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REVIEW

Alveolar ridge preservation. A systematic review

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Abstract
Objective The objective of this paper is to examine the effect of alveolar ridge preservation (ARP) compared to unassisted socket healing.
Methods Systematic review with electronic and hand search was performed. Randomised controlled trials (RCT), controlled clinical trials (CCT) and prospective cohort studies were eligible.
Results Eight RCTs and six CCTs were identified. Clinical heterogeneity did not allow for meta-analysis. Average change in clinical alveolar ridge (AR) width varied between −1.0 and −3.5±2.7 mm in ARP groups and between −2.5 and −4.6±0.3 mm in the controls, resulting in statistically significantly smaller reduction in the ARP groups in five out of seven studies. Mean change in clinical AR height varied between +1.3±2.0 and −0.7±1.4 mm in the ARP groups and between −0.8±1.6 and −3.6±1.5 mm in the controls. Height reduction in the ARP groups was statistically significantly less in six out of eight studies. Histological analysis indicated various degrees of new bone formation in both groups. Some graft interfered with the healing. Two out of eight studies reported statistically significantly more trabecular bone formation in the ARP group. No superiority of one technique for ARP could be identified; however, in certain cases guided bone regeneration was most effective. Statistically, significantly less augmentation at implant placement was needed in the ARP group in three out of four studies. The strength of evidence was moderate to low.
Conclusions Post-extraction resorption of the AR might be limited, but cannot be eliminated by ARP, which at histological level does not always promote new bone formation. RCTs with unassisted socket healing and implant placement in the ARP studies are needed to support clinical decision making.
Clinical relevance This systematic review reports not only on the clinical and radiographic outcomes, but also evaluates the histological appearance of the socket, along with site specific factors, patient-reported outcomes, feasibility of implant placement and strength of evidence, which will facilitate the decision making process in the clinical practice.

Keywords Tooth extraction · Bone resorption · Implant site development · Bone substitute · Bone regeneration · Human histology

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Introduction

Periodontal disease, periapical pathology and mechanical trauma often result in bone loss prior to tooth removal [1]. Furthermore, traumatic extraction has also been associated with additional loss of bone. In the healing phase after extraction, alveolar bone undergoes additional atrophy as a result of the natural remodelling process [2–7]. This begins immediately

after extraction and may result in up to 50 % resorption of the alveolar ridge (AR) width even in 3 months [1]. Post-extraction AR resorption may have an impact on dental implant placement, since sufficient vertical and horizontal volume of alveolar bone should ideally be present at the site of insertion [8].

Alveolar ridge preservation (ARP) procedures have been introduced to maintain an acceptable ridge contour in areas of aesthetic concern, as well as to prevent alveolar ridge atrophy and maintain adequate dimensions of bone in order to facilitate implant placement in prosthetically driven positions [9, 10]. Several methods have already been investigated for ARP in preclinical models [11–14] and clinical studies, such as socket grafting with autogenous bone [15], demineralised freeze-dried bone allograft (DFDBA) [15–17], xenografts, like deproteinized bovine-bone mineral (DBBM) [18], alloplasts [19] and bone morphogenic proteins (BMP) [20]. Guided bone regeneration (GBR) with or without bone grafts has also been evaluated [9, 10, 21–25].

Although some of the above bone substitutes were able to limit the resorption of post-extraction alveolar ridge up to a certain extent, the quality of the new tissue in the socket varied broadly. The remnants of the grafts often interfered with the normal healing process in line with preclinical results [15–17, 26]. A number of review articles on ARP have been published in the last decade [27–32]. However, a systematic assessment of the nature and quality of the newly formed tissue alongside methodological quality and risk of bias of the studies has not been carried out. Furthermore, non-controlled prospective and retrospective studies as well as case series were also included in most of the previous reviews without the comparison to the control group of unassisted socket healing [33–36].

Therefore, the objective of the present systematic review was to investigate the effect of ridge preservation on the residual alveolar ridge dimensions and on histological characteristics, compared to unassisted socket healing.

Methods

Prior to commencement of the study, a detailed protocol was developed and agreed upon by the authors based on the Cochrane Collaboration guidelines and previous reviews published by our group [37–41].

Focused question

Following tooth/root extraction in humans, what is the effect of ridge preservation on the residual alveolar ridge dimension and on histological characteristics, compared to unassisted socket healing?

Definition

Whilst ‘socket preservation’ has widely been employed to depict a certain procedure, we believe that the objective of these interventions is to preserve the dimension of the AR. Therefore, we have used the term ‘Alveolar Ridge Preservation’ to define such procedures.

Types of studies

Longitudinal prospective studies were included, i.e. RCTs, CCTs and cohort studies with control group.

Populations of studies

Healthy individuals, without any age limit, who underwent any type of ridge preservation following permanent tooth extraction, were included. Smokers and patients with history of periodontal disease were not excluded. The minimum number of subjects per group was five. However, no limit was set for study follow-up period.

Types of interventions

Test groups

Studies reporting on any of the following types of interventions were included: socket grafting (autograft, allograft, xenograft, alloplastic materials); socket sealing (soft tissue grafts); GBR (resorbable/non-resorbable barriers); biological active materials (growth factors) and combinations of the above techniques/materials.

Control groups

The control groups of the included studies comprised empty sockets, i.e. unassisted socket healing.

Outcome variables

The *primary outcome* was the change in oro-facial (horizontal) and apico-coronal (vertical) AR dimensions. *Secondary outcomes* were the following: (1) change in buccal plate thickness; (2) bone volume alteration following extraction; (3) complications; (4) histological healing characteristics; (5) site eligibility for placement of an adequate size dental implant with or without further augmentation; (6) patient-reported outcomes, such as quality of life and (7) health economics.

Risk of bias and methodological quality assessment

In order to evaluate the methodological quality and risk of bias of individual studies, we used a combination of

parameters from the Cochrane Collaboration and Consolidated Standards of Reporting Trials (CONSORT) statement. The following parameters were assessed and taken into consideration in the final analysis: sample size calculation, statement of eligibility criteria, ethics approval, informed consent, baseline homogeneity, randomisation method, allocation concealment, masking, calibration, follow up, protocol violation, method of statistics, unit of analysis, CONSORT implementation, International Standard Randomised Controlled Trial Number Register (ISRCTN) and funding disclosure. Methodology unique to RCTs was not assessed in CCTs, i.e. randomisation and concealment of allocation.

Randomisation was accepted as adequate, in case the allocation sequence was correctly generated either by computer, toss of a coin, throwing dice, etc. Quasi randomisation, e.g. birth dates, hospital numbers were not accepted. Adequacy of allocation concealment was accepted if the sequence was concealed, until intervention was assigned (e.g. in sequentially numbered and sealed opaque envelopes, remote computer or central telephone). Statistical analysis was judged as adequate if appropriate statistical method was selected to accommodate to the characteristic of the each individual data (e.g. number of groups and investigated categories, size of samples, normally distributed or skewed data, parametric or non-parametric, paired or unpaired, numerical or categorical variables). Statistical significance was accepted in case of confidence interval (CI) >95 % ($p<0.05$), while 'statistically highly significant' referred to CI>99.9 % ($p<0.001$).

Based on the above, we attempted to categorize the possible risk of bias as low, moderate or high. Low risk referred to studies with adequate randomisation method, sequence concealment and masking of examiner. Studies were classified as moderate, if one of the above key categories were missing, or high risk of bias, if more than one were lacking.

Inclusion criteria

1. All prospective longitudinal studies (i.e. RCTs, CCTs and cohort studies) were included, where one of the above mentioned types of interventions were carried out in the test group, whereas unassisted socket healing served as control.
2. Studies on healthy individuals, without any age limit, who underwent ARP following tooth extraction, were included.
3. Studies had to report on minimum of five patients per group.
4. Studies, performing clinical or three-dimensional (3D) radiographic evaluation of hard tissue or histological assessment, were included.

Exclusion criteria

1. Case reports, case series, retrospective analyses were excluded.
2. Studies without a control group comprising unassisted socket healing were excluded.
3. Studies on medically compromised patients, e.g. uncontrolled diabetes mellitus or cancer were excluded.
4. Studies reporting on immediate placement of dental implant were excluded.
5. Studies describing extraction of third molars were excluded.

Search strategy

A sensitive search strategy was designed as we anticipated that relevant studies might be difficult to locate. The search strategy incorporated both electronic and hand searches. The following electronic databases were utilised in Apr 2010: (1) MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE 1950 to present via Ovid interface; (2) EMBASE Classic + EMBASE 1947 to present via Ovid interface; (3) The Cochrane Central Register of Controlled Trials (CENTRAL); (4) LILACS.

The electronic search strategy used the following combination of key words and *MeSH terms*: ("tooth extraction" OR "tooth removal" OR "socket" OR "alveol$" OR "ridge" OR "crest" OR *"tooth socket"* OR *"alveolar bone loss"* OR *"bone resorption"* OR *"bone remodeling"*) AND ("preserv $" OR "reconstruct$" OR "augment$" OR "fill$" OR "seal $" OR "graft$" OR "repair$" OR "*alveolar ridge augmentation*" OR "*bone regeneration"* OR *"bone substitutes"* OR *"transplantation"*).

Cochrane search filters for RCTs and CCTs were implemented. In addition, cohort trials were also searched. The results were limited to humans only.

