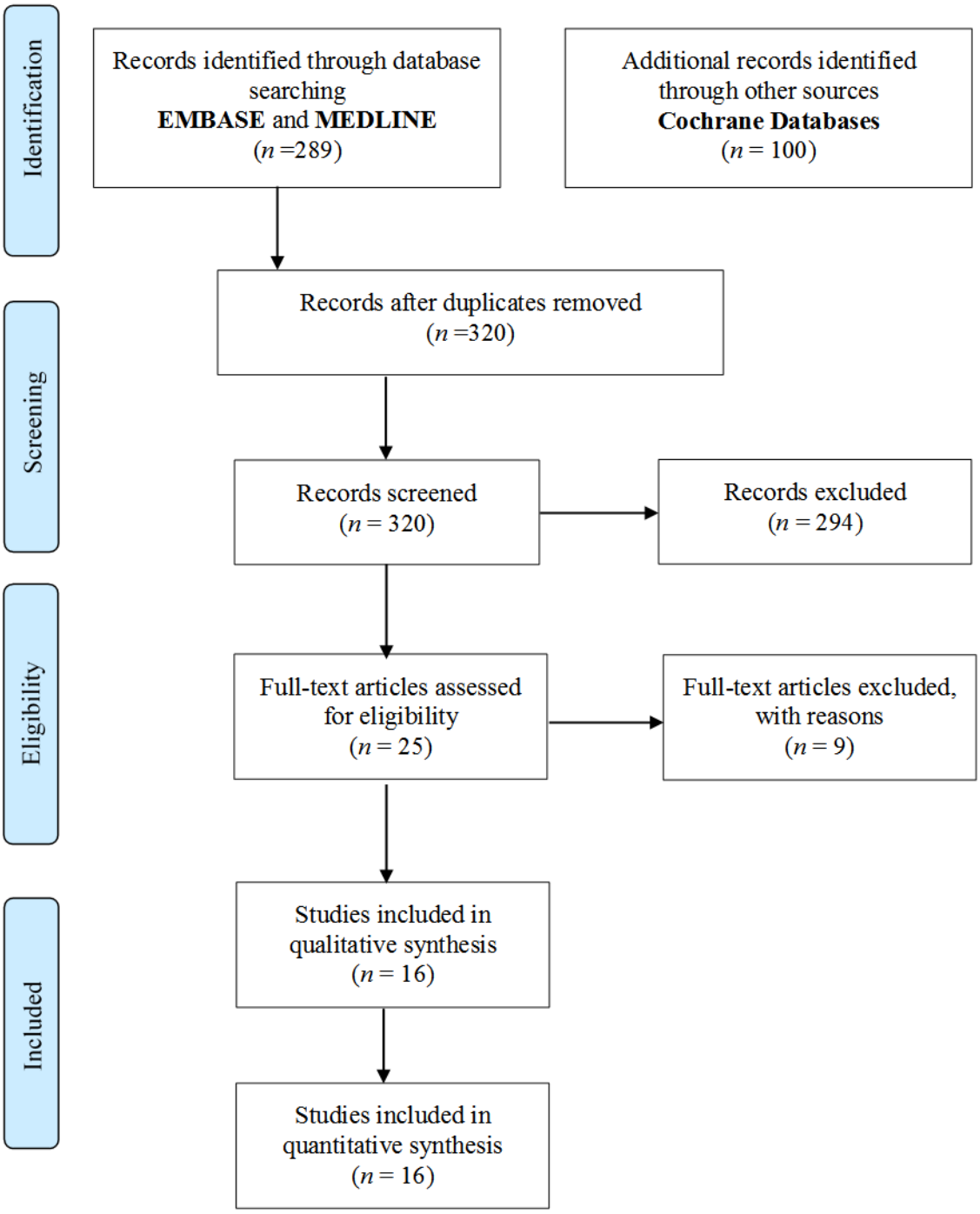

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