KEY WORDS
Bone substitutes, Meta-analysis, Systematic review, Tooth extraction, Tooth socket

Cochrane systematic review

ALVEOLAR RIDGE PRESERVATION: A COCHRANE SYSTEMATIC REVIEW AND META-ANALYSIS

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PURPOSE. To evaluate the effects of various materials and techniques for alveolar ridge preservation (ARP) after tooth extraction compared with extraction alone or other methods of ARP in patients requiring dental implant placement.

MATERIALS AND METHODS. Electronic databases were searched to identify randomized controlled trials (RCTs) on the use of ARP techniques with at least six months of follow-up. The risk of bias was assessed using the Cochrane Collaboration's Risk of Bias tool. Data were analysed using a statistical software program.

RESULTS. A total of 16 RCTs with 524 extraction sockets in 426 participants were included. The meta-analysis showed a very low certainty evidence of a reduction in loss of alveolar ridge width (mean difference (MD) -1.18 mm, 95% confidence interval (CI) -1.82 to -0.54; P = 0.0003) and height (MD -1.35 mm, 95% CI -2.00 to -0.70; P < 0.0001) in favour of xenograft when compared to extraction alone. There are no significant differences in the need for additional augmentation or implant failure between xenograft and extraction alone. No serious adverse events were reported with most trials indicating that the procedure was uneventful.

CONCLUSIONS. ARP techniques may minimise the overall changes in residual ridge height and width six months after extraction but the evidence is very uncertain. There is no evidence of any clinically significant difference between different grafting materials and barriers used for ARP.

CONFLICT OF INTEREST STATEMENT. The authors report no conflicts of interest related to this review

This article is a short version of a Cochrane Review previously published in the *Cochrane Database of Systematic reviews* 2021, Issue 4, DOI: 10.1002/14651858.CD010176.pub3. Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback and *Cochrane Database of Systematic Reviews* should be consulted for the most recent version of the review.

INTRODUCTION

The overall alveolar bone changes following tooth extraction may compromise the prosthodontic rehabilitation and may not allow the placement of dental implants in optimal position[1,2]. Therefore, the planning for a prosthodontically-driven implant placement may require preservation of the original alveolar ridge dimensions following tooth extraction. The practice of bone preservations following tooth extraction was first described as "bone maintenance"[3-5]. Different terms were then used to describe the same procedure, such as "socket preservation", "socket augmentation", "socket grafting", "ridge preservation", "alveolar bone grafting" and "alveolar augmentation". Alveolar ridge preservation (ARP), the term used in this review, is defined as the procedure of arresting or minimizing the alveolar ridge resorption following tooth extraction for future prosthodontic treatment including placement of dental implants[6]. Despite that several techniques and materials have been introduced to preserve the alveolar ridge, there is still lack of evidence regarding the efficacy of these techniques and the superiority of one technique over the other. Conflicting views have also been reported in the literature with some authors considering the use of grafting material for ARP as effective technique in limiting alveolar ridge resorption[7,8], while others argue that intra-socket grafts may compromise the normal healing process of the extraction socket[9,10]. Several systematic reviews[11-18] were published to evaluate the evidence on ARP, but none of these reviews have attempted to minimize the risk of bias by limiting their selection criteria to randomized trials and have mostly compared different grafting materials in one group against extraction alone. The aim of this Cochrane review was to evaluate the clinical effects of ARP techniques (including guided bone regeneration (GBR) and socket seal) and materials (including grafting materials, biologics and growth factors) compared with extraction alone or other ARP techniques or materials in patients requiring dental implant placement following healing of extraction sockets.

MATERIALS AND METHODS

The current systematic review was developed following the guidelines provided by the Cochrane Collaboration[19]. The participant, intervention, comparison, outcome (PICO) framework[19,20] was used to structure our research question:

Participant: Human adults aged ≥18 years that require ARP following tooth extraction and future implant placement.

Intervention: ARP.

Comparison: extraction alone or other ARP methods.

Outcomes: Changes in ridge width and height, complications, need for additional augmentation at the time of implant placement, aesthetic and prosthodontic outcomes of future prosthodontic rehabilitation, implant failure, changes in peri-implant marginal bone level, probing depth and clinical attachment level at teeth adjacent to the extraction site.

Types of studies

This review included randomized controlled trials (RCTs) on the use of ARP techniques with at least six months of follow-up. The follow-up was regarded as the period from tooth extraction until the final measurements of the alveolar ridge prior to or at the time of implant placement.

Type of participants

Participants that were 18 years of age or older and received ARP following tooth extraction. Participants who had undergone ARP procedures as part of non-implant related prosthodontic treatment were excluded.

Types of interventions

Any method of ARP (including use of grafting materials, biologics, and growth factors) and techniques (including GBR and socket seal) with or without the use of any type of barrier membranes after tooth extraction was accepted. ARP was compared to either extraction alone (no ARP was performed), or another type of ARP.