An extensive hand search was also performed encompassing the bibliographies of the included papers and review articles. Furthermore the following journals were screened from 2001 to April 2010: *Clinical Oral Implants Research, Clinical Implant Dentistry and Related Research, European Journal of Oral Implantology, Implant Dentistry, International Journal of Oral and Maxillofacial Implants, International Journal of Periodontics and Restorative Dentistry, Journal of Clinical Periodontology, Journal of Dental Research, Journal of Oral and Maxillofacial Surgery, Journal of Periodontology, Oral Surgery, Oral Medicine, Oral Radiology, Oral Pathology and Endodontics, Periodontology 2000.* No language restrictions were applied. Translations were carried out as necessary by two reviewers (AH, LAM).

The extracted data were copied into Reference Manager 10 software (Thomson Reuters, New York, NY, USA). Thus the further steps of screening were performed on this

interface. A three-stage selection of the resulted hits was performed independently and in duplicate by two reviewers (AH and LAM). In order to reduce errors and bias, a calibration exercise was performed with the first 500 titles, resulting in 96.4 % agreement. In case of disagreement at the title selection stage, the trial was included in the abstract stage. At the abstract and full text selection any disagreements between the above reviewers were resolved by discussion. If unresolved, a third reviewer (NM) was involved for arbitration. The reasons for exclusion were recorded either in the Reference Manager (abstract stage) or in a specific data extraction form (full text stage). The level of agreement was determined by Kappa score calculation.

Research synthesis

Studies were grouped by research design and their chief characteristics. Outcomes were recorded in evidence tables. In view of the marked heterogeneity, no meta-analysis was conducted. Instead, a narrative synthesis was undertaken.

Results

Search sequence

The electronic search yielded 6,216 relevant hits after removal of duplicates (Fig. 1). Subsequently, 157 titles were selected for the abstract stage. Following investigation of the abstracts, 42 articles qualified for full text evaluation. Four extra papers were then added as a result of the hand search. Assessment of these articles resulted in the following 14 publications eligible for the review [17, 19–21, 23–25, 42–48]. The excluded full text papers along with the reasons for exclusion are listed in Table 1. The most typical reasons for exclusion were lack of control group with unassisted socket healing; use of retrospective design; assessment of dimensional changes of the AR only on periapical two-dimensional radiographs, or on casts taken from soft tissue level; and surgical removal of third molars.

The Kappa score for agreement between the reviewers (AH, LAM) at the abstract and full text selection level, was 0.96 and 0.90, respectively, indicating a high level of agreement.

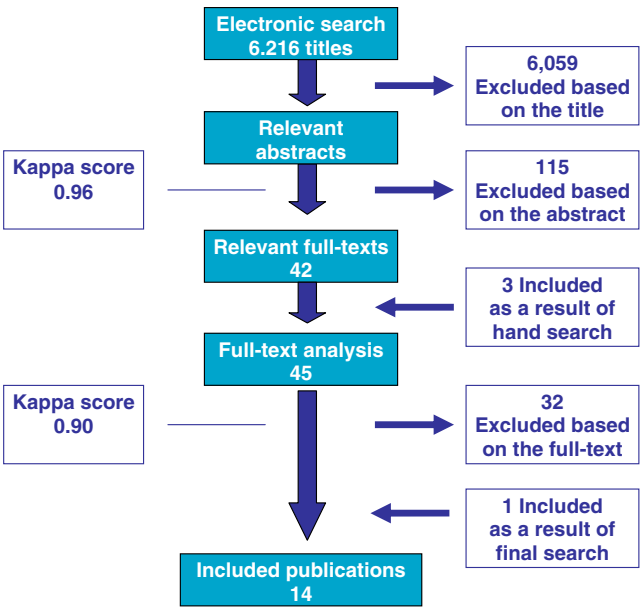

Fig. 1 Flow chart of the screening process

Study characteristics

In the 14 included articles (eight RCTs and six CCTs) the efficacy of ARP techniques was evaluated clinically by means of direct measurements of the residual alveolar ridge dimensions during re-entry procedures, radiographically by means of computer tomography or histologically from trephine biopsies taken at re-entry during osteotomies for implant placement (Tables 3 and 4). No cohort studies were indentified. Limited data were reported on confounding factors, such as periodontitis, smoking, systemic disease and medication. The extraction site distribution was fairly heterogeneous. In some studies ARP was performed only in maxillary anterior sockets [42, 46, 47], whereas such restriction was not employed in other studies. The residual bone volume around the investigated sockets, e.g. the presence/absence and width of the buccal bone plate varied from severely compromised [20, 46], to completely intact, buccal bone (Table 3) [17, 21, 42].

Intervention characteristics

With regard to the techniques or materials used for ARP, the included studies were grouped into three categories (Table 3);

1. Bone grafts/substitutes
2. GBR
3. Biological active materials.

In the majority of the included studies, various bone grafts were utilised, such as autologous bone marrow [47], plasma rich in growth factor (PRGF) with or without autologous bone [43], DFDBA [17], DBBM [46], calcium sulphate hemihydrates [42, 45] and bioactive glass [17]. Alloplastic polyglycolide/polylactide (PGPL) sponge was also employed [19, 48]. GBR technique was applied using non-resorbable expanded polytetrafluoroethylene (e-PTFE) [24] or resorbable (PGPL) [25] barrier. Resorbable collagen membrane was also employed in combination with FDBA [23] or corticocancellous porcine bone [21]. Biological active material, namely bone morphogenic protein (rhBMP-2) was used on a collagen sponge carrier in one study [20].

Table 1 List of excluded full text papers and reasons for exclusion

First author (year of publication)	Journal	Reasons for exclusion
Bianchi (2004)	Int J Periodont Rest Dent	Retrospective analysis
		Single-arm of the included Fiorellini et al. (2005)
Bolouri (2001)	Comp Cont Educ Dent	Reported on optical density on two-dimensional radiographs
Brawn (2007)	Impl Dent	Case report
Brkovic (2008)	J Can Dent Assoc	Case report
Carmagnola (2003)	Clin Oral Impl Res	Lack of real control group, resembles to a retrospective analysis (extreme difference in follow-up period between tests and controls. T1: 4 months; T2: 7 months; C: 1-15 years, mean: 7.8 years)
Cranin (1988)	J Biomed Mat Res	Case series without control group
De Coster (2009)	Clin Impl Dent Relat Res	Case series
		Retrospective study as stated by the authors in the discussion
		Healing period varied between 1.5 months and 1.5 years
		Neither histomorphometry nor clinical or radiographic measurements reported in the results
Graziani (2008)	J Cranofac Surg	Extraction of fully impacted third molars
		Linear measurements on OPG
Gulaldi (1998)	Oral Surg Oral Med Oral Pat Oral Rad End	Extraction of fully impacted third molars
		Linear measurements on OPG and scintigraphy
		Primary outcome was to analyze bone metabolism
Heberer (2008)	Clin Oral Impl Res	Case series without control group
Hoad-Reddick (1994)	Eur J Prosth Rest Dent	Two-dimensional linear measurements obtained from OPG and cephalometry
		Lack of defined landmarks
		Surgical procedure was not described
Hoad-Reddick (1999)	Eur J Prosth Rest Dent	Description of a method for measurements on casts
		Neither socket preservation procedure nor the results were described. Soft tissue punch technique only
Howell (1997)	Int J Periodont Rest Dent	Case series without control group
Jung (2004)	Int J Periodont Rest Dent	Case series without control group
		Primary outcome was soft tissue healing
Kangvonkit (1986)	Int J Oral Maxillofac Surg	Based on OPG and lateral cephalogram only
		Evaluation method remains unclear
		Primary outcome was the biocompatibility of HA cones
Karapataki (2000)	J Clin Periodontol	Extraction of fully impacted third molars
		Primary outcome was to assess the periodontal status of second molars after extraction of third molars
Kerr (2008)	J Periodontol	No biomaterials were used to preserve the ridge dimensions, therefore did not address the focused question
Kwon (1986)	J Oral Maxillofac Surg	Based on OPG and lateral cephalogram only
		Evaluation method remains unclear
		Lack of description of the measurement methods
Molly (2008)	J Periodontol	Control group was covered by an e-PTFE membrane, thus lack of unassisted control sockets
Munhoz (2006)	Dento Maxillofac Radiol	Extraction of fully impacted third molars
		Two-dimensional evaluation of periapical radiographs
Norton (2002)	Int J Oral Maxillofac Impl	Case series without control group
		Resembles to a retrospective design (healing period ranged from 3 to 11 months)
Page (1987)	J Oral Maxillofac Surg	Case report
Pape (1988)	Deutsche Zahnarztliche Zeitschrift	Augmentation of a resorbed ridge

Table 1 (continued)

First author (year of publication)	Journal	Reasons for exclusion
		Case series without control group
Penteado (2005)	Braz J Oral Sci	Immunohistochemical analysis
		Did not address the focused question
Quinn (1985)	J Am Dent Assoc	Clinical measurements at soft tissue level only based on tattoo points, thus failed to address the focused question
		Resembles to a retrospective analysis
Schepers (1993)	Impl Dent	Retrospective case series without control group
Simon (2004)	Ind J Dent Res	Extraction of fully impacted third molars
		Evaluated soft tissue healing and radiographic analysis based on the two-dimensional periapical radiographs
Simion (1994)	Int J Periodont Rest Dent	Titanium implants placed simultaneously
		No control group
		Primary outcome was microbiological analysis
Smukler (1999)	Int J Oral Maxillofac Impl	Healed edentulous ridge as control instead of empty socket
		No compatibility of the follow-up periods of the different groups
Svrtecky (2003)	J Prosth Dent	Case report
Throndson (2002)	Oral Surg Oral Med Oral Pat Oral Rad End	Extraction of fully impacted third molars
		Measurements based on two-dimensional periapical radiographs
Yilmaz (1998)	J Clin Periodontol	Measurement at soft tissue level on study casts

None of the included studies used the socket sealing technique. Primary flap closure was achieved in 9 out of 14 studies, while the sockets left uncovered in the rests. Various types and amounts of antibiotics and antiseptic rinses were administered for different duration in studies reporting on postoperative care. Finally, average healing period ranged from one to nine months.