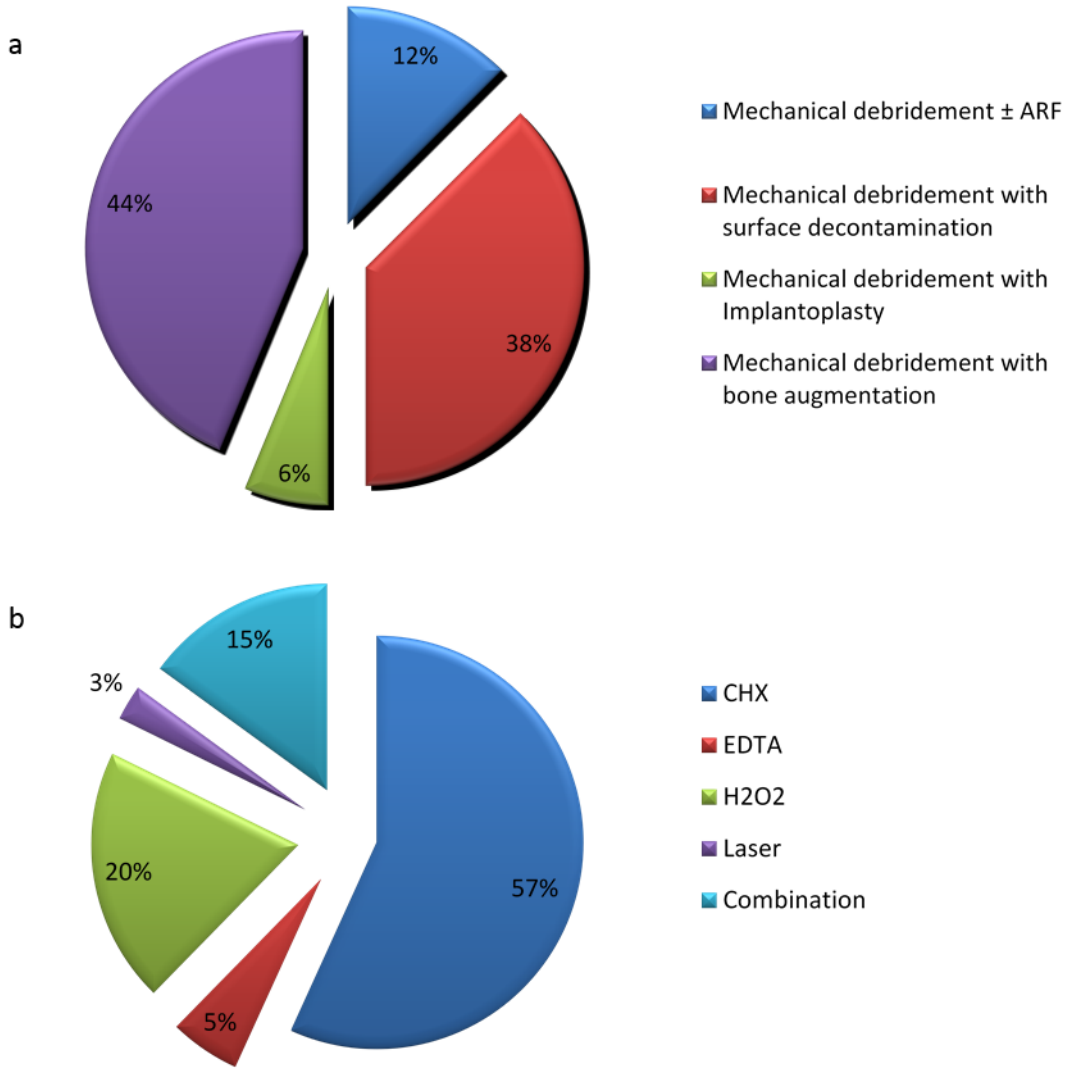

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555 Figure 4:

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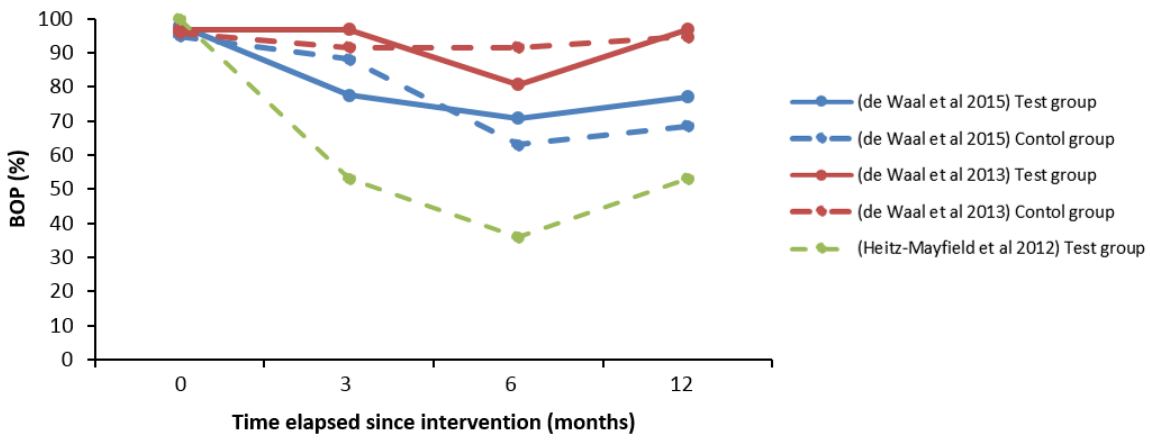

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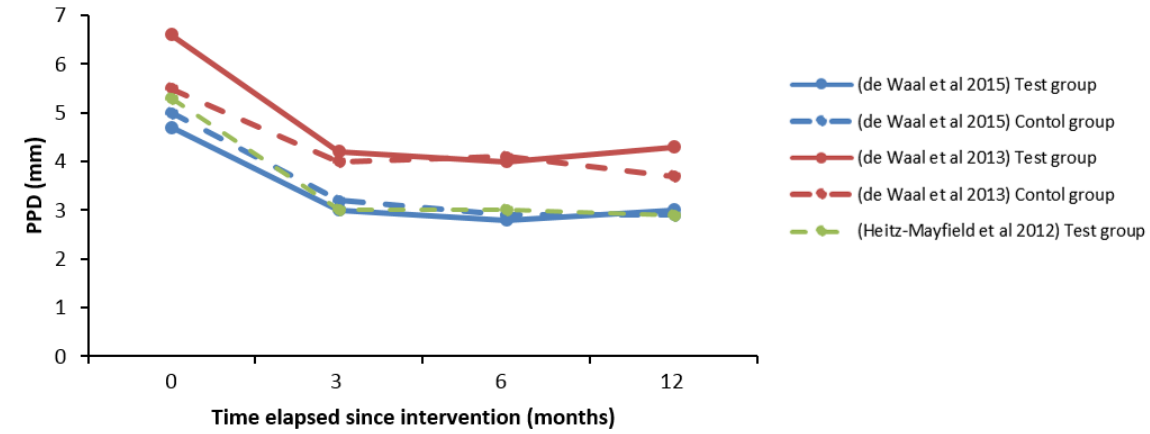

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564 Figure 5:

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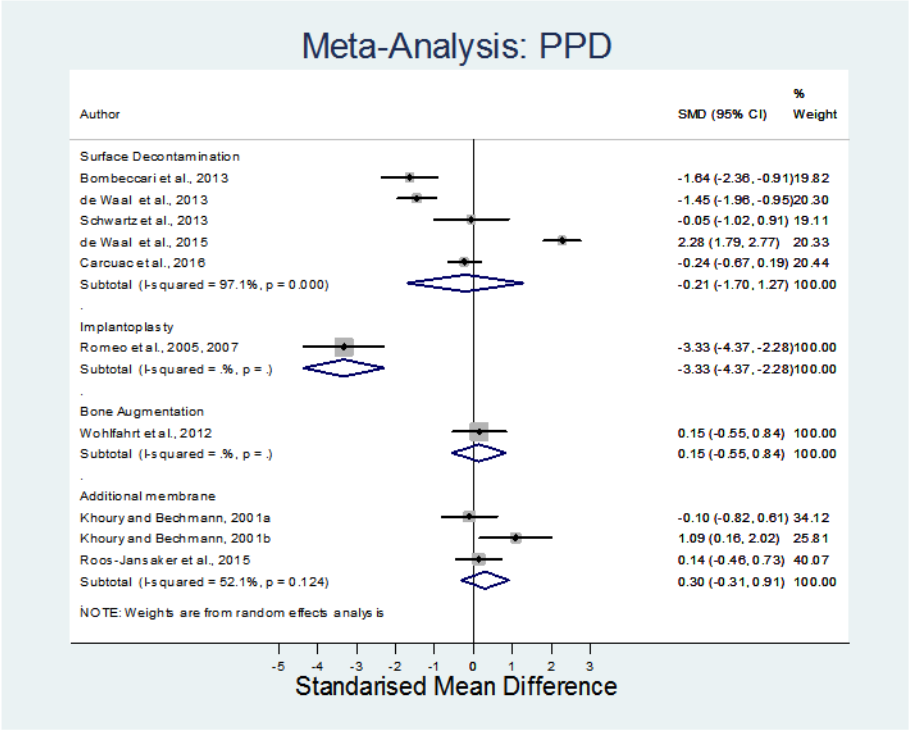

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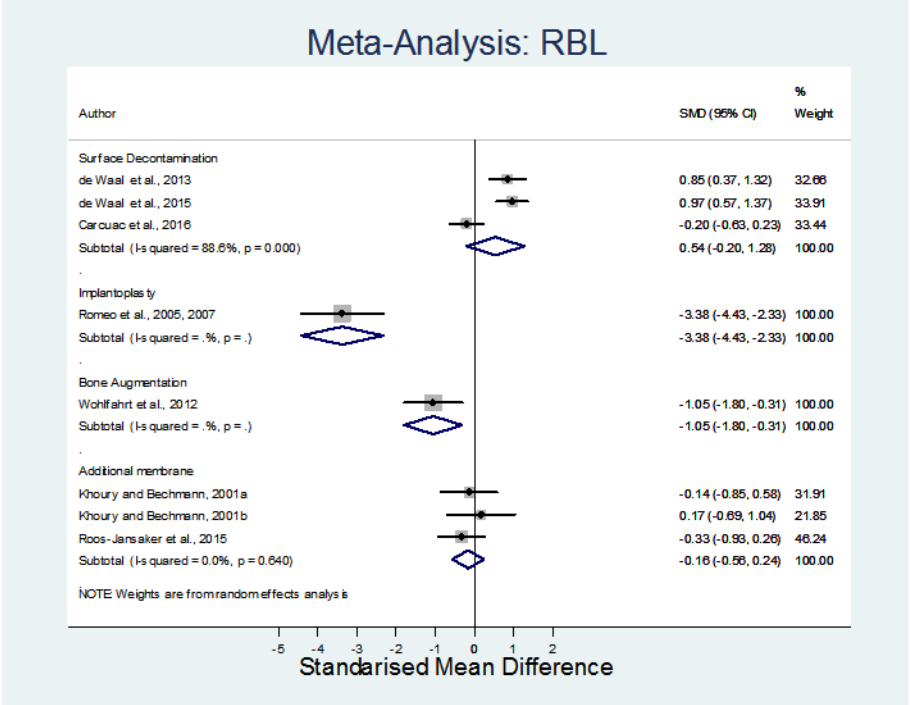

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