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Ridge preservation techniques to avoid invasive bone reconstruction: A systematic review and meta-analysis: Naples Consensus Report Working Group C

KEY WORDS

alveolar bone atrophy, bone remodelling, soft graft, tooth extraction, tooth socket

ABSTRACT

Purpose: To analyse and compare the dimensional changes of unassisted extraction sockets with alveolar ridge preservation (ARP) techniques and investigate any factors that impact the resorption of the alveolar bone.

Materials and methods: A systematic search was conducted to identify randomised clinical trials (RCTs). All data were extracted, and a meta-analysis was performed for the changes in all buccolingual ridge width, midbuccal and midlingual ridge height, and mesial and distal ridge height, and horizontal width at reference points apical to the crestal area.

Results: Based on 14 RCTs, the effectiveness of ARP in reducing the dimensions of the post-extraction alveolar socket was confirmed. The clinical magnitude of this effect was 1.95 mm in the buccolingual ridge width, 1.62 mm in the midbuccal ridge height, and 1.26 mm on the midlingual ridge height. Additionally, 0.45 mm and 0.34 mm for mesial and distal ridge height, and 1.21 mm, and 0.76 mm for ridge width changes at points 3 and 5 mm apical to the crest were noted. Meta-regression analyses revealed that the reflection of flaps and primary wound coverage during ARP may have detrimental effects on bone remodelling, while no statistical significance was observed for any of the bone graft substitutes or the percentage of molar sockets.

Conclusions: Regardless of the protocol, ARP can only minimise ridge resorption. ARP is most effective on horizontal ridge width, providing the most benefit coronally (approximating the crest), followed by the midbuccal ridge height.

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Introduction

Alveolar ridge atrophy is an unavoidable consequence of tooth loss that involves a series of biological events that occur during the healing of an extraction socket[1,2]. This progressive and irreversible phenomenon can give rise to aesthetic, functional and prosthodontic challenges as well as interfere with ideal implant placement for tooth replacement therapy[3-5].

Several therapeutic attempts aimed at minimising the postextraction ridge atrophy have been employed[6-8], a concept defined as 'alveolar ridge preservation' (ARP)[9]. Many of these ARP techniques have involved minimally invasive tooth extraction aiming at maintaining the integrity of the bony walls, followed by immediate grafting of the socket with a variety of biomaterials, such as autologous bone, bone graft substitutes (allo- and xenografts, or alloplasts) and bioactive agents[10-15]. The use of a bone grafting material for socket filling is based on the notion that it can enhance new bone formation through osteoinduction and/or osteoconduction[16,17]. Several studies have also adopted the concept of guided bone regeneration (GBR), utilising a barrier membrane for prevention of soft tissue ingrowth and encapsulation of the graft particles in an attempt to promote bone formation[18-20].

Other methods for ARP have involved flapless procedures to minimise the surgical trauma, under the assumption that this would facilitate greater bone gain and maintain the buccal keratinised mucosa[21,22]. Contemporary approaches have also been aimed at utilising novel prefabricated extraction socket devices[23], or retaining a section of a root at the time of immediate implant placement (the 'socket shield')[24] for limiting the postextraction loss of the bony contour.

Although many of the proposed techniques for ARP have been investigated in human and animal models[1,10,11,13,25-28], a consensus on the ideal clinical protocol has not yet been reached. This could be due to the large body of evidence containing a wealth of clinical, radiographic and histological findings and the unavoidable heterogeneity that follows as a result of this. Moreover, many of the published studies concerning ARP are case series or case reports, and lack sufficient power and sample size, while many more do not evaluate clinically relevant outcomes and some even lack an appropriate control group. Regrettably, these drawbacks can also be applied to many of the currently existing systematic reviews[29-32]. Many deficiencies remain as a result of different local or systemic variables and the marked methodological differences that create confounding factors that have not been previously addressed. With this premise, the aim of this paper was to construct a review based on the information derived exclusively from randomised controlled trials (RCTs), in the format of an up-to-date systematic review and meta-analysis.

Materials and methods

Reporting format

The current review was prepared in accordance with the 27-item Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[33] and the Cochrane Handbook[34]. Additionally, Assessment of Multiple Systematic Reviews (AMSTAR) checklist[35], and the checklist revised by Glenny et al[36] were referred to for reaching the predetermined standards of reporting set for systematic reviews.

Focused question

What is the effect of ARP via socket grafting of postextraction sockets compared to the unassisted healing of extraction alone in maintaining the dimensions of the alveolar ridge reported in RCTs involving healthy human adults?

The following Population, Intervention, Comparison, Outcome, Time (PICOT) question[37] was formulated:

- Population (P): In patients undergoing tooth extraction for any reason.
- Intervention (I): ARP through grafting materials identified in the studies (allograft, xenograft, alloplast) with or without utilisation of a barrier membrane.

- Comparison (C): Natural spontaneous healing of the extraction socket.
- Outcome (O): The primary outcome measures were the mean horizontal (buccolingual) ridge resorption and vertical (apicocoronal) ridge dimensional changes on the midbuccal and midlingual sites from baseline (tooth extraction) to the final point of follow-up. Secondary outcome measures included vertical changes on a mesial and distal reference point and the changes in the horizontal ridge width at reference points 3 mm and 5 mm below the crest.
- Time (T): After a minimum healing time of 3 months for all the sockets.

Eligibility criteria

The search in the literature was limited to human RCTs, without any language restriction, and strictly based on the following criteria: to be considered for inclusion, studies must have recruited healthy adult individuals (≥ 18 years of age) who had at least one tooth extracted. Potential studies must have contained at least a test and a control group, comparing postextraction ARP via socket grafting to unassisted natural healing in noncompromised and intact extraction sockets, while allowing at least 3 months for the healing process. Additionally, the approach for the test group must have involved utilisation of a bone-grafting material (whether or not covered with a barrier membrane) and no use of any additional therapy that may have interfered with the healing outcomes (such as growth factors, healing enhancers, immediate implant placement or simultaneous soft tissue grafting). Subsequently, the changes in the outcome measures (alveolar ridge dimensions) must have been assessed either clinically or with the use of three-dimensional radiography with standardisation to ensure reliability in reporting.

Therefore, studies without an appropriate control group (unassisted healing without socket grafting), without reporting of clinical outcomes (such as pure histological research on bone quality or immunohistochemistry), or with the use of two-dimensional radiographic assessment of ridge dimensions were not considered for inclusion. All other non-RCT studies such as prospective controlled clinical studies, case series, case reports and retrospective studies were also excluded. The authors of the studies were contacted in case of any doubts in the selection process.

Information sources and search strategy

A highly sensitive computerised systematic literature search was performed in the following electronic data bases for selection of articles that met the inclusion criteria: National Library of Medicine (MEDLINE and EMBASE), the Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, Google Scholar and Medicine Gray Literature Report (to check for unpublished trials, government research, nonprofit reports or other materials that may not have been available through conventional channels). The following search strategy was designed for the MEDLINE database and then modified appropriately for other database searches: (socket[All Fields] AND ("preservation, biological"[MeSH Terms] OR ("preservation"[All Fields] AND "biological"[All Fields]) OR "biological preservation"[All Fields] OR "preservation"[All Fields])) OR (ridge[All Fields] AND ("preservation, biological"[MeSH Terms] OR ("preservation"[All Fields] AND "biological"[All Fields]) OR "biological preservation"[All Fields] OR "preservation"[All Fields])) AND Clinical Trial[ptyp]. No restriction was assigned regarding the date of publication, journal, or language used and the last search was performed in June 2018 (details regarding the search strategy are presented in Supplementary Data S1 and Table S1 [available at http://ijoi.quintessenz.de]).

To compliment the electronic search, an additional manual search of the following periodontics/implantology-related resources from January 2004 to July 2018 was performed to ensure a complete and thorough screening process: Journal of Dental Research, Clinical Oral Implants Research, Journal of Clinical Periodontology, Journal of Periodontology, Clinical Oral Investigations, Clinical Implant Dentistry and Related Research, International Journal of Oral and Maxillofacial Implants, International Journal of Oral

and Maxillofacial Surgery, Implant Dentistry, and International Journal of Periodontics and Restorative Dentistry. Additionally, reference lists of the retrieved studies for full-text screening and previous reviews[6-8,16,29,38-44] were hand-searched for possible article identification and eligibility.