Outcome characteristics

Clinical outcomes

Eight out of the 14 included studies investigated the efficacy of various ARP techniques to preserve the pre-extraction ridge dimensions using intra-surgical hard tissue measurements taken during re-entry procedure [19, 21, 23–25, 42, 44, 47]. In these studies, ARP was performed in 137 sockets of 119 patients and compared to 120 sockets that left to heal without any treatment in a total of 92 patients (Table 3).

Bone 'graft' Four studies evaluated changes in AR dimensions following grafting of the socket. Two studies were RCTs [42, 47] and two were CCTs [19, 44]. Healing time varied from 3 to 6 months [19, 42, 44, 47].

The *horizontal* (bucco-lingual) changes of the alveolar ridge were assessed in three studies [42, 44, 47]. The AR reduced in width from baseline to re-entry between −1.0 mm and −3.5±2.7 mm following ARP ($p<0.05$) and between −2.5 mm and −3.2±1.8 mm in the control groups ($p<0.05$). In two out of the three studies, the width reduction was statistically significantly smaller in the test groups compared to the controls [42, 47].

Four studies investigated the mean change in *ridge height* at the *mid-buccal* aspect [19, 42, 44, 47]. The AR height changed from baseline to re-entry between +1.3±1.9 mm and −0.5±1.1 mm following ARP, and between −0.8±1.6 mm and −1.2±0.6 mm in the control groups. The height reduction between baseline and re-entry was not statistically significant in one study in both test and control groups [44], while one study reported an increase in height instead of loss following ARP with a PGPL sponge ($p<0.05$) [19]. In two out of the four studies, the height reduction was statistically significantly smaller in the test groups compared to the controls [42, 47].

The vertical dimension changes at the *mesial* and *distal* aspects of the socket were measured in two studies [19, 42] and did not present any statistically significant difference for both groups.

Three studies captured data on *socket fill* and reported statistically significant differences between baseline and re-entry in both groups [42, 44, 47], but only one reported statistically significantly higher socket fill, where bioactive glass was covered by calcium sulphate, compared to the unassisted healing [44].

GBR Four studies evaluated changes in AR dimensions following ARP with GBR alone [24, 25], or in combination with bone graft [21, 23]. Three studies were RCTs [21, 23,

25] and one was CCT [24]. Healing time varied between 4 and 9 months.

Horizontal (bucco-lingual) changes of the AR were assessed in all four studies. AR width reduction from baseline to re-entry varied between −1.2±0.9 mm and −2.5±1.2 mm in the GBR-treated sockets and between −2.6±2.3 mm and −4.6±0.3 mm in the control groups. With the exception of one study [23], a statistically significantly smaller reduction of the alveolar ridge width was observed when e-PTFE [24], PGPL [25], or collagen membranes in combination with xenograft [21] were used.

All the four studies investigated the mean change in *AR height* at the *mid-buccal* aspect. The AR height changed from baseline to re-entry between +1.3±2.0 mm and −0.7±1.4 mm in the ARP groups and between −0.9±1.6 mm and −3.6±1.5 mm in the control groups. The resorption in the ARP group was not statistically significant in three out of four studies [23–25]. All studies reported a statistically significantly less post-extraction reduction in AR height when the socket was treated by GBR compared to unassisted healing.

Vertical dimension changes at *mesial* and *distal* aspects of the socket were measured in two studies [21, 23]. The observed differences between baseline and re-entry were not statistically significant in both groups. In one out of the two studies the height reduction was statistically significantly smaller in the test group compared to the control [23].

Two studies captured data on the *socket fill* [24, 25] and reported statistically significant socket fill in both groups between baseline and re-entry, as well as between tests and controls.

No data were found on either initial *buccal plate thickness* or *alteration of bone volume*. However, one study measured the buccal bone thickness loss and reported statistically significantly less reduction in the ARP group [47].

Radiographic measurements

Two RCTs, reporting on 3D radiographic assessment, met the inclusion criteria [20, 46]. The healing time varied from 1 to 4 months. In one study, where the post-extraction socket was grafted with a radiopaque material (DBBM), treatment resulted in significantly less reduction in radiographic AR height compared to unassisted socket healing [46]. The test group in the other study, where the higher concentration (1.5 mg/ml) of RhBMP-2 was utilised [20], resulted in a mean increase of the radiographic AR width by 3.27±2.53 mm at the most coronal part, compared to the 0.57±2.56 mm increase in the group of unassisted healing. AR height was reduced by 0.02±1.2 mm in the same test group and by 1.17±1.23 mm in the control group (Table 3). The differences between test and control were statistically significant.

Histological results

Eleven studies carried out a histological analysis based on trephine biopsies retrieved at re-entry [17, 19–21, 23, 42, 43, 45–48]. Seven studies were RCTs [17, 20, 21, 23, 46, 47] and four were CCTs [19, 43, 45, 48]. In these studies, ARP was performed in 181 sockets of 158 patients and compared to 149 sockets that left to heal without any treatment in 131 patients (Table 4). Only two out of eight studies reported statistically significantly higher trabecular bone volume following ARP in comparison to unassisted socket healing [21, 42] and two studies reported statistically significantly more connective tissue in the post-extraction socket when no ARP was performed [17, 21]. On the contrary, one study reported more vital bone in the unassisted socket healing group compared to the ARP group [23]. None of the differences of the investigated histomorphometric parameters reached statistical significance in other studies.

Bone 'grafts' Eight studies evaluated histologically the healing of post-extraction sockets following the application of some type of bone grafts/substitutes [17, 19, 42, 43, 45–48]. Four studies were RCTs [17, 42, 46, 47] and four were CCTs [19, 43, 45, 48]. New mineralised bone was observed at various levels in all studies in both ARP and control groups in a healing period from 2.5 to 8 months. Connective tissue occupied a portion of the socket in both groups. When DFDBA, bioactive glass or DBBM were used, the graft particles were embedded either in new bone or in connective tissue. In most studies, there was no significant difference in the type of healing, or amount of bone formation between bone grafts and unassisted socket healing.

GBR in combination with graft GBR in combination with graft was utilised in two RCTs. ARP with a collagen membrane and deproteinized porcine bone resulted in statistically significantly higher new bone and lower connective tissue formation after 7 to 9 months of healing in comparison to unassisted socket healing [21]. However, residual graft materials were present in the ARP biopsies. FDBA and collagen membrane resulted in similar amounts of new bone formation to untreated sockets, although more vital bone was observed in the untreated sockets at 4 to 6 months of healing ($p>0.05$) [23].

Biological active material RhBMP-2 in a collagen sponge carrier was completely resorbed at 4 months following ARP regardless of the concentration of the growth factor [20]. Mineralised tissue was found and trabecular bone formation was noticed in two third of both the test and control biopsies in the RCT.

Adverse events, complications

Adverse events were reported in six RCTs [17, 20, 21, 25, 42, 47] and four CCTs [19, 24, 44, 48] including oedema, pain, erythema and membrane exposure/infection. In two studies, more adverse events, i.e. oedema, erythema [20] or membrane exposure [24] were observed in the ARP group compared to the natural socket healing. No comparison between tests and controls were reported in the other studies (Table 3).

Feasibility of implant placement

Seven studies [17, 19, 23, 42, 45, 46, 48] reported that implant placement in the previous sockets were successful, but no differences between the ARP and untreated sites were revealed. The outcome of implant placement remained unclear in one article [43] and only re-entry without implantation was performed in three trials [24, 44]. Four studies reported the need of further augmentation at the stage of implant placement. Three of them favoured the ARP group over the controls, since less [20] or no sites [21, 47] in the ARP group presented with residual dehiscence or fenestration defects around the inserted implants (Table 3).

Patient-reported outcome and health economics

No data were found for patient-reported outcome measures or health economic evaluation.

Quality assessment

Considerable heterogeneity was found among the studies in terms of methodological quality. Detailed description of the quality assessment of the included studies is presented in Table 2. Among the 14 included controlled studies, eight were randomised [17, 20, 21, 23, 25, 42, 46, 47] although in four of them the randomisation technique was not reported [20, 42, 46, 47]. None of the RCTs reported the method of allocation concealment. Masking of the examiner was reported at the clinical level in two out of eight [23, 25], at radiological level in one out of two [20] and at histological level in four out of 11 studies [17, 21, 42, 43]. Examiner calibration was declared in three papers [20, 23, 42], whilst inclusion and exclusion criteria were defined in seven publications [17, 21, 23, 42, 43, 46, 47]. Apart from three studies [21, 43, 46] all the other reported the approval of the ethical committee. Three studies were funded by industry [17, 20, 44], two studies by academic institution [45, 48] and the remaining nine did not report the source of funding.

Nine trials implemented patient-based analysis [20, 21, 23–25, 42, 44, 47, 48], whilst the extraction site served as unit of analysis in the rest of the five investigations [17, 19, 43, 45, 46]. Sample size calculations were reported only in three studies [20, 23, 42], although with insufficient data to evaluate the validity of the calculations. Statistical analysis was appropriately carried out and described in one study only [47]. Appropriate statistics were either not carried out [17, 19–21, 43, 45, 46], or the reported data were insufficient to determine the validity [23–25, 42, 43, 48]. In addition, no RCTs were either registered with ISRCTN or reported using the CONSORT guidelines (Table 3).

Risk of bias

Four studies were classified as moderate risk of bias [17, 21, 23, 25] and the rest were categorised as high risk of bias (Table 2).