Types of outcome measures

Primary outcomes

Changes in the bucco-lingual/palatal width of alveolar ridge.
Changes in the vertical height of the alveolar ridge.
Complications (e.g. discomfort, pain and swelling).
Need for additional augmentation at the time of implant placement.
Aesthetic outcomes of future prosthodontic rehabilitation.
Implant failure (defined as implant loss) rate.

Secondary outcomes

Peri-implant marginal bone level changes.
Changes in probing depth (PD) at teeth adjacent to the extraction site.
Changes in clinical attachment level (CAL) at teeth adjacent to the extraction site.
Prosthodontic outcomes of rehabilitation.

Search Strategy

There were no language, publication year, or publication status restrictions. The following databases were searched for RCTs by Cochrane Oral Health's Information Specialist: Cochrane Oral Health's Trials Register (searched 19 March 2021), Cochrane Central Register of Controlled Trials (CENTRAL; 2021, issue 2) in the Cochrane Library (searched 19 March 2021), MEDLINE Ovid (1946 to 19 March 2021), Embase Ovid (1980 to 19 March 2021), LILACS BIREME Virtual Health Library (Latin American and Caribbean Health Science Information database; from 1982 to 19 March 2021), Web of Science Conference Proceedings (1990 to 19 March 2021), Scopus (1966 to 19 March 2021), ProQuest Dissertations and Abstracts service (1861 to 19 March 2021), OpenGrey (www.opengrey.eu) (19 March 2021).

Manual search of relevant dental journals (Clinical Implant Dentistry and Related Research, Clinical Oral Implants Research, International Journal of Oral Implantology, International Journal of Oral and Maxillofacial Implants, Journal of Clinical Periodontology, Journal of Periodontology, and Clinical Trials in Dentistry) and bibliographies of all eligible papers was carried out to look for other additional studies.

Selection of studies

Three reviewer authors (MAA, NHMA, and SA) independently and in duplicate examined the retrieved citations on the basis of the title, abstract, and keywords. Irrelevant papers were excluded and the full-texts of the remaining ones were obtained. An eligibility form was used to examine papers for inclusion in the review. Any disagreements were resolved by discussion to reach a consensus or by consultation with a fourth review author (AGTP). In the presence of more than one publication of the same trial, all the publications were reviewed and relevant information were obtained from all related publications but the most relevant one was quoted. All the reasons for exclusion were reported.

Data collection

Three review authors (MAA, NHMA, and SA) used a data extraction form and independently collected the following information from the included studies: 1) Study characteristics: title, authors' names, contact address, study location, language of publication, year of publication, published or unpublished data, source of study funding, study design (parallel group or split mouth), method of randomization, allocation concealment and blinding (participants, investigators, outcome examiners). 2) Participants: demographic characteristics, inclusion/exclusion criteria, number of participants in test and control groups, number of withdrawals and reasons for dropouts. 3) Interventions: types of ARP techniques and grafting materials. 4) Comparison: extraction alone (no ARP is performed) or another method of ARP. 5) Outcomes: the previously described outcomes in addition to any other outcomes evaluated in the study. 6) The method of assessment. 7) Length of the observation period. 8) Adverse events. Any disagreements between reviewers were resolved by discussion to reach a consensus or by consultation with a fourth review author (AGTP). Corresponding authors of the included studies were contacted for additional information if required.

Quality assessment of included studies

Three review authors (MAA, NHMA, and SA) assessed the risk of bias independently, and in duplicate, for the included studies by using the Cochrane Collaboration's Risk of Bias (RoB) tool for randomized studies of interventions[19]. The RoB tool consists of seven domains include sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. The first part of the tool describes each domain while the second part categorizes studies into those having (i) low risk of bias if all the criteria were met, (ii) unclear risk of bias if one or more criteria were partially met, or (iii) high risk of bias if one or more criteria were not met.

Data synthesis

A statistical software program (Review Manager (RevMan) software, version 5.4, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to conduct meta-analyses for studies of similar comparisons reporting the same outcome measures. Continuous data, such as changes in width and height of the alveolar ridge, were expressed in mean difference (MD) and 95% confidence intervals (CIs). Dichotomous data, such as need for additional augmentation, were expressed in risk ratio (RR) estimates and 95% CIs. Random-effects model was used to pool the results from more than one study as heterogeneity between studies was expected. Split-mouth and parallel group studies were combined using the generic inverse variance option in the statistical software program. With fewer than 10 studies, publication bias was not formally assessed because the power to detect publication bias was limited[19]. The statistical heterogeneity across different studies was assessed by means of the Cochran's test for heterogeneity and I^2 statistic[19]. An I^2 value of >50 indicated a significant heterogeneity. The statistical unit of randomization for parallel-group studies was the participant, and for split-mouth studies it was the site.

RESULTS

Results of the search

A total of 113 studies were retrieved from the databases for full-text review (**FIG. 1**), of which 97 studies[8,21-114] were excluded (**TABLE 1**). A total of 16 studies[115-130] were included (**TABLE 2**).

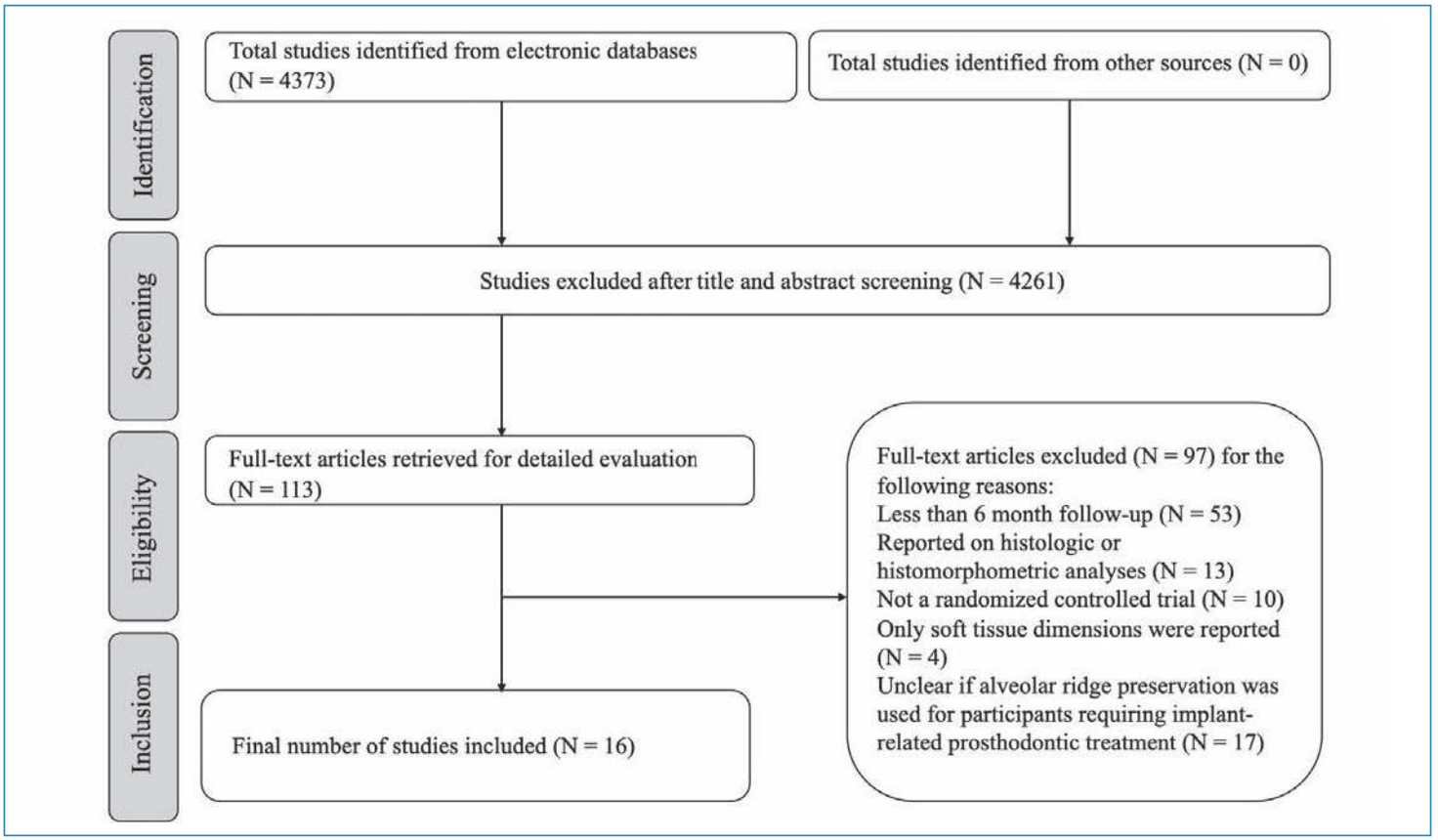

FIG. 1: *Flowchart of the search process.*

TABLE 1 LIST OF THE EXCLUDED STUDIES AND REASONS FOR EXCLUSION

STUDY	REASON FOR EXCLUSION
Abdelhamid, 2016	Unclear whether alveolar ridge preservation was used for participants requiring implant-related prosthodontic treatment
Aimetti, 2009	The study followed up participants for less than 6 months
Aimetti, 2018	Unclear whether alveolar ridge preservation was used for participants requiring implant-related prosthodontic treatment
Alkan, 2013	A histological study
Alkanan, 2019	The study followed up participants for less than 6 months
Al Qabbani, 2018	Unclear whether alveolar ridge preservation was used for participants requiring implant-related prosthodontic treatment
Amirzargar, 2018	Unclear whether alveolar ridge preservation was used for participants requiring implant-related prosthodontic treatment
Araujo, 2015	The study followed up participants for less than 6 months
Arbab, 2016	The study followed up participants for less than 6 months
Areewong, 2019	The study followed up participants for less than 6 months
Bakhshalian, 2018	A histological and histomorphometrical study
Barone, 2013	A histological study
Barone, 2015	A histological and histomorphometrical study
Barone, 2016	The study followed up participants for less than 6 months

(continues)

STUDY	REASON FOR EXCLUSION
Barone, 2017	The study followed up participants for less than 6 months
Borg, 2015	The study followed up participants for less than 6 months
Calasans-Maia, 2014	A histological and histomorphometrical study
Canellas, 2020	The study followed up participants for less than 6 months
Cardaropoli, 2012	The study followed up participants for less than 6 months
Cardaropoli, 2014	The study followed up participants for less than 6 months
Casado, 2010	The study is not a randomized controlled trial
Cavdar, 2017	Unclear whether alveolar ridge preservation was used for participants requiring implant-related prosthodontic treatment
Checchi, 2011	A histological and histomorphometrical study
Clark, 2018	The study followed up participants for less than 6 months
Clementini, 2020	The study followed up participants for less than 6 months
Cook, 2013	The study followed up participants for less than 6 months
Coomes, 2014	The study followed up participants for less than 6 months
Corning, 2019	The study followed up participants for less than 6 months
Crespi, 2009	The study is not a randomized controlled trial
Debel, 2021	The study only reported the soft tissue volumetric changes
Demetter, 2017	The study followed up participants for less than 6 months
Eskow, 2014	The study followed up participants for less than 6 months
Fernandes, 2016	Unclear whether alveolar ridge preservation was used for participants requiring implant-related prosthodontic treatment
Fiorellini, 2005	The study followed up participants for less than 6 months
Flugge, 2015	The study only reported the soft tissue volumetric changes
Fotek, 2009	The study followed up participants for less than 6 months
Froum, 2002	A histological study
Geurs, 2014	A histological and histomorphometrical study
Girish Kumar, 2018	Unclear whether alveolar ridge preservation was used for participants requiring implant-related prosthodontic treatment
Guarnieri, 2017	The study followed up participants for less than 6 months
Hassan, 2017	Unclear whether alveolar ridge preservation was used for participants requiring implant-related prosthodontic treatment
Hauser, 2013	The study followed up participants for less than 6 months
Iasella, 2003	The study followed up some participants for less than 6 months. Some of the data were recorded at 4 months
Jo, 2019	The study followed up participants for less than 6 months
Jonker, 2021	The study followed up participants for less than 6 months
Jung, 2013	Unclear whether alveolar ridge preservation was used for participants requiring implant-related prosthodontic treatment
Jung, 2018	Unclear whether alveolar ridge preservation was used for participants requiring implant-related prosthodontic treatment
Karaca, 2015	Unclear whether alveolar ridge preservation was used for participants requiring implant-related prosthodontic treatment
Kim, 2011	The study is not a randomized controlled trial
Kim, 2014	The study followed up participants for less than 6 months
Kotsakis, 2014	The study followed up participants for less than 6 months
Kutkut, 2012	The study followed up participants for less than 6 months
Lai, 2020	The study followed up participants for less than 6 months
Lee, 2020	Unclear whether alveolar ridge preservation was used for participants requiring implant-related prosthodontic treatment
Lekovic, 1997	The study is not a randomized controlled trial
Lekovic, 1998	The study followed up participants for less than 6 months

(continues)

STUDY	REASON FOR EXCLUSION
Lim, 2017	The study followed up participants for less than 6 months
Lim, 2019	The study followed up participants for less than 6 months
Llanos, 2019	The study followed up participants for less than 6 months
Machtei, 2019	The study followed up participants for less than 6 months
Mandarino, 2018	The study followed up participants for less than 6 months
Marconcini, 2018	The study followed up participants for less than 6 months
Mayer, 2016	The study followed up participants for less than 6 months
Meloni, 2015	The study followed up participants for less than 6 months
Molly, 2008	A histological study
Nart, 2017	The study followed up participants for less than 6 months
Natto, 2017	Unclear whether alveolar ridge preservation was used for participants requiring implant-related prosthodontic treatment
Neiva, 2011	The study is not a randomized controlled trial
Nevins, 2006	The study followed up participants for less than 6 months
Nevins, 2011	A histological and histomorphometrical study
Oghli, 2