Subsequent to the initial search, all titles and abstracts (if available) of the entries were independently scanned by two authors (SB, AR). Next, the full-text version of the potential articles for inclusion were examined by the same authors and in case of any unsettled disagreement or difference of opinion in the determination of eligibility, an author with expertise in the matter (HLW) was referred to for reaching an agreement.

Data extraction

Two authors (SB, AR), independently extracted the data according to a pre-determined data extraction form to confirm the eligibility of each study based on the aforementioned criteria. If inconsistencies were present in the data extraction, a third author (HLW) was consulted for reaching consensus. Data collected from the RCTs included:

- general study and population characteristics (date of publication, number of groups and the participants and extraction sites in each group, the country where the study was conducted at and the setting)
- clinical procedures (grafting material, application and type of membrane used, whether a flap was raised, if primary wound closure was achieved, the allocated time for healing)
- outcome measures (changes in the horizontal and vertical dimensions of the alveolar ridge)
- the type of extracted teeth (number of molar extraction sockets in each arm)
- source of funding (self, government, company).

Whenever necessary the primary and corresponding authors of the trials were contacted for any clarification or further information regarding the study design. In the absence of response and/or if the data was unusable, the studies were excluded from the final review.

Risk of bias and qualitative assessment

For assessing the quality of the RCTs, two authors (SB, AR) individually classified the studies according to The Cochrane Risk of Bias Tool for Randomized Controlled Trials[45]. The potential risk of bias was considered low only if a study provided detailed data on all the parameters. A trial that had not provided information on even one of the parameters was considered as having a moderate risk of bias, and if a study lacked information regarding two or more parameters, it was viewed as having a high risk of bias.

Meta-analysis and meta-regression

All analyses were performed by using statistical software for Macintosh (Rstudio Version 1.1.383, Rstudio, Boston, Massachusetts, USA) and the metafor package[46]. In summary, changes in the primary and secondary outcomes were considered for comparison between the treated (test), and nontreated spontaneous healing (control) group. To estimate an effect size, and to obtain the weighted mean (WM) of the outcomes for the test or the control group, all trials (and every arm) was weighted according to the inverse variance of the mean (to account for the standard deviation and the sample size) and the random effects model was selected (the DerSimonian-Laird method)[47], based on the presumed heterogeneity among the trials. Then, the difference between the test and control groups was estimated for all investigated parameters and expressed as the weighted mean differences (WMD) with a standard deviation (SD, in mm). Forest plots were produced to visualise the WMD between the test and control groups, confidence intervals (CI) were calculated, and a P value of 0.05 was set for statistical significance. Heterogeneity was assessed with the chi-square (χ^2) test and the I^2 statistic and interpreted according to the Cochrane Handbook for systematic reviews[45]. Attempts were made to pinpoint the source of heterogeneity, and funnel plots were produced to display potential bias among the RCTs.

To test the significance of a variable and its influence on the primary outcomes, meta-regression

models were created for binary (flap versus flapless approach, and achieved primary wound closure or not) and categorical data (bone graft materials). According to the number of molar sites treated in each arm and the total sample size, a continuous category of the 'percentage of molars' was created and a linear regression model was fit to assess the difference in healing of molar versus non-molar sockets. A *P* value of 5% or below was assumed statistically significant. Additionally, if the sample size allowed, the generated models were plotted with box plots to visualise the effects to the studied outcomes utilising the package ggplot2[48].

Results

Study selection

The initial search yielded 755 articles, from which more than 500 remained subsequent to the removal of duplicates. Seventeen additional records were identified through manual hand-search of the journal and other references. After elimination by screening all titles and abstracts, 110 studies were left for full-text assessment. Following thorough examination of the studies against the predetermined criteria, 14 RCTs[10-14,28,49-56] were selected for inclusion in the meta-analysis. The most common reasons for exclusion of the studies were lack of an appropriate control group, concomitant use of biologics and growth factors, and study design not matching the review research protocol. Additionally, excellent inter-reviewer agreement presented throughout the selection process and data extraction. Details regarding the search, screening process and the exclusion criteria are summarised in Fig 1 and detailed in Supplementary Data 1 (available at http://ijoi/quintessenz.de).

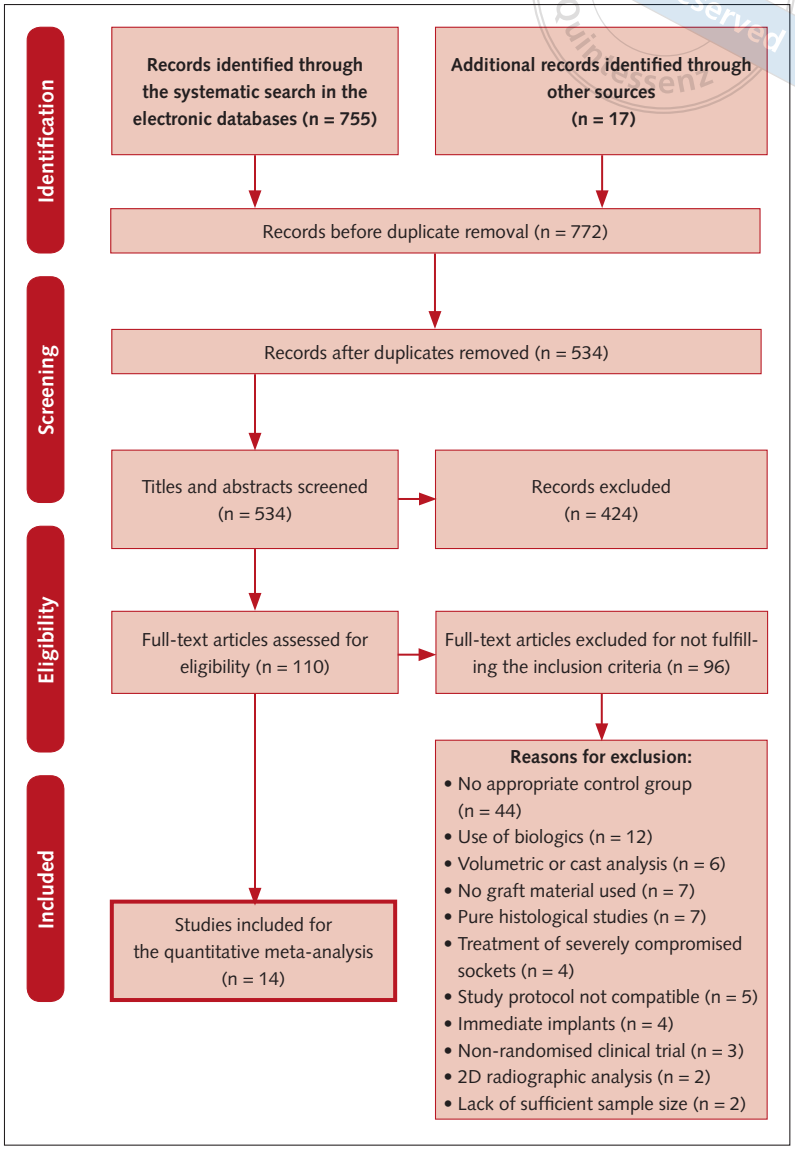


Fig 1 PRISMA flowchart illustrating the search strategy and selection process.

Characteristics of the included trials

All 14 selected studies for the meta-analysis were RCTs aimed at evaluating the effects of ARP in comparison with a control group where the sockets were allowed to heal spontaneously without any intervention. All studies were published in the English language, except one that was in Farsi[28]. Eleven studies consisted of only one treatment arm, while the studies of Kotsakis et el[55], Guarnieri et al[52], and Barone et al[50] included two, and the study of Jung et al[53] included three treatment arms. For the purpose of the meta-analytic comparison, the two treatment arms of Kotsakis et al[55] and Barone et al[50] were combined and regrouped as a single test group according to the recommendations of the Cochrane Handbook[34]. The additional treatment arms of the studies by Guarnieri et al[52] and Jung[53] were excluded as they failed to meet the inclusion criteria. Hence, only one treatment arm

from each of the two mentioned trials was used for the meta-analysis (the test sites treated with porcine-derived bone and covered with a collagen membrane in the study by Guarnieri et al[52], and the group treated with demineralised bovine bone mineral (DBBM) with 10% collagen and a collagen matrix in the study by Jung et al[53]). Two studies employed a split-mouth design[12,54], while the rest had parallel treatment arms. Except for the study of Barone et al[50], which was conducted at two centres (Italy and Spain), the rest of the trials were carried out at a single centre, and in the following countries: six were performed in Italy[10-12,49,51,52], two were conducted in China[54,56], two were in the United States[13,55], one in Switzerland[53], one in Iran[28], and one in Israel[14]. The year of publication of the included RCTs ranged from 2003 to 2018.

The selection of RCTs rendered the inclusion of 445 patients (age from 18 to 79 years) with a total of 522 sockets (286 allocated to the test, and 236 to the control group). Four studies did not allow the participation of smokers[10,12,28,56], nine studies allowed for consumption of up to 10 cigarettes per day[11,14,49-52,54,55], one included patients smoking up to 20 cigarettes/day[53], whereas only one[13] excluded smokers. The follow-up time for the trials ranged from 3 to 7 months. Five studies solely investigated non-molar extraction sockets[10-13,53], whereas eight[14,49-52,54-56] allowed for the inclusion of molar sites as well, and one study[28] did not specify about the tooth location. Regarding the socket morphology, three studies reported that the four bony walls were intact at the time of extraction[10,11,13], two studies mentioned that for consideration into the trial at least three walls and 50% of the fourth wall needed to be present[52,55], and one required at least 80% of the fourth wall to be intact; however, in eight studies[12,14,28,49,50,53,54,56], no information was reported in this regard. The outcome measures were clinically taken utilising a custom-made template in 11 studies[10-14,28,49-52,55], while in three trials[53,54,56], cone beam computed tomography was also used for evaluation.

Regarding the materials used for socket augmentation, eight trials utilised a xenogenic material[11,12,28,49,50,52,54,56], three used an alloplast[10,14,51], one used an allograft bone substitute[13], and two studies utilised both an alloplast and a xenograft material in different groups[53,55]. All selected treatment arms included utilisation of a barrier membrane except the two studies by Aimetti et al[10] and Mayer et al[14], which did not report using a membrane. Detailed description of the study characteristics can be found in Table 1.

Quality assessment

The results of bias risk assessment for the included RCTs and the criteria used according to the recommendations of The Cochrane Risk of Bias Tool for Randomized Controlled Trials[45] are summarised in Supplementary Data S2 and Table S2 (available at http://ijoi.quintessenz.de). Two articles were considered as having a low risk of bias[50,52], four articles were characterised by a moderate risk of bias[14,51,54,55], and eight were determined to have a high risk of bias[10-13,28,49,53,56].

Synthesis of results from meta-analysis

Data from the included trials were extracted and organised into tables to condense an overview of the reported primary and secondary outcomes. All trials reported data on horizontal ridge resorption; however, vertical ridge height changes were not pooled from the studies by Kotsakis et al[55] (as the measurements were based on periapical radiographs), and Mayer et al[14] (due to inadequate reporting). Additionally, the study of Cardaropoli et al[51], did not report on changes of the midlingual ridge height. For the secondary outcomes, six trials additionally evaluated the changes of the ridge height on the mesial and distal of the socket[10-13,28,49], and three trials measured horizontal changes of the ridge at 3-mm and 5-mm reference points below the crest[14,53,54]. Table 2 presents an overview of the outcomes from the included RCTs.

Ridge width changes

Results of the meta-analysis demonstrated a significant positive effect associated with the treatment group for this primary outcome. As indicated by the forest plots, the WMD between the untreated

Table 1 General overview of the characteristics of the selected RCTs

Study (year)	Follow-up (mo)	No. patients (control/test)	No. sockets (control/test)	Inclusion of molars (% in control/% in test)	Grafting material in the test group	Barrier membrane	Flap raised	Primary closure obtained?	Setting	Country	Funding	Method of measurement
Aimetti et al[10] (2009)	3	18/22	18/22	No	MGCSH	None	No	No	University	Italy	NR	Clinical
Azizi and Moghaddam[28] (2009)	6	15/15	15/15	NR	DBBM	Collagen	Yes	Yes	University and private practice	Iran	NR	Clinical
Barone et al[11] (2008)	7	20/20	20/20	No	Corticocancellous porcine bone	Collagen	Yes	Yes	University	Italy	NR	Clinical
Barone et al[49] (2013)	4	29/29	29/29	Yes (72.4/72.4)	Corticocancellous porcine bone	Collagen	No	No	University	Italy	NR	Clinical
Barone et al[50] (2017)	3	30/60	30/60	Yes (73.3/60.0)	Collagenated cortico-cancellous (30) and cortical (30) porcine bone	Collagen	No	No	University	Italy, Spain	self	Clinical
Cardaropoli et al[51] (2014)	4	NR	24	Yes (66.6/66.6)	Bovine bone mineral blended with collagen	Collagen	No	No	Private practice	Italy	Partially supported by company	Clinical
Festa et al[12] (2011)	6	15/15	15/15	No	Corticocancellous porcine bone	Soft cortical collagen membrane	Yes	Yes	University	Italy	NR	Clinical
Guarnieri et al[52] (2017)	3	9/8	9/8	Yes (55.5/50.0)	Porcine-derived bone	Collagen	No	No	University	Italy	Company	Clinical
Jung et al[53] (2013)	6	10/10	10/10	No	DBBM-C	Collagen	No	No	University	Switzerland	University and company	CBCT
Jung et al[54] (2018)	6	18/18	18/18	Yes (55.5/55.5)	DBBM-C	Collagen	No	No	University	China	Company	CBCT
Kotsakis et al[55] (2014)	5	6/20	6/24	Yes (50.0/45.8)	Calcium phosphosilicate putty alloplast (12), bovine bone mineral (12)	Collagen	No	No	University	USA	Government and company	Clinical
Iasella et al[13] (2003)	6	12/12	12/12	No	Tetracycline hydrated FDBA	Collagen	Yes	No	University	USA	NR	Probe
Mayer et al[14] (2016)	4	15/14	15/14	Yes (53.33/57.1)	Biphasic calcium sulphate with Tri-calcium phosphate and hydroxyapatite	None	Yes	Yes	University	Israel	Partially supported by company	Probe
Pang et al[56] (2014)	6	15/15	15/15	NR	DBBM	Collagen	Yes	Yes	University	China	NR	CBCT

CBCT, cone beam computed tomography; DBBM, de-proteinised bovine bone mineral; DBBM-C, de-proteinised bovine bone mineral with 10% collagen; FDBA, freeze-dried bone allograft; MGCSH, medical-grade calcium sulphate hemihydrate; NR, not reported.

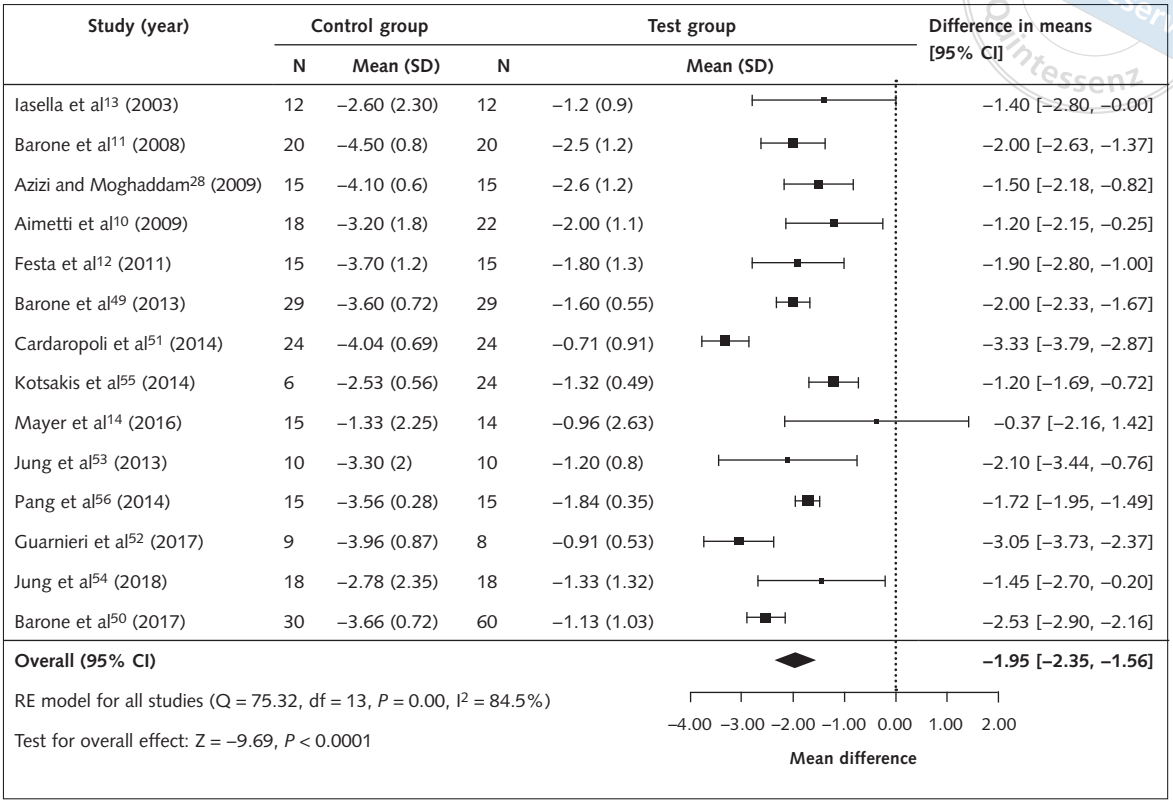


Fig 2 Forest plot illustrating the differences in the horizontal ridge width.

(control) and treated (test) arms amounted to −1.95 mm (95% CI −2.35 to −1.56, $P < 0.0001$) (1.95 mm less horizontal ridge resorption in the test group) (Fig 2). Substantial heterogeneity presented with this comparison ($I^2 = 84.5\%$, $P < 0.001$), as visualised by the funnel plot (Supplementary Fig S3a [available at http://ijoi.quitessenz.de]).

Midbuccal ridge height changes

A greater reduction in midbuccal height of the control group was observed when compared with the test group (Fig 3a). The WMD of −1.62 mm (95% CI −2.13 to −1.11, $P < 0.0001$), signifies the additional ridge resorption on the midbuccal sites of the untreated arms when compared to the treated sites. Considerable heterogeneity accompanied this analysis ($I^2 = 93.4\%$, $P < 0.0001$), as shown by the funnel plot (Supplementary Fig S3b).

Midlingual ridge height changes

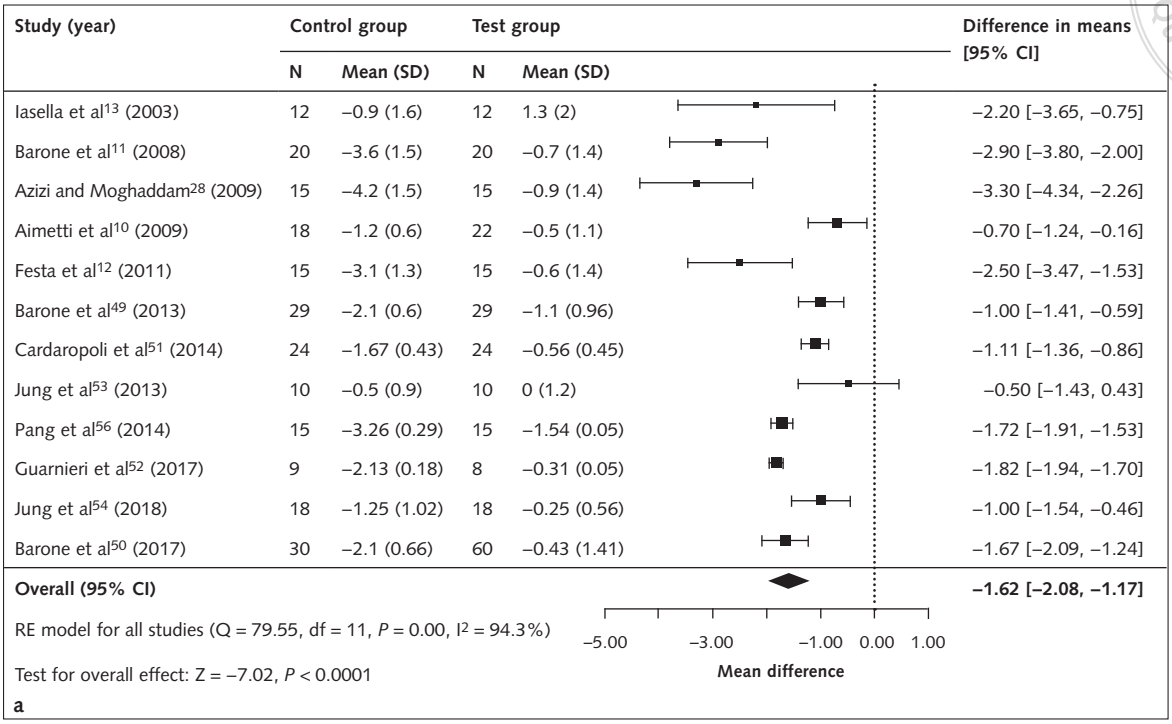
The meta-analysis revealed a significant WMD of −1.27 mm (95% CI −1.83 to −0.70, $P < 0.0001$) between the test and control groups (Fig 3b), illustrating the benefit of treatment for minimising the midlingual ridge height resorption compared with the control group. Substantial heterogeneity was noted as the result of the analysis ($I^2 = 82.4\%$, $P < 0.0001$) (Supplementary Fig S3c).

Mesial height changes

The meta-analysis revealed a positive effect in ridge preservation favouring the test group. The WMD between the two groups amounted to −0.46 mm (95% CI −0.71 to −0.2, $P = 0.0005$) (Fig 4). This comparison yielded low heterogeneity ($I^2 = 21.8\%$, $P = 0.29$) (Supplementary Fig S3d).

Distal height changes

The comparison of test and control groups yielded a significant WMD of −0.34 mm (95% CI −0.62 to −0.07, $P = 0.01$) in favour of the treated sites (Fig 4), and low heterogeneity was present among the results ($I^2 = 27.4\%$, $P = 0.27$) (Supplementary Fig S3e).



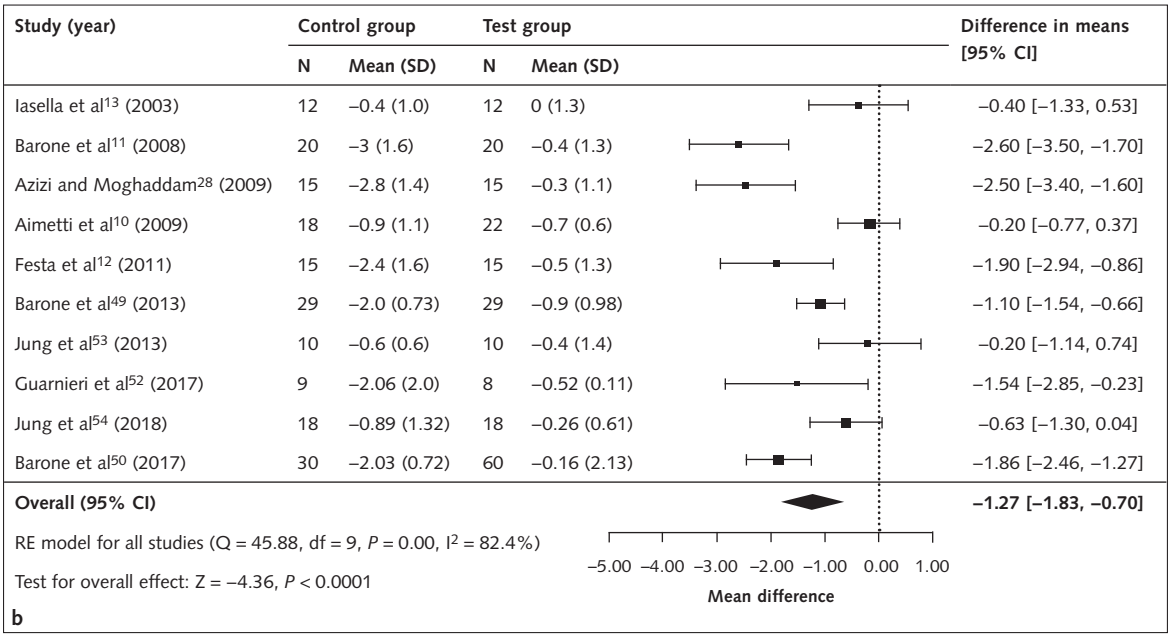


Fig 3a-b Forest plot illustrating the differences in **(a)** midbuccal and **(b)** midlingual vertical height.

Changes in horizontal ridge width 3 mm below the crest

The meta-analysis demonstrated a positive ridge preservation effect favouring the treated group. The WMD of −1.22 mm (95% CI −1.73 to −0.7, $P < 0.0001$) between the test and control groups displayed a significantly less width resorption in the test group compared to the untreated control (Fig 5). This analysis yielded a low heterogeneity ($I^2 = 0.0\%$, $P = 0.42$) (Supplementary Fig S3f).

Changes in horizontal ridge width 5 mm below the crest

The comparison of test and control groups resulted in a significant WMD of −0.77 mm (95% CI −1.05

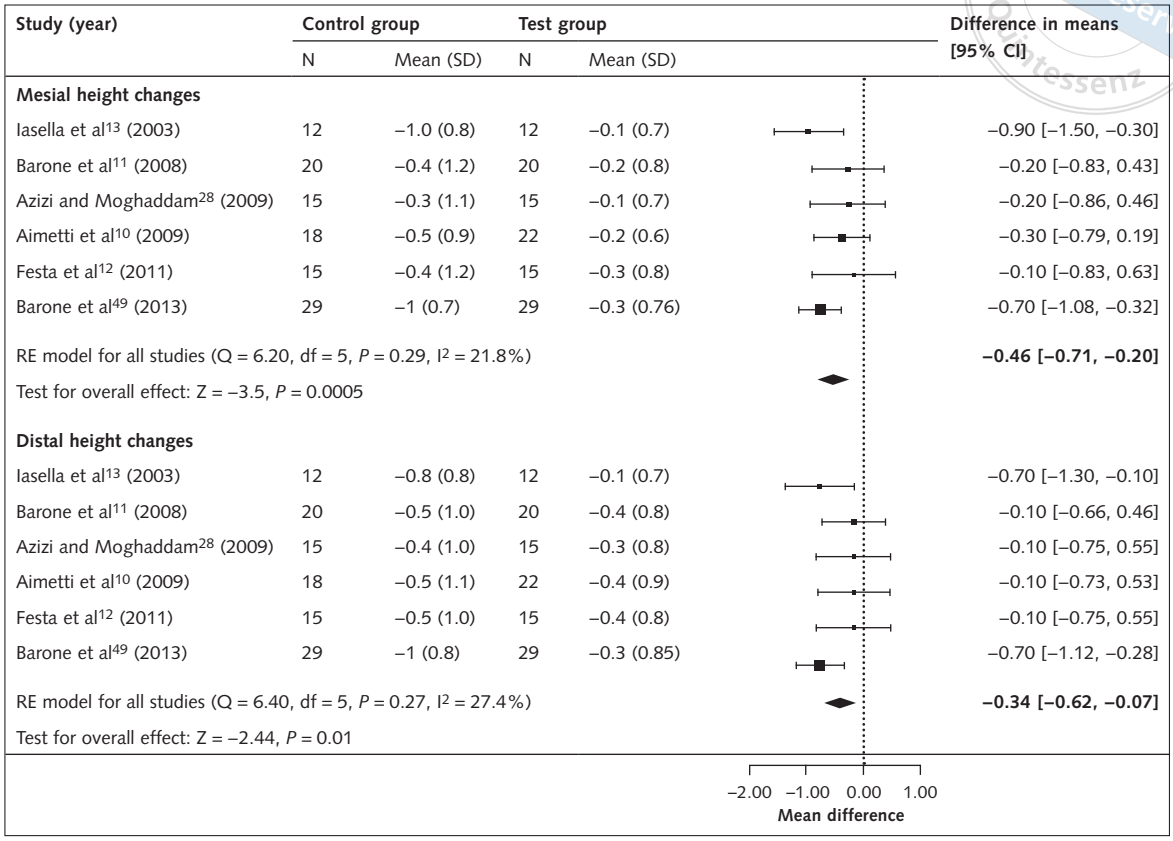


Fig 4 Forest plots illustrating the differences in mesial and distal height.

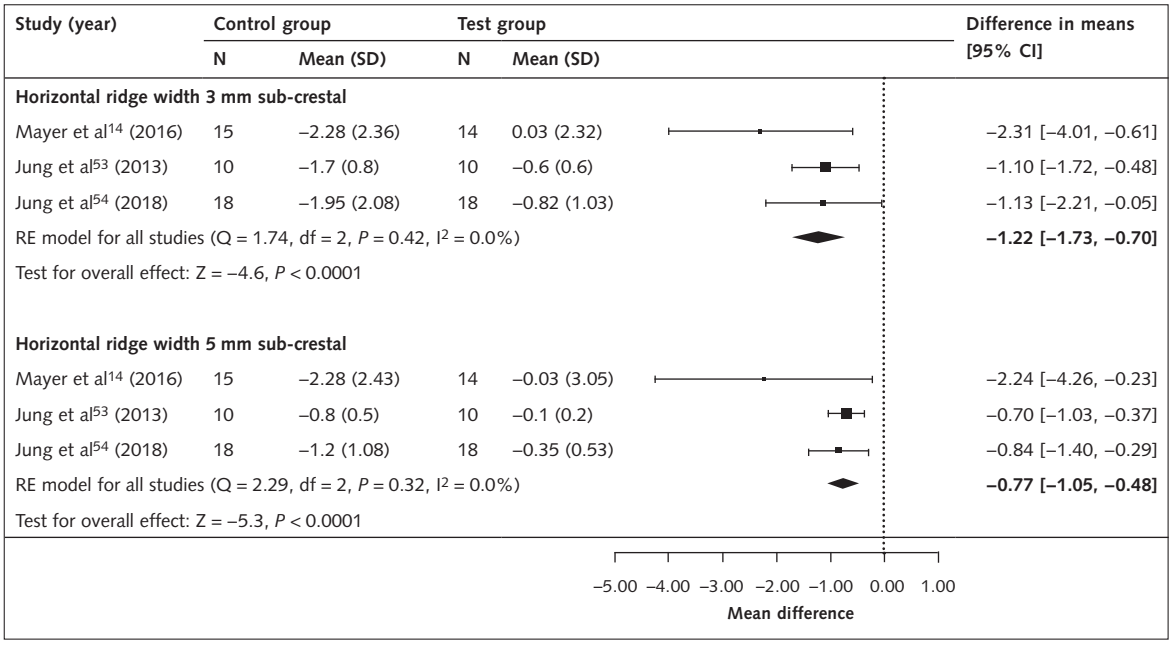


Fig 5 Forest plot illustrating the differences in horizontal ridge width at 3 and 5 mm below the crest.

to −0.48]), $P < 0.0001$ in favour of the treatment (Fig 4). Low heterogeneity was achieved with this comparison, as displayed by the funnel plot ($I^2 = 0.0\%$, $P = 0.32$) (Supplementary Fig S3 g). Table 3 depicts a summary of the investigated primary and secondary outcomes from the meta-analysis comparing untreated sockets (control) versus treated (test) sites.

Meta-regression analyses

The results of the meta-regression analyses exploring correlations of the primary outcomes (horizontal, midbuccal height, midlingual height) with the variables (flap elevation, achieving primary wound coverage, bone graft types) are presented below.

Flap reflection

Meta-regression analyses revealed a significant correlation between flap elevation and horizontal ridge loss with an estimated coefficient of –0.86 (95% CI –1.73 to –0.03, $P = 0.04$). Additionally, when a subgroup analysis of the treatment arms was performed, the data showed that reflection of a flap during the surgical procedure resulted in significantly more buccolingual ridge resorption (–0.56; 95% CI –0.96 to –0.15, $P = 0.01$). A similar trend was noted for the outcome of midbuccal ridge height resorption (–0.71; 95% CI –1.55 to 0.12, $P = 0.09$), although this lacked statistical significance at the P value 0.05 level. However, no trend or statistical correlation was observed for changes in the ridge height on the midlingual (–0.01; 95% CI –0.69 to 0.68, $P = 0.98$). These findings are visualised with boxplots in Fig 6a to c.

Obtaining primary closure

The analyses demonstrated a strong correlation between achieving primary wound closure and horizontal ridge loss with an estimated coefficient of –0.36 (95% CI –0.68 to –0.04, $P = 0.02$). Subgroup analysis of the treatment arms demonstrated a strengthened link between studies that attempted to obtain primary closure after socket grafting and horizontal ridge width reduction (–0.63; 95% CI –1.01 to –1.09, $P = 0.003$). This significant interaction was also present with ridge height reduction on the midbuccal with an estimated coefficient of –1.02; 95% CI –1.86 to –0.18, $P = 0.01$), while lacking statistical significance for changes in the midlingual ridge height (–0.37; 95% CI –1.14 to 0.38, $P = 0.31$) (Figs 6d to f).

Bone graft material

The choice of grafting material (whether allograft, xenograft or alloplast) did not seem to have a strong effect the on any of the primary outcomes. When studies utilising xenograft and alloplast bone substitutes were compared to the use of an allograft (as the intercept), the estimated coefficients of –0.31 (95% CI –1.88 to 1.24, $P = 0.66$), and –0.2 (95% CI –1.85 to 1.45, $P = 0.79$) from the model were noted for xenograft and alloplast, respectively, for changes in buccolingual ridge width. Regarding the effect of different bone substitutes on ridge height, no statistical difference was found when comparing the use of a xenograft (–1.62 (95% CI –4.29 to 1.03, $P = 0.19$) or an alloplast (–1.8; 95% CI –4.67 to 1.07, $P = 0.18$) to an allograft for changes in midbuccal ridge height as well. Similarly for midlingual ridge height, no significant difference was observed between the bone graft substitutes when compared to using an allograft (estimated coefficient of –5.06 [95% CI –1.57 to 0.55, $P = 0.3$] for xenograft, and –7.1 [95% CI –1.82 to 0.42, $P = 0.18$] for alloplast).

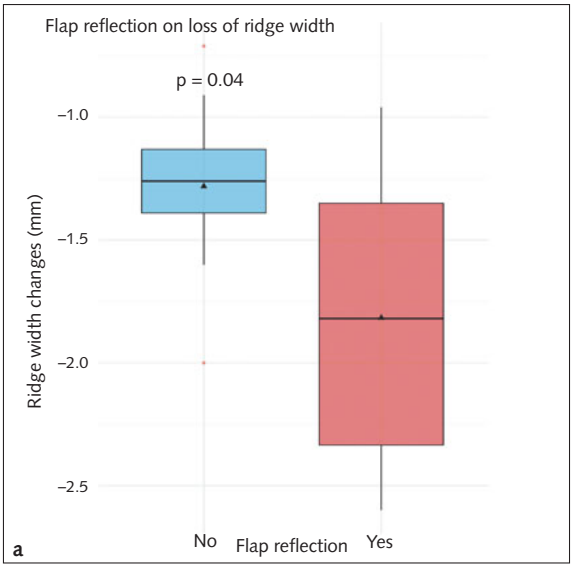
Molar versus non-molar extraction socket

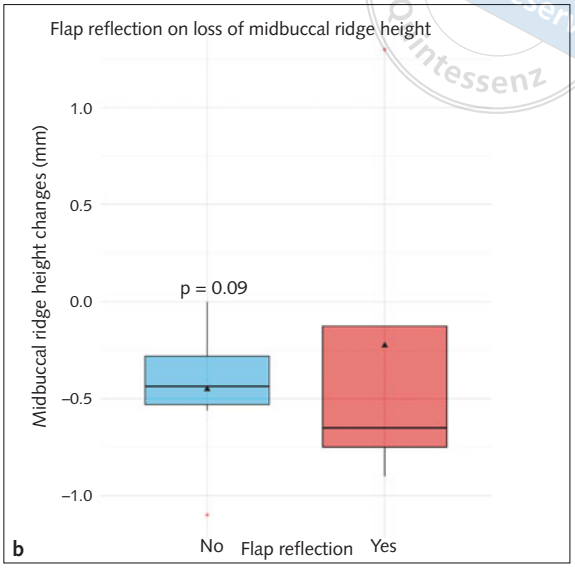
Meta-regression analyses did not show a significant association between the percentage of molar sockets treated among the studies and the primary outcomes of buccolingual ridge width (0.004; 95% CI –0.002 to 0.012, $P = 0.19$), midbuccal height (–0.005; 95% CI –0.01 to 0.003, $P = 0.18$) and midlingual height (–0.005; 95% CI –0.01 to 0.001, $P = 0.12$).

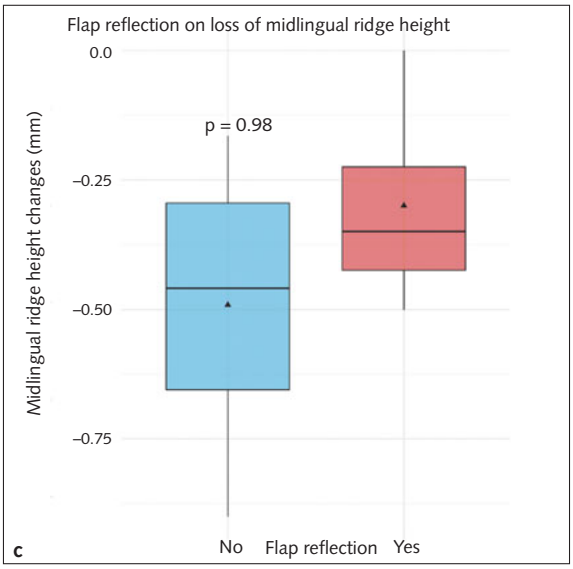
Discussion

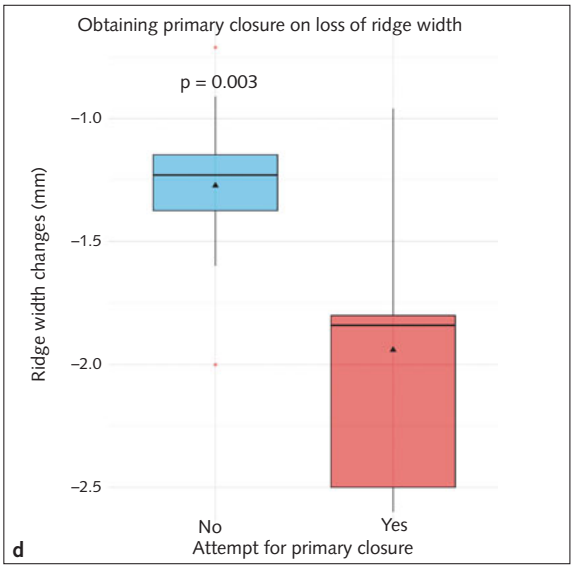
Over the last two decades, ARP techniques have gained a great deal of interest for minimising the bone loss following tooth extraction. Several systematic reviews, with or without a quantitative meta-analysis, have been conducted to evaluate the efficacy of ARP procedures. However, a number of critical aspects, such as inclusion of non-randomised studies that can increase the overall bias and heterogeneity[7] and other structural and methodological

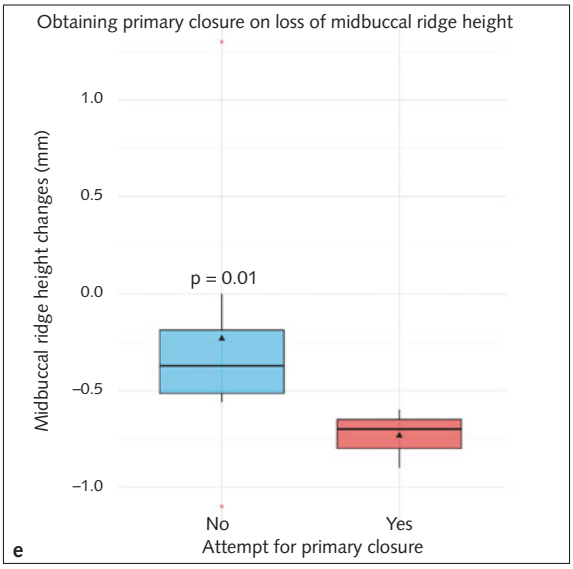
Fig 6a-f Box plots visualising the effect of flap reflection **(a-c)** and achieving primary wound closure **(d-f)** on the primary outcomes of ridge width changes, midbuccal ridge height changes and midlingual ridge height changes, respectively.

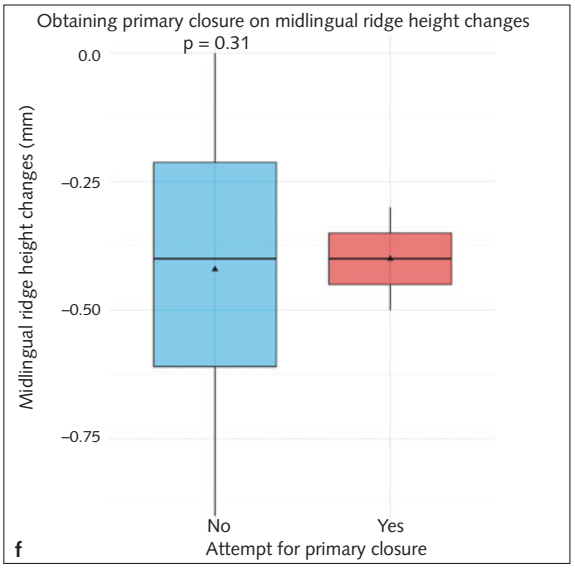












discrepancies, have raised concerns[31,32]. To maximise the clinical relevance of the present results and decrease the variability among the selected articles, only studies with a well-defined protocol and an appropriate control group (unassisted socket healing) were considered for inclusion.

Main findings

Results from the meta-analysis confirmed the effectiveness of ARP in reducing the ridge loss in all the investigated outcomes. Indeed, in comparison with unassisted healing of extraction sockets, ARP proved to be beneficial in minimising the resorption of buccolingual ridge width by 1.95 mm, mid-buccal ridge height by 1.62 mm, midlingual ridge height by 1.26 mm, mesial and distal ridge height by 0.45 mm and 0.34 mm, respectively, and changes in the horizontal width at 3 mm and 5 mm below the crest by 1.21 mm and 0.76 mm, respectively.

The findings of the investigated primary outcomes are in line with results from previous reviews of similar design[6,38,43,57]. However, a recent systematic review by MacBeth et al[16] reported a 1.19-mm difference between the treated and untreated sockets for horizontal ridge width, and 0.73 mm in regard to midbuccal ridge height. This difference may have been due to the combination of the three non-homogenous treatment arms in the study by Jung et al[53] and the inclusion of the study by Fiorellini et al[15] that focused on ridge augmentation of buccal wall defects with recombinant bone morphogenetic protein-2. The same concern was present in another published meta-analysis by Willenbacher et al[43] that included non-RCT studies as well. In addition, the authors performed separate meta-analyses based on different study designs and arrived at values ranging from 1.33 to 1.52 mm for horizontal ridge width, and 0.91 to 1.12 mm for alveolar ridge height[43]. It should be noted that the present meta-analysis only included RCTs with a minimum follow-up time of 3 months and excluded studies that treated severely compromised extraction sockets (if the socket walls exhibited more than 50% of dehiscence).

Due to the expected collapse of soft tissue and the rounding off of the alveolar crest that occurs due to extraction and bone remodelling, the present study aimed to further investigate the changes in the horizontal (buccolingual) width at reference points 3 mm and 5 mm apical to the crest. Based on the three trials that evaluated this outcome[14,53,54], it appeared that horizontal bone loss generally decreased with an increasing distance to the alveolar crest (WMD of –1.82 mm at 3 mm, and –1.22 mm at 5 mm below the crest) and that ARP provided the most benefit to the bony changes coronally at the level of the crest, results that are aligned with the current literature.

Meta-regression

Many factors that could have influenced the pattern of ridge resorption (single- vs. multiple-rooted teeth, grafting material, reflection of a flap, or obtaining primary wound closure) were assessed through meta-regression analyses to determine their significance. The present results indicated significantly less horizontal and midbuccal vertical bone loss when reflection of flaps was avoided during the surgical procedure. This analysis was further highlighted when analysed for obtaining primary wound closure. Despite the general agreement on the detrimental effect of flap elevation on periosteal vasculature supply and bone remodelling[58,59], the scientific literature is divided over whether or not primary wound coverage is required for a more advantageous healing of the extraction socket. In an article by Barone et al[22], which investigated ARP techniques, patients were randomised to receive porcine bone and collagen membrane, either with a full-thickness mucoperiosteal flap followed by obtaining a primary soft tissue seal (control) or with a flapless approach aiming for a secondary soft tissue closure (test). After a 3-month healing period, all scheduled implants were placed in the test and control sites, and no significant differences between the flap and the flapless techniques were noticed in terms of the percentage of newly formed bone and residual graft particles. Another RCT[60] showed that after 6 months of healing, while there was an apparent coronal displacement of the mucogingival junction, no significant differences were present between the extraction sockets that achieved

Table 2 Overview of the outcomes from the selected RCTs

Study (year)	Horizontal ridge width changes in mm (mean ± SD)		Width changes 3 mm apical to the crest in mm (mean ± SD)		Width changes 5 mm apical to the crest in mm (mean ± SD)	
	Control	Test	Control	Test	Control	Test
Aimetti et al[10] (2009)	–3.2 ± 1.8	–2 ± 1.1	NR	NR	NR	NR
Azizi and Moghaddam[28] (2009)	–4.1 ± 0.6	–2.6 ± 1.2	NR	NR	NR	NR
Barone et al[11] (2008)	–4.5 ± 0.8	–2.5 ± 1.2	NR	NR	NR	NR
Barone et al[49] (2013)	–3.6 ± 0.72	–1.6 ± 0.55	NR	NR	NR	NR
Barone et al[50] (2017)	–3.66 ± 0.72	–1.13 ± 1.03	NR	NR	NR	NR
Cardaropoli et al[51] (2014)	–4.04 ± 0.69	–0.71 ± 0.91	NR	NR	NR	NR
Festa et al[12] (2011)	–3.7 ± 1.2	–1.8 ± 1.3	NR	NR	NR	NR
Guarnieri et al[52] (2017)	–3.96 ± 0.87	–0.91 ± 0.53	NR	NR	NR	NR
Jung et al[53] (2013)	–3.3 ± 2	–1.2 ± 0.8	–1.7 ± 0.8	–0.6 ± 0.6	–0.8 ± 0.5	–0.1 ± 0.2
Jung et al[54] (2018)	–2.78 ± 2.35	–1.33 ± 1.32	–1.95 ± 2.08	–0.82 ± 1.03	–1.2 ± 1.08	–0.35 ± 0.53
Kotsakis et al[55] (2014)	–2.53 ± 0.56	–1.32 ± 0.49	NR	NR	NR	NR
Iasella et al[13] (2003)	–2.6 ± 2.3	–1.2 ± 0.9	NR	NR	NR	NR
Mayer et al[14] (2016)	–1.33 ± 2.25	–0.96 ± 2.63	–2.28 ± 2.36	0.03 ± 2.32	–2.28 ± 2.43	–0.03 ± 3.05
Pang et al[56] (2014)	–3.56 ± 0.28	–1.84 ± 0.35	NR	NR	NR	NR

NR, not reported; SD, standard deviation.

primary closure, versus ones that had the membranes left exposed. Interestingly, this split-mouth clinical trial also found that postoperative discomfort was significantly lower in the group without primary wound closure. Moreover, some authors have noticed bone resorption in association with primary soft tissue coverage[61], and some concerns regarding the additional negative effects such as marginal recession at adjacent teeth, defective papilla, and loss of keratinised mucosa have also been raised[62].

Arguments can be made in regard to the present findings of less favourable outcomes with flap advancement and primary wound closure. The systematic review of Avila-Ortiz et al[38] recognised that sites that underwent flap elevation exhibited less midbuccal and midlingual height loss, while the buccolingual ridge width seemed unaffected. A possible explanation maybe due to the fact that their results were based on subgroup analyses, comparing ridge resorption of three articles that raised a flap during tooth extraction[11,13,28] versus three that did not[10,49,63]. The present meta-regression, based on 14 RCTs, may provide a more accurate assessment of this outcome.

Another interesting finding of the present analysis was in the case of healing of molar vs non-molar extraction sockets, which was not previously explored in other reviews. While the analyses failed to reveal a significant link between the percentage of molars in the selected RCTs and the primary outcomes, other authors believe that a greater ridge resorption in the molar areas should be expected due to difference in the morphology and the increased time required for bone to bridge over a wider socket[60,64,65].

Additionally, no difference was observed in reducing the alveolar bone remodelling among the investigated grafting materials (whether allograft, xenograft or alloplast). A recent systematic review on socket grafting after flapless tooth extraction reported an overall estimate that the lowest mean buccolingual crestal bone loss occurred with xenografts (1.3 mm), followed by allografts (1.63 mm) and alloplasts (2.13 mm)[40]. However, in the present review, it may be speculated that the unequal distribution of studies for each graft category, along with other confounding variables (primary wound closure, flap reflection, etc.), could have attributed to a non-significant finding. Inherently, some neutral or non-significant results in a meta-analysis may be representative of a lack of statistical power or inequality in distribution. As an example, only one study reported

Midbuccal height changes in mm (mean ± SD)		Midlingual height changes in mm (mean ± SD)		Mesial height changes in mm (mean ± SD)		Distal height changes in mm (mean ± SD)	
Control	Test	Control	Test	Control	Test	Control	Test
–1.2 ± 0.6	–0.5 ± 1.1	–0.9 ± 1.1	–0.7 ± 0.6	–0.5 ± 0.9	–0.2 ± 0.6	–0.5 ± 1.1	–0.4 ± 0.9
–4.2 ± 1.5	–0.9 ± 1.4	–2.8 ± 1.4	–0.3 ± 1.1	–0.3 ± 1.1	–0.1 ± 0.7	–0.4 ± 1	–0.3 ± 0.8
–3.6 ± 1.5	–0.7 ± 1.4	–3 ± 1.6	–0.4 ± 1.3	–0.4 ± 1.2	–0.2 ± 0.8	–0.5 ± 1	–0.4 ± 0.8
–2.1 ± 0.6	–1.1 ± 0.96	–2 ± 0.73	–0.9 ± 0.98	–1 ± 0.7	–0.3 ± 0.76	–1 ± 0.8	–0.3 ± 0.76
–2.1 ± 0.6	–0.43 ± 1.41	–2.03 ± 0.72	–0.16 ± 2.13	NR	NR	NR	NR
–1.67 ± 0.43	–0.56 ± 0.45	NR	NR	NR	NR	NR	NR
–3.1 ± 1.3	–0.6 ± 1.4	–2.4 ± 1.6	–0.5 ± 1.3	–0.4 ± 1.2	–0.3 ± 0.8	–0.5 ± 1	–0.4 ± 0.8
–2.13 ± 0.18	–0.31 ± 0.05	–2.06 ± 2	–0.52 ± 0.11	NR	NR	NR	NR
–0.5 ± 0.9	0 ± 1.2	–0.6 ± 0.6	–0.4 ± 1.4	NR	NR	NR	NR
–1.25 ± 1.02	–0.25 ± 0.56	–0.89 ± 1.32	–0.26 ± 0.61	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR
–0.9 ± 1.6	1.3 ± 2	–0.4 ± 1	0 ± 1.3	–1 ± 0.8	–0.1 ± 0.8	–0.8 ± 0.8	–0.1 ± 0.7
NR	NR	NR	NR	NR	NR	NR	NR
–3.26 ± 0.29	–1.54 ± 0.25	NR	NR	NR	NR	NR	NR

Table 3 Summary of the investigated primary and secondary outcomes from the meta-analysis

Outcome	Weighted mean values in mm [95% CI]		Weighted mean difference (control–test) [95% CI]	*P* value	Heterogeneity	
	Control	Test			I^2	*P* value
Horizontal ridge width changes	–3.47 [–3.85, –3.09]	–1.5 [–1.77, –1.22]	–1.95 [–2.347, –1.557]	< 0.001	84.50%	< 0.001
Midbuccal ridge height changes	–2.16 [–2.79, –1.53]	–0.56 [–0.87, –0.24]	–1.62 [–2.075, –1.170]	< 0.001	94.29%	< 0.001
Midlingual ridge height changes	–1.68 [–2.26, –1.09]	–0.48 [–0.65, –0.32]	–1.26 [–1.834, –0.697]	< 0.001	82.36%	< 0.001
Mesial height changes	–0.65 [–0.93, –0.38]	–0.21 [–0.34, –0.08]	–0.45 [–0.710, –0.201]	0.001	21.75%	0.28
Distal height changes	–0.66 [–0.89, –0.44]	–0.32 [–0.47, –0.17]	–0.34 [–0.618, –0.067]	0.01	27.44%	0.26
Horizontal ridge width changes 3 mm below crest	–1.82 [–2.23, –1.40]	–0.64 [–0.93, –0.36]	–1.21 [–1.728, –0.704]	< 0.001	0.00%	0.41
Horizontal ridge width changes 5 mm below crest	–1.22 [–1.87, –0.56]	–0.20 [–0.44, 0.03]	–0.76 [–1.051, –0.484]	< 0.001	0.01%	0.317

CI, confidence interval.

using an allograft[13], whereas three arms had been treated with alloplast material[10,14,55], and the rest were treated using xenograft bone substitutes. This same reason prevented investigation of the effect of a barrier membrane, as only two treatment arms performed ARP without utilising one[10,14].

Limitations

Although a comprehensive search strategy was employed and complemented through extensive manual cross-reference searching for identification of all relevant articles, it may still be possible that some grey literature was missed. Additionally, given the uneven distribution of some of the articles in the investigated categorical variables (i.e. bone graft), the meta-regression results should be considered with caution. Considerable heterogeneity arose as a result of some of the analyses. This could have been due to the different graft materials, membrane types and the many RCTs included (which can simultaneously be considered an attribute of the present paper and are inherent to its nature). With this in mind, it must be acknowledged that the thickness

of the buccal plate, which has been shown to affect the ridge resorption outcomes, was an element for which there was no information and that could not be controlled, and the same is true for patient-reported outcomes in terms of pain or discomfort,. Additionally, it should be noted that most of the current literature report relatively short-term results, as reflected by the average follow-up time being from 3 to 7 months. Finally, despite having prepared and finalised the methods in advance, the PROSPERO website was not utilised to record the protocol.

Implication for future research

There is still a need to assess differences between ARP procedures through high-quality RCTs with sufficient power and sample size. Patient-reported outcomes and the cost-effectiveness of any ARP should also be included in future studies. Future RCTs should emphasise the following aspects:

- inclusion of a negative control group (spontaneous healing)
- decrease in heterogeneity and control of reported sources of bias
- soft tissue dimensional changes and their standardisation by using modern technologies such as three-dimensional computer-aided analyses and impression techniques.

The possible role of confounding variables, such as reason for extraction, tooth type and location, that pertain to the present meta-regression findings should also undergo further investigation.

Conclusions

Within the limitations of this study, the following conclusions can be made:

- Regardless of the ARP protocol, the alveolar ridge of the extraction socket constantly undergoes a certain amount of resorption, most pronounced in the buccolingual (horizontal) dimension at the ridge crest (of about 2 mm), followed by the midbuccal ridge height.
- ARP procedures with the use of bone graft substitutes have proven to reduce but not eliminate the physiological cascade of postextraction bone remodelling.

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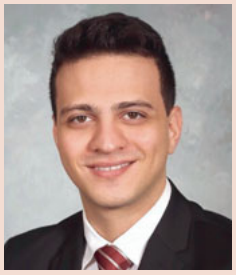

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