Discussion

Key findings

This systematic review has demonstrated that different ARP techniques do not totally eliminate post-extraction alveolar ridge resorption or predictably promote new bone formation. However, the reduction in ridge width and height following ARP may be less than that which occurs following natural socket healing. The clinical data suggest that the horizontal ridge contraction was most successfully limited in the two studies applying GBR without additional bone grafts [24, 25], whereas the vertical shrinkage was most efficiently limited by employing GBR with additional bone graft [21, 23].

Strengths of the review

The present systematic review was limited to randomised controlled trials, controlled clinical trials and prospective cohort studies with a control group of empty untreated sockets. Furthermore, the inclusion criteria of our systematic review were based on the fact that the clinical merit of applying the different ARP techniques could only be validated, if the clinical and histological outcomes following the application of a technique are superior to that of unassisted socket healing.

In comparison to the previous systematic reviews [28, 32] the present review has evaluated the histological characteristics of the alveolar socket healing with or without ARP. The amount and the quality of the newly formed osseous tissues in the socket area are essential, especially when the justification of ARP is to facilitate the placement of a dental implant in the position of a previously extracted tooth. It is doubtful, whether an ARP technique should be claimed successful, if it only preserves the external contour

Table 2 Quality assessment of the included studies

Study First author Year of publication Type Reference number	Quality Criteria Randomisation 1. Randomised 2. Adequate sequence generation 3. Allocation concealment 4. Concealment adequate	Masking 1. Therapist 2. Patient 3. Examiner 4. Statistician	Calibration 1. Intra-examiner 2. Inter-examiner	Eligibility Criteria 1. Inclusion criteria defined 2. Exclusion criteria defined	Follow up 1. Percentage of completed follow ups 2. Adequate correction	Ethical considerations 1. Ethics approval 2. Informed consent	Funding Source of Funding	Statistical analysis 1. Appropriate sample size calculation and power 2. Unit of analysis 3. Appropriate statistics applied	Miscellaneous 1. Comparable experimental groups 2. CONSORT implemented 3. ISRCTN registered 4. Other comments	Estimated risk of bias
Aimetti 2009 RCT .#42	1. Yes 2. N/R 3. N/R 4. N/A	1. N/R 2. N/R 3. Yes (histo), N/R (clin) 4. N/R *Reported as 'double blind'	1. Yes (histo), N/R (clin) 2. N/A	1. Yes 2. Yes	1. N/R 2. N/A	1. Yes 2. Yes	N/R	1. Insufficient data to determine 2. Patient 3. Insufficient data to determine	1. Yes 2. N/R 3. N/R	High
Anitua 1999 CCT #43	1. Yes (btw T-C) No (within T) 2. N/A 3. N/R 4. N/A	1. N/R 2. N/R 3. Yes 4. N/R	1. N/R 2. N/A	1. Yes 2. Yes	1. 100% 2. Yes	1. N/R 2. Yes	N/R	1. N/R 2. Patient + site 3. No statistical analysis was carried out	1. N/R 2. N/R 3. N/R 4. At severe defects autogenous bone was added to PRGF. Different healing periods.	High
Barone 2008 RCT #21	1. Yes 2. Yes 3. N/R 4. N/A	1. N/R 2. N/R 3. Yes (histo), N/R (clin) 4. N/R	1. N/R 2. N/A	1. Yes 2. Yes	1. 100% 2. Yes	1. N/R 2. Yes	N/R, declared no conflict of interest	1. N/R 2. Patient 3. No	1. Yes 2. N/R 3. N/R 4. Different healing periods.	Moderate
Camargo 2000 CCT #44	N/A	1. N/R 2. N/R 3. N/R 4. N/R	1. N/R 2. N/A	1. Yes 2. Yes	1. 100% 2. Yes	1. Yes 2. Yes	Industry	1. N/R 2. Patient 3. Insufficient data to determine	1. N/R 2. N/R 3. N/R	High
Fiorellini 2005 RCT #20	1. Yes 2. N/R 3. N/R 4. N/A	1. N/R 2. N/R 3. Yes (CT scans) 4. N/R * Reported as 'double blind'	1. N/R 2. Yes	1. No 2. No	1. 100% 2. Unclear	1. Yes 2. Yes	Industry	1. Insufficient data to determine 2. Patient 3. No	1. N/R 2. N/R 3. N/R 4. Standardisation of CT scans N/R. Final number of sockets, patients remain unclear.	High
Froum 2002 RCT #17	1. Yes 2. Yes 3. N/R 4. N/A	1. N/R 2. N/R 3. Yes 4. N/R	1. N/R 2. N/A	1. Yes 2. Yes	1. 100% 2. Unclear	1. Yes 2. Yes	Industry	1. N/R 2. Site 3. No	1. N/R 2. N/R 3. N/R 4. Different healing periods. Enrolment of sites of subjects inconsistent.	Moderate

Table 2 (continued)

Study First author Year of publication Type Reference number	Quality Criteria Randomisation 1. Randomised 2. Adequate sequence generation 3. Allocation concealment 4. Concealment adequate	Masking 1. Therapist 2. Patient 3. Examiner 4. Statistician	Calibration 1. Intra-examiner 2. Inter-examiner	Eligibility Criteria 1. Inclusion criteria defined 2. Exclusion criteria defined	Follow up 1. Percentage of completed follow ups 2. Adequate correction	Ethical considerations 1. Ethics approval 2. Informed consent	Funding Source of Funding	Statistical analysis 1. Appropriate sample size calculation and power 2. Unit of analysis 3. Appropriate statistics applied	Miscellaneous 1. Comparable experimental groups 2. CONSORT implemented 3. ISRCTN registered 4. Other comments	Estimated risk of bias
Guarnieri 2004 CCT #45	N/A	1. N/R 2. N/R 3. N/R 4. N/R	1. N/R 2. N/A	1. Yes 2. No	1. N/R 2. N/A	1. Yes 2. Yes	Government; institution	1. N/R 2. Site 3. No	1. N/R 2. N/R 3. N/R	High
Iasella 2003 RCT #23	1. Yes 2. Yes 3. N/R 4. N/A	1. N/R 2. N/R 3. Yes 4. N/R	1. Yes 2. N/A	1. Yes 2. Yes	1. 100% 2. Yes	1. Yes 2. Yes	N/R	1. Insufficient data to determine 2. Patient 3. Insufficient data to determine	1. Yes 2. N/R 3. N/R	Moderate
Lekovic 1997 CCT #24	N/A	1. N/R 2. N/R 3. N/R 4. N/R	1. N/R 2. N/A	1. No 2. No	1. 70% (premature exposure of e-PTFE barrier in 3/10) 2. Yes	1. Yes 2. N/R	N/R	1. N/R 2. Patient 3. Insufficient data to determine	1. Yes 2. N/R 3. N/R	High
Lekovic 1998 RCT #25	1. Yes 2. Yes 3. N/R 4. N/A	1. N/R 2. N/R 3. Yes 4. Yes	1. N/R 2. N/A	1. No 2. No	1. 100% 2. Yes	1. Yes 2. Yes	N/R	1. N/R 2. Patient 3. Insufficient data to determine	1. Yes 2. N/R 3. N/R	Moderate
Nevins 2006 RCT #46	1. Yes 2. N/R 3. N/R 4. N/A	1. N/R 2. N/R 3. N/R 4. N/R	1. N/R 2. N/A	1. Yes 2. Yes	1. 100% 2. Yes	1. N/R 2. N/R	N/R	1. N/R 2. Site 3. No	1. Yes 2. N/R 3. N/R 4. Standardisation of CT scans N/R. Test material radiopaque. Different healing periods.	High
Pelegrine 2010 RCT #47	1. Yes 2. N/R 3. N/R 4. N/A	1. N/R 2. N/R 3. N/R 4. N/R	1. N/R 2. N/A	1. Yes 2. Yes	1. 100% 2. Yes	1. Yes 2. Yes	N/R	1. N/R 2. Patient 3. Yes	1. N/R 2. N/R 3. N/R	High
Serino 2003 CCT #19	N/A	1. N/R 2. N/R 3. N/R 4. N/R	1. N/R 2. N/A	1. Yes 2. No	1. 80% 2. Unclear	1. Yes 2. Yes	N/R	1. N/R 2. Site 3. No	1. N/R 2. N/R 3. N/R 4. Molars only in T.	High

Table 2 (continued)

Study First author	Quality Criteria									Estimated risk of bias
Year of publication Type Reference number	Randomisation 1. Randomised 2. Adequate sequence generation 3. Allocation concealment 4. Concealment adequate	Masking 1. Therapist 2. Patient 3. Examiner 4. Statistician	Calibration 1. Intra-examiner 2. Inter-examiner	Eligibility Criteria 1. Inclusion criteria defined 2. Exclusion criteria defined	Follow up 1. Percentage of completed follow ups 2. Adequate correction	Ethical considerations 1. Ethics approval 2. Informed consent	Funding Source of Funding	Statistical analysis 1. Appropriate sample size calculation and power 2. Unit of analysis 3. Appropriate statistics applied	Miscellaneous 1. Comparable experimental groups 2. CONSORT implemented 3. ISRCTN registered 4. Other comments	
Serino 2008 CCT #48	N/A	1. N/R 2. N/R 3. N/R 4. N/R	1. N/R 2. N/A	1. Yes 2. No	1. 80% 2. Unclear	1. Yes 2. Yes	Government; institution	1. N/R 2. Patient 3. Insufficient data to determine	1. N/R 2. N/R 3. N/R	High

N/A not applicable; *N/R* not reported, *T* test; *C* control; *RCT* randomised controlled trial; *CCT* controlled clinical trial; *PRGF* platelet-rich growth factor; *CONSORT* Consolidated Standards of Reporting Trials; *ISRCTN* International Standard Randomised Controlled Trial Number Register

of the AR, but the newly formed tissue is of inferior quality and quantity (percentage of matured trabecular bone) to what is normally achieved following a tooth extraction.

Finally, the quality of the included studies has also been meticulously assessed in this review. Such a quality evaluation of the retrieved data is essential to estimate the source and magnitude of potential bias that may lead to delusive conclusions.

Strength of evidence—risk of bias

The quality assessment of the included studies in this systematic review revealed that none of the trials have qualified for a low risk of bias category. Ten out of the 14 studies presented with high risk of bias thus their results must be evaluated with caution. The lack of clear reporting of research methodology elements, such as adequate randomization and concealment and/or masking of the therapist and the examiner were among the primary reasons for the high risk of bias [49]. We did not contact authors for clarification of unclear methodology. Therefore, it is possible that actual study conduct was better than that reported in the publication. Statistical considerations played important role as well, since appropriate analytical statistics was completed and reported merely in one study [47]. Power calculation was conducted in three trials only [21, 23, 42], nevertheless the reported data were insufficient to determine the validity of the calculation.

Dimensional changes and histological characteristics

Sufficient ridge width and height have been considered as one of the key requirements for successful implant therapy and for the establishment of an aesthetically pleasing emergence profile at fixed partial dentures [8, 50, 51]. Therefore, the alterations in oro-facial (horizontal) and apico-coronal (vertical) AR dimensions were selected as the primary outcomes of the present review. Direct intra-surgical measurements on the AR at re-entry are considered as the most precise method to evaluate the bone volume changes following ARP. It is desirable though to establish and validate a surrogate measure that avoids the need for re-entry surgery, while providing the clinician with a reliable measure. Two-dimensional radiographs, such as periapical or panoramic radiographs, are not ideal to estimate the 3D changes of the AR [52]. Also, measurements of the alveolar mucosa level or study casts incorporate not only the alveolar bone, but also the overlaying soft tissue. For these reasons only studies performing clinical or 3D radiographic evaluation of hard tissue were included in this review. Cone-beam computerised tomography (CBCT) appears to offer a valid technique to assess alveolar ridge changes, with newer models greatly reducing radiation exposure [53]. However, a

Table 3

First author Year of publication Type Design Methodology Reference number	*Trial characteristics* 1. Country 2. Number of centres 3. Setting	*Population characteristics* 1. Age range (mean) in years 2. Number of patients (sockets)	*Confounding factors* 1. Smoking 2. Periodontitis	*Defect characteristics* 1. Socket location 2. Defect morphology	*Test material (number of sockets/ subjects)*	*Control (number of sockets/ subjects)*	*Surgical management* 1. Type of flap 2. Soft tissue closure 3. Postoperative antimicrobials	*Follow-up* 1. Healing period 2. Number of drop-outs 3. Adverse events	*Alveolar ridge dimension changes in horizontal width Mean/median mm 1. Whole ridge 2. Buccal plate*	*Alveolar ridge dimension changes in vertical height Mean/median mm (reference point)* 1. Mid-buccal 2. Mesial 3. Distal 4. Socket Fill	*Implant* 1. Feasibility of implant placement 2. Necessity of simultaneous augmentation
Aimetti 2009 RCT Parallel Clin+Histo #42	1. Italy 2. 1 3. University	1. 36-68 (51.27 ±8.4) 2. 40 (40)	1. No 2. N/R	1. Maxillary anterior 2. 4-wall configuration	Calcium sulphate Hemihydrate (22/22)	Empty (18/18)	1. Flapless 2. No primary closure 3. Amoxicillin 2g/day for 5 days, Chlorexidine 0.12% for 2 weeks	1. 3 months 2. N/R 3. Uneventful healing	1. T: -2.0±1.1** C: -3.2±1.8**, *** 2. N/R	1. T: -0.5±1.1*, C: -1.2±0.6**, *** 2. T: -0.2±0.6, C: -0.5±0.9 3. T: -0.4±0.9, C: -0.5±1.1 4. T: 11.3±2.8**, C: 10.0±2.3** (Acrylic stent)	1. Implants were inserted 2. N/R
Anitua 1999 CCT Parallel+Split-mouth Histo #43	1. Spain 2. 1 3. Private practice	1. T: 35-55 (41) C: 38-54 (42) 2. 23 (26)	1. Yes 2. Yes	1. Any 2. Variable	T1: PRGF (5+3/5+3) T2: PRGF+ Autologous bone (5/5)	Empty (10+3/ 10+3)	1. Full-thickness 2. Primary closure 3. Amoxicillin 1.5g/day for 5 days	1. 2.5 – 4 months 2. 0 3. N/R	N/A	N/A	1. N/R 2. N/R
Barone 2008 RCT Parallel Clin+Histo #21	1. Italy 2. 1 3. Hospital	1. 26-69 2. 40 (40)	1. <10/day 2. Yes (treated)	1. Non-molars 2. 4-wall configuration	Corticocancellous porcine bone+ collagen membrane (20/20)	Empty (20/20)	1. Full-thickness 2. Primary closure 3. Amoxicillin 2g/day for 4 days+ Chlorexidine 0.12% for 3 weeks	1. 7-9 months 2. 0 3. Uneventful healing (pain, swelling)	1. T: -2.5±1.2*, C: -4.5±0.8*, *** 2. N/R	1. T: -0.7±1.4*, C: -3.6±1.5*, *** 2. T: -0.2±0.8, C: -0.4±1.2 3. T: -0.4±0.8, C: -0.5±1.0 4. N/R (Acrylic stent)	1. 'Implants were inserted in both groups' 2. Some GBR were needed due to buccal dehiscence in the control group
Camargo 2000 CCT Split-mouth Clin #44	1. USA, Yugoslavia 3. University 2. N/R	1. 28-60 (44±15.9) 2. 16 (32)	1. N/R 2. N/R	1. Maxillary anterior, premolars 2. N/R	Bioactive glass+ covered by calcium sulphate layer (16/8)	Empty (16/8)	1. Full-thickness with 4 vertical releasing incisions 2. No primary closure 3. Penicillin 1.5g/day for 7 days+ Chlorexidine 0.12% for 2 weeks	1. 6 months 2. N/R 3. Uneventful healing	1. T: -3.48±2.68**, C: -3.06±2.41** 2. N/R	1. T: -0.38±3.18, C: -1.00±2.25 (titanium tack) 2. N/R 3. N/R 4. T: 6.43±2.78**, C: 4.00±2.33**, *** (to buccal bone crest)	1. Reentry only 2. N/A

Table 3 (continued)

First author Year of publication Type Design Methodology Reference number	*Trial characteristics* 1. Country 2. Number of centres 3. Setting	*Population characteristics* 1. Age range (mean) in years 2. Number of patients (sockets)	*Confounding factors* 1. Smoking 2. Periodontitis	*Defect characteristics* 1. Socket location 2. Defect morphology	*Test material (number of sockets/ subjects)*	*Control (number of sockets/ subjects)*	*Surgical management* 1. Type of flap 2. Soft tissue closure 3. Postoperative antimicrobials	*Follow-up* 1. Healing period 2. Number of drop-outs 3. Adverse events	*Alveolar ridge dimension changes in horizontal width Mean/median mm 1. Whole ridge 2. Buccal plate*	*Alveolar ridge dimension changes in vertical height Mean/median mm (reference point)* 1. Mid-buccal 2. Mesial 3. Distal 4. Socket Fill	*Implant* 1. Feasibility of implant placement 2. Necessity of simultaneous augmentation
Fiorellini 2005 RCT Parallel Radiogr+ Histo #20	1. USA 2. 8 centres 3. University	1. 47.4 2. 80 (95)	1. N/R 2. N/R	1. Maxillary anterior, premolars 2. ≥50% buccal bone loss	T1: 1.5mg/ml rhBMP-2 (?/21?) T2: 0.75mg/ml rhBMP-2 (?/22?) T3: Collagen sponge (?/17?)	Empty (?/20?)	1. Full-thickness with vertical incisions 2. Primary closure 3. Penicillin (?mg) for 7-10 days+ Chlorexidine 0.12%	1. 4 months 2. No drop-outs reported. (3 patients incorrectly randomized, 1 patient received different graft) 3. 250 (T>C)	1. Coronal: T1: +3.27±2.53*, T2: +1.76±1.67*, T3: +0.82±1.40, C: +0.57±2.56, *** (T1 vs T2/T3/C) 2. N/R	1. T1: -0.02±1.2, T2: -0.62±1.39*, T3: -1.00±1.40*, C: -1.17±1.23*, *** (T1 vs C) 2. N/R 3. N/R 4. N/R	1. N/R 2. No need for augmentation T1: 18/21 (86%) T2: 12/22 (55%) T3: 10/17 (59%) C: 9/20 (45%) (T1 vs T2/C)***
Froum 2002 RCT Split mouth Histo #17	1. USA 2. Single centre 3. University	1. 35-77 (54.9±11.9) 2. 19 (30)	1. No 2. N/R	1. Any 2. 4-wall configuration, ≤2mm buccal plate loss	T1: Bioactive glass (10/8) T2: DFDBA (10/8)	Empty (10/10)	1. Full-thickness without vertical incisions 2. Primary closure 3. Doxycycline 100mg/day for 13 days+ Chlorexidine 0.12% for 30 days	1. 6-8 months 2. 0 3. Uneventful healing	N/A	N/A	1. 'An implant of appropriate size was placed in the healed sockets.' 2. N/R
Guarnieri 2004 CCT Parallel+ Split mouth Histo #45	1. Italy 2. N/R 3. N/R	1. 35-58 2. 10 (25)	1. N/R 2. Yes	1. Maxillary, mandibular anteriors, premolars 2. socket with ridge resorption ≥50% were excluded	Calcium sulphate Hemihydrate (10/10)	Empty (5/5)	1. Full-thickness without vertical incisions 2. Primary closure 3. Amoxicillin (?mg) for 1 week+Chlorexidine 0.2% for 2 weeks	1. 3 months 2. N/R 3. N/R	N/A	N/A	1. 'Bucco-lingual dimensions of the alveolar ridge enabled safe insertion of titanium implant.' 2. N/R
Iasella 2003 RCT Parallel Clin+Histo #23	1. USA 2. N/R 3. N/R	1. 28-76 (51.5±13.6) 2. 24 (24)	1. Yes 2. N/R	1. Maxillary anteriors, premolars and mandibular premolars 2. N/R	Tetracycline hydrated FDBA + collagen membrane (12/12)	Empty (12/12)	1. Full-thickness without vertical incisions 2. No primary closure 3. Doxycyclin 200mg/day for 1 week+ Chlorexidine 0.12% for 2 weeks	1. 4 or 6 months (combined) 2. 0 3. N/R	1. T: -1.2±0.9*, C: -2.6±2.3* 2. N/R	1. T: +1.3±2.0, C: -0.9±1.6*** 2. T: -0.1±0.7, C:-1.0±0.8*** 3. T: -0.1±0.7, C: -0.8±0.8*** 4. N/R (Acrylic stent)	1. Implants successfully placed at all sites 2. Some sites had slight dehiscence and required further augmentation

Table 3 (continued)

First author Year of publication Type Design Methodology Reference number	*Trial characteristics* 1. Country 2. Number of centres 3. Setting	*Population characteristics* 1. Age range (mean) in years 2. Number of patients (sockets)	*Confounding factors* 1. Smoking 2. Periodontitis	*Defect characteristics* 1. Socket location 2. Defect morphology	*Test material (number of sockets/ subjects)*	*Control (number of sockets/ subjects)*	*Surgical management* 1. Type of flap 2. Soft tissue closure 3. Postoperative antimicrobials	*Follow-up* 1. Healing period 2. Number of drop-outs 3. Adverse events	*Alveolar ridge dimension changes in horizontal width Mean/median mm 1. Whole ridge 2. Buccal plate*	*Alveolar ridge dimension changes in vertical height Mean/median mm (reference point)* 1. Mid-buccal 2. Mesial 3. Distal 4. Socket Fill	*Implant* 1. Feasibility of implant placement 2. Necessity of simultaneous augmentation
Lekovic 1997 CCT Split-mouth Clin #24	1. Yugoslavia / USA 2. N/R (presumably single centre) 3. University	1. (49.8) 2. 10 (20)	1. N/R 2. N/R	1. Maxillary and mandibular anteriors, premolars 2. N/R	e-PTFE membrane (10/10)	Empty (10/10)	1. Full-thickness with 4 vertical releasing incisions 2. Primary closure 3. Penicillin 1g/day for 7 days+ Chlorexidine 0.2%	1. 6 months 2. 3/10 drop-outs due to premature membrane exposure 3. 3/10 exposed, 7/10 no infection	1. 10/10:, T: -1.80±0.51, C: -4.40±0.61**, *** 7/10: T: -1.71±0.75, C: -4.43±0.72**, *** 3/10: T: -2.00±0.00, C: -4.33±0.88* 2. N/R	1. 10/10: T: -0.5±0.22, C: -1.2±0.13**, *** 7/10: T: -0.28±0.18, C: -1.0±0.0**, *** 3/10: T: -1.0±0.58, C: -1.66±0.33 (titanium tack) 2. N/R 3. N/R 4. 10/10: T: 4.9±0.86*, C: 3.0±0.63, *** 7/10: T: 5.43±1.1*, C:2.92±1.61, *** 3/10: T: 3.66±1.20, C: 4.33±1.45 (to buccal bone crest)	1. Reentry only 2. N/A
Lekovic 1998 RCT Split-mouth Clin #25	1. Yugoslavia 2. 1 3. University	1. (52.6±11.8) 2. 16 (32)	1. N/R 2. Yes (treated)	1. Maxillary and mandibular anteriors, premolars 2. N/R	PG/PL membrane (16/16)	Empty (16/16)	1. Full-thickness with 4 vertical releasing incisions 2. Primary closure 3. Penicillin 1g/day for 7 days+ Chlorexidine 0.12% for 2 weeks	1. 6 months 2. 0 3. Uneventful healing	1. T: -1.31±0.24* C:-4.56±0.33*, *** 2. N/R	1. T: -0.38±0.22, C: -1.50±0.26*, *** (titanium tack) 2. N/R 3. N/R 4. T: 5.81±0.29*, C: 3.94±0.35*, *** (to buccal bone crest)	1. Reentry only 2. N/A
Nevins 2006 RCT Split-mouth Radiogr+ Histo #46	1. USA / Italy 2. N/R 3. N/R	1. N/R 2. 9 (36)	1. N/R 2. Yes	1. Maxillary anterior 2. Buccal plate was compromised	DBBM (19/9)	Empty (17/9)	1. Partial thickness 2. Primary closure 3. N/R	1. 1 – 3 months (biopsies at 6M) 2. 0 3. N/R	N/A	1. T: -2.42±2.58, C: -5.24±3.72*** 2. N/R 3. N/R 4. N/R (At 6 mm ridge width)	1. Implants were placed, but number unknown 2. N/R

Table 3 (continued)

First author Year of publication Type Design Methodology Reference number	*Trial characteristics* 1. Country 2. Number of centres 3. Setting	*Population characteristics* 1. Age range (mean) in years 2. Number of patients (sockets)	*Confounding factors* 1. Smoking 2. Periodontitis	*Defect characteristics* 1. Socket location 2. Defect morphology	*Test material (number of sockets/ subjects)*	*Control (number of sockets/ subjects)*	*Surgical management* 1. Type of flap 2. Soft tissue closure 3. Postoperative antimicrobials	*Follow-up* 1. Healing period 2. Number of drop-outs 3. Adverse events	*Alveolar ridge dimension changes in horizontal width Mean/median mm 1. Whole ridge 2. Buccal plate*	*Alveolar ridge dimension changes in vertical height Mean/median mm (reference point)* 1. Mid-buccal 2. Mesial 3. Distal 4. Socket Fill	*Implant* 1. Feasibility of implant placement 2. Necessity of simultaneous augmentation
Pelegrine 2010 RCT Parallel Clin+histo #47	1. Brazil 2. 1 3. University	1. 28-70 (47.5±10.3) 2. 13 (30)	1. No 2. N/R	1. Maxillary anteriors 2. Sockets with severe bone loss were excluded	Autologous bone marrow (15/7)	Empty (15/6)	1. Full-thickness with 2 buccal vertical releasing incisions 2. Primary closure 3. N/R	1. 6 months 2. 0 3. Uneventful healing	1. T: -1.0*, C: -2.5*, *** 2. T: -0.75, C: -1.75, ***	1. T: -0.5*, C: -1.0*, *** (Titanium screw) 2. N/R 3. N/R 4. T: 10.33*, C: 10.32* (to buccal bone crest)	1. All implants osseointegrated 2. T: without further augmentation, C: At 5 sites augmentation or expansion carried out
Serino 2003 CCT Parallel+ split-mouth Clin+Histo #19	1. Italy 2. 1 3. N/R	1. 35-64 2. 45 (39) before drop-out	1. N/R 2. Yes (treated)	1. Any 2. Buccal plate could be partially or completely lost	PG/PL sponge (26/24) after drop-out	Empty (13/12) after drop-out	1. Full-thickness buccally and lingually 2. No primary closure 3. No antibiotics; Chlorexidine 0.2% for 2 weeks	1. 6 months 2. 9 drop-outs for reasons unrelated to the therapy 3. Uneventful healing	N/A	1. T: +1.3±1.9*, C: -0.8±1.6 2. T: -0.2±1.0, C: -0.6±1.0 3. T: -0.1±1.1, C: -0.8±1.5 4. N/R (Acrylic stent)	1. Placement of implants in all C and T sites with good primary stability 2. N/R
Serino 2008 CCT Parallel Histo #48	1. Italy 2. 1 3. N/R	1. 32-64 2. 20 (20) before drop-out	1. N/R 2. Yes (treated)	1. Any non-molars 2. Alveolar bone height ≥8mm	PG/PL sponge (7/7) after drop-out	Empty (9/9) after drop-out	1. Full-thickness buccally and lingually 2. No primary closure 3. No Antibiotics; Chlorexidine 0.2% for 2 weeks	1. 3 months 2. 4 drop-outs for reasons unrelated to the therapy 3. Uneventful healing	N/A	N/A	1. Placement of implants in all C and T sites with good primary stability 2. N/R

* $p < 0.05$; statistically significant intra-group difference, baseline to final; ** $p < 0.001$ statistically highly significant intra-group difference, baseline to final; *** $p < 0.05$ statistically significant inter-group difference, between test and control;

N/A not applicable; *N/R* not reported; *T* test; *C* control; *M*= month(s); *Clin* clinical analysis; *Histo* histological analysis; *Radiogr* radiographic analysis; *RCT* randomised controlled trial; *CCT* controlled clinical trial; *PRGF* plasma rich in growth factors; *DFDBA* demineralised freeze-dried bone allograft; *FDBA* freeze-dried bone allograft; *e-PTFE* expanded-polytetrafluorethylen*; PG/PL* polyglycolide/polylactide; *DBBM* demineralised bovine-bone mineral

Table 4

First author Year of publication Type *Healing period* *Reference number* *RCT*	Number of biopsies (test material)	Histomorphology Test	Control	Histomorphometry (mean or median %)				Statistical difference between test and control
Aimetti 2009 *3 M* *#42*	T: N/R 22? (MGCSH) C: N/R 18?	No residual graft material. No inflammatory infiltrate. New bone formation in all specimens, 100% living trabecular bone with woven and lamellar structure.	100% living bone (mostly woven) in all biopsies. Lamellar bone remodeling was starting.	*Trabecular bone:* T: 58.8±3.5 C: 47.2±7.7	*Residual substitute material:* T: 0.0 C: N/A	*Woven bone:* *Coronal:* T: 83.6±6.6 C: 88.9±7.6 *Middle:* T: 59.6±13.2 C: 81.1±7.6 *Apical:* T: 56.4±10.9 C: 77.8±8.1	*Lamellar bone:* *Coronal:* T: 16.4±6.6 C: 11.1±7.6 *Middle:* T: 40.4±13.2 C: 18.9±7.6 *Apical:* T: 43.6±10.9 C: 22.2±8.1	T vs C*
Anitua 1999 *CCT* *2.5 – 4 M* *#43*	T: N/R (PRGF± autogen bone) C: N/R	Compact mature bone with well-organized trabeculae and morphology in 8/10 patients. Connective tissue with non-organized trabeculae in 2/10 patients. Significant intra-group differences 10 vs. 16 weeks!	Connective tissue fills the main part of the defect. No mature bone.					N/R
Barone 2008 *RCT* *7 – 9 M* *#21*	T: 20 (Corticocancellous porcine bone+ collagen membrane) C: 20	Residual graft material embedded in newly formed bone in all specimens. Complete bone fill.	Typically trabecular bone pattern. Large marrow spaces filled with adipocytes. Lamellar bone was also present within the bone marrow.	*Total bone volume:* T: 35.5±10.4 C: 25.7±9.5	*Connective tissue:* T: 36.6±12.6 C: 59.1±10.4	*Residual graft material:* T: 29.2±10.1 C: N/A		Bone: T>C* Connective tissue: T<C*
Fiorellini 2005 *RCT* *4 M* *#20*	T1: 16 (rhBMP-2 1.5mg/ml) T2: 15 (0,75mg/ml) T3: 11 (Collagen sponge) C: 14	No evidence of inflammation or residual graft. Trabecular bone formation in 2/3 of the samples. Mineralized tissue formation presented with different level of remodeling. Minor osteoclastic activity. No comparison reported between T and C!						N/R
Froum 2002 *RCT* *6 – 8 M* *#17*	T1: 10 (Bioactive glass) T2: 10 (DFDBA) C: 10	T1: New bone formation. Osteoid surrounded and penetrated the bioactive glass particles. T2: Varying degrees of reossification around DFDBA.	N/R	*Vital bone:* T1: 59.5 T2: 34.7 C: 32.4	*Connective tissue:* T1: 35.3 T2: 51.6 C: 67.0	*Residual bone substitute:* T1: 5.5 T2: 13.5 C: N/A		Connective tissue: T1<T2 or C*

Table 4 (continued)

First author Year of publication Type *Healing period* *Reference number*	Number of biopsies (test material)	Histomorphology Test	Control	Histomorphometry (mean or median %)		Statistical difference between test and control
Guarnieri 2004 *CCT* *3 M* *#45*	T: 10 (MGCSH) C: 5	Almost complete absence of MGCSH. Absence of connective tissue and inflammatory cells. In all sections trabecular bone formation with no differences between the apical, middle and coronal levels.	Less bone formation compared to test sites.	*Trabecular bone area:* T: Coronal: 58.6±9.2 Middle: 58.1±6.2 Apical: 58.3±7.8 C: ≤ 46		No statistical significance could be drawn due to small number of control specimens.
Iasella 2003 *RCT* *4 – 6 M* *#23*	T: 4M: 5, 6M:7 (Tetracycline hydrated FDBA+ Collagen membrane) C: 4M: 5, 6M: 5	Residual graft particles surrounded by woven bone or by connective tissue.	Similar amount of total bone and trabecular spaces as in test. (No biopsy from 2 C sites due to minimal bone fill)	*Vital bone:* 4M T: 31±9 C: 58±11 6M T: 25±17 C: 50±14 Combined T: 28±14 C: 54±12	*Non-vital bone:* 4M T: 32±19 C: N/A 6M T: 41±18 C: N/A Combined T: 37±18 C: N/A	N/R
Nevins 2005 *RCT* *6 M* *#46*	T: 5 (DBBM) C: 5	DBBM granules present. Apically integrated in cancellous bone but coronally in soft tissue. No signs of inflammation or foreign body reaction.	New bone formation			No comparison made.
Pelegrine 2010 *RCT* *6 M* *#47*	T: 7 (Autologous bone marrow) C: 6			*Mineralized bone:* T: 45.0 C: 43.75		No significant difference.
Serino 2003 *CCT* *6 M* *#19*	T: 10 (PG/PL sponge) C: 3	No residual graft material. Presence of matured, mineralized bone. Lack of coronal soft tissue ingrowth.	Presence of mineralized bone. Wide marrow spaces.	*Mineralized bone:* T: 66.7 C: 43.7		Statistical comparison cannot be made due to the small number of control specimens.
Serino 2008 *CCT* *3 M* *#48*	T: 7 (PG/PL sponge) C: 9	No residual graft material. Scarce presence of inflammatory tissue. Coronal: newly formed trabecular bone with large marrow spaces. Apical: more mature and compact bone.	Coronal: trabecular bone with wide marrow spaces with connective tissue. Apical: more mature and compact bone.	*Mineralized bone:* T: 59.9±22.4 C: 48.8±14.4		No significant difference.

*$p<0.05$; statistically significant difference between test and control

T test; *C* control; *M* month(s); *N/R* not reported; *N/A* not applicable; *vs*. versus; *TBV* total bone volume; *MGCSH* medical grade calcium sulphate hemihydrate; *DFDBA* demineralised freeze-dried bone allograft; *FDBA* mineralised freeze-dried bone allograft; *DBBM* demineralised bovine-bone mineral; *PG/PL* polyglycolide/polylactide

prerequisite of this technique would be some type of standardisation, so that the captured image is being always taken from exactly identical positions [54]. None of the two included radiographic studies reported on such standardisation [20, 46].

For the interpretation of the results we attempted to cluster the studies in respect to the type of intervention.

Unassisted sockets In the present review, the mean reduction of the AR width of the untreated sites varied between 2.6±2.3 mm and 4.6±0.3 mm and the mean reduction of the AR height was between 0.8±1.6 mm and 3.6±1.5 mm after 1 to 9 months of healing. This corroborates the result of a previous clinical study which indicated that 95 % of AR reduction should be expected after three months of extraction [1]. Furthermore, it is in agreement with a recent systematic review, which reported that the average reduction of the AR width seemed to be higher (3.87 mm), than the reduction in AR height (1.67 mm) [55].

Even though both AR width and height present resorption, histologically, new bone formation up to a variable extent was also observed in some studies as result of unassisted socket healing [19–21, 23, 42, 45, 46, 48]. In addition, a large area was occupied by bone marrow [19, 21, 48], as reported in preclinical studies [11, 13, 56]. Only a single study reported on connective tissue fill and lack of mature bone [43].

Bone grafts and substitutes Effective grafting procedures for bone augmentation have been associated with the osteoconductive, osteoinductive or osteogenetic properties of the graft [56–59]. This led to the assumption that the placement of these materials in the extraction socket may accelerate new bone formation by the above biological properties and may also reduce AR resorption by stabilising the blood clot, providing a scaffold and external source of minerals and/or collagen [11, 12, 60, 61]. The placement of DBBM with collagen in fresh extraction sockets resulted in limited reduction of the AR dimensions, although delayed initial socket healing in terms of new bone formation was also observed [11, 12]. Human studies reported similar unfavourable histological observations when DFDBA was employed for ARP [15, 16].

In the present review of human experiments, two out of three studies reported that socket grafting with autologous bone marrow [47] or alloplastic material [42] have significantly limited the reduction of the AR width compared to the unassisted socket healing. Three out of five studies reported that reduction of the resorption in AR height was significant [42, 46, 47], while the ridge height was even increased in one study, where sockets were grafted with polymer sponge [19]. We should emphasise though that since the graft material (DBBM) in a CT study possessed radiopaque characteristic, the alteration of the AR contour on the CT image should be interpreted with caution [46].

Based on the histological evaluation of these studies, the above AR dimensional changes were not necessarily accompanied by higher amount of new bone formation in the socket, since the quality of newly formed tissue in the ARP sites was comparable to that in the control sites. Furthermore, the sockets were occupied by a mixture of new bone and connective tissue which in many occasions was surrounding the graft particles [17, 21, 46] (Table 4).

GBR (membrane alone or in combination with 'graft') The conception of guided bone and tissue regeneration [62] was translated to ARP procedures in order to exclude epithelial cells from the extraction socket by the use of barrier membrane in four studies of the present review [21, 23–25].

(a) GBR with membrane alone

ARP with GBR resulted in statistically significantly less resorption in ridge width and height compared to unassisted socket healing, regardless of the type of membrane [24, 25]. It should be noted that in one study [24], in three out of 10 cases, the exposed non-resorbable e-PTFE barrier had to be removed prematurely, highlighting the importance of sufficient soft tissue closure and timing of removal of the barrier. The outcomes in these three cases were similar to the control sites. Where healing was uncompromised, a statistically significant difference was found after 6 months in width and height changes in favour of the ARP group.

(b) GBR with membrane and 'graft'

ARP resulted in statistically significantly less resorption in width [21, 23] and height [23] in comparison to unassisted socket healing. The histological evaluation of the GBR procedures in the included studies demonstrated new bone formation [21, 23], but the presence of graft particles was also evident in both studies, embedded either in newly formed bone [21] or in connective tissue [23]. This is in agreement with a recent trial, where a collagen membrane in combination with DBBM or a biphasic bone substitute was used for ARP [9, 10].

Biological active materials The potential benefit of biological active molecules was investigated in periodontal and bone regeneration through fostering the proliferation and differentiation of different mesenchymal cells in various preclinical models [63, 64]. The safety and feasibility of rhBMP-2 on human ARP or ridge augmentation was evaluated and shown to be safe in a two-centre clinical study [35]. Dimensional changes of the alveolar ridge were measured on CT scans in an RCT [20]. Treatment with recombinant BMP-2 resulted in an increase in ridge width which was statistically significantly greater than controls. However, this observation needs to be

interpreted in light of the surprise finding of an increase in ridge width of the untreated controls. This was a unique finding amongst the studies that we reviewed. Histologically, no comparison between ARP and controls sites was reported.

The human histological results of the included papers of the present review were generally found to be comparable to preclinical studies [11–13, 60, 65]. There are a number of aspects to consider in the interpretation of the results. Firstly, it has to be kept in mind that whilst the biopsies of the animal model incorporate the cross section of the whole AR, the biopsy retrieval at human studies is limited to a trephine core sample of part of the former socket. This location may not necessarily coincide with the exact position of the previous extraction, thus making interpretation of the results challenging. Furthermore, the differentiation between apical, mid and coronal, as well as the central and lateral aspects of the biopsies was not always apparent.

Another important parameter when considering a histological overview of the studies was the variation in healing time. Due to the nature of post-extraction healing, the direct comparison of the new tissue formation in studies between 1 and 9 months of healing could be misleading. This was highlighted in three studies which did not make a distinction between the variable healing times within the groups, ranging from 2.5 months to 9 months [17, 21, 43]. It has to be kept in mind also that the only study, which completed and reported appropriate statistical methodology [47], did not observe statistically significant difference between the test and control biopsies.

Furthermore, small sample sizes in the majority of the studies may also limit the generalisability of the histological findings.

Two studies found statistically significant histological differences in new bone formation favouring the test group [21, 42]. Drawing conclusions across the studies is difficult since the test groups differed in many respects compared with each other, including different technique (bone substitute only [42]/GBR + graft [21]), different material (MGCSH [42]/porcine bone with collagen membrane [21]), different flap management (flapless, no primary closure [42]/mucoperiosteal flap, primary closure [21]), different healing time (3 months [42]/7–9 months [21]). One common feature was that both groups limited their intervention to sockets with four intact walls. It is noteworthy that all three studies that included intact socket walls only, reported statistically significant differences both on AR width and height in favour of ARP [21, 42, 47], while only one [20] out of two studies [19, 20] with initial buccal bone loss reported similar significant difference between test and control. Therefore, socket morphology could be an important predicator of improved ARP. The need for ARP in such sockets, in terms of future clinical success/implant placement needs further investigation.

Flap management All studies reporting statistically significant inter-group differences in both horizontal and vertical clinical measurements achieved either primary flap closure [21, 24, 25, 47], or did not detach the periosteum in a flapless procedure [42]. Furthermore, none of the studies without primary closure demonstrated statistically significant differences between test and control in terms of both horizontal and vertical clinical measurements [19, 23, 44]. Therefore, both achieving and maintaining the epithelial seal above the socket may be crucial to improving ARP. Further corroboration of this concept was suggested where e-PTFE barriers were prematurely exposed. The healing of these three exposed cases demonstrated no statistically significant differences compared to the control sites [24].

Other factors affecting interpretation of the findings

Healing time

The optimal timing of re-entry following ARP is determined by the implant insertion. Since the volume of the AR is gradually decreasing, while the quality of the newly formed tissue is gradually increasing during the post-extraction remodelling [1, 6] the implant placement could be considered as early as possible, but as late as necessary, in order to maintain AR volume, as well as to achieve complete epithelial seal with some extent of osseous fill. The healing periods of the trials in the present review varied considerably (one to nine months). Therefore, interpretation of the results was complicated by the heterogeneity present in the included studies.

Antimicrobials

Improvement of clinical parameters was demonstrated as a result of regular rinsing with chlorhexidine following tooth extraction [66]. Subjects of the included trials in the present review were prescribed various types of antibiotics and instructed to rinse with chlorhexidine for 2 to 3 weeks. Therefore, no conclusion could be drawn on the necessity or benefit of employment of antibiotics/antimicrobials following ARP.

Smoking

Smoking is associated with delayed socket healing and increased reduction in post-extraction alveolar width [67]. Three trials in this review included smokers [21, 23, 43] and the half of the studies did not report on smoking as an exclusion factor, thus any conclusions about the impact of this well-recognised risk factor for impaired healing are difficult to draw [68].

Periodontal treatment/health

Four studies included patients whose periodontal treatment was carried out prior to the ARP [19, 21, 25, 48]. ARP resulted in statistically significant difference between tests and controls in clinical [21, 25] and in histological parameters [21]. In addition, in the studies where periodontitis was present, but periodontal treatment was not reported, no statistically significant histological differences were demonstrated [43, 44, 46]. This suggests that treated periodontitis may not hinder the success of ARP.

Hard and soft tissue morphology

No data were reported on factors, such as gingival biotype, width of the keratinised gingiva, thickness of buccal plate or total volume of AR that may modify the outcome of ARP. Therefore, the possible impact of these factors on ARP cannot be determined.

Clinical relevance

The clinical rationale for ARP is to minimise the necessity for one or two stage alveolar ridge reconstruction to allow successful implant placement. If the ARP procedure fails to meet this requirement, it may be considered as an unnecessary or even unsuccessful procedure. Therefore, a statistical significance favouring ARP does not necessarily lead to a clinical benefit, unless the whole treatment is simplified or made more successful [9]. In the present systematic review, seven out of ten studies did not report differences in feasibility of implant insertion at re-entry [17, 19, 23, 42, 45, 46, 48]. Only two studies reported that there was no need for further reconstruction in the ARP group, whilst GBR or ridge expansion were carried out in some of the control sites alongside implant insertion [21, 47]. One study reported that statistically significantly less augmentation had to be performed in the ARP group, compared to the control [20]. In relation to illuminating the understanding of possible long term benefits of ARP, the success rate of the inserted dental implants in the former test, versus control sites should be examined. No studies have yet reported this.

Patient-reported outcome and health economics

It would be helpful to understand patient experiences such as concomitant discomfort at/following ARP in order to avoid a further, extensive reconstructive surgery. On the other hand, the additional costs of ARP at the time of extraction may not be desirable if the outcome and benefit of such extra treatment were not predictable. There are no data yet to inform on these questions.

Conclusions

Within the limits of the above findings the following conclusions can be drawn:

1. The results of the control groups confirm that tooth extraction results in a statistically significant horizontal and vertical resorption of the AR, as part of the natural remodelling.
2. The magnitude of the horizontal shrinkage is more pronounced than the vertical.
3. The resorption of the AR cannot be totally prevented by ARP.
4. Dimensional changes of the AR may be limited by some of the ARP techniques.
5. No evidence was identified to inform on the possible impact of the following factors on ARP outcomes: (a) site location, (b) buccal plate thickness, (c) healing time, (d) antibiotic regime, (e) light smoking, (f) history of treated periodontitis.
6. The presence of intact socket walls and primary flap closure are often associated with favourable results.
7. Conflicting evidence exists on the benefit of ARP at the histological level. ARP does not appear to promote de novo hard tissue formation routinely. In addition, some graft materials may interfere with healing.
8. Due to the broad variety of employed materials, techniques, defect morphologies, healing periods, as well as the relatively small sample sizes, meta-analysis or comparative assessment of ARP cannot be made. Consequently no material or method can be claimed to serve superior to another. However, in certain cases GBR appeared to be most effective.
9. Only limited evidence supports the clinical benefit of ARP, namely the reduction of necessity of further augmentation in conjunction with implant placement.
10. No evidence exists on comparison of the survival or success rate of implants, placed in the former ARP or control sites.
11. No evidence exists on cost-effectiveness, patient's preference or quality of life following ARP.
12. The case selection criteria for performing ARP remain still undetermined.
13. The strength of evidence ranges from weak to moderate and therefore, the conclusions of this review should be interpreted with caution.

Recommendations for further research

- Randomised controlled trials on adequately powered sample sizes are needed where unassisted socket healing serves as the negative control.

- Appropriate follow-up periods are required. Ideally, this should reflect implant insertion protocols, such as six weeks (Type 2), three to four months (Type 3) or >6 months (Type 4) placement following extraction.
- Clinical studies should be designed to perform not only clinical (quantitative), but also histological (qualitative) assessment.
- The role of additional factors like smoking, reason for extraction, tooth location, initial buccal plate thickness, flap reflection and closure, antimicrobial regime should also be investigated.
- Comparative studies should also be designed in order to identify the most successful treatment options.
- It may be beneficial to seek for a cell occlusive barrier membrane that does not require extensive soft tissue mobilization for flap approximation.
- Necessity of re-augmentation at implant placement should be investigated.
- Survival and success rates of implants, placed in former ARP sites should be evaluated.
- Outcome evaluation should ideally incorporate patient's preference, quality of life, as well as treatment economy.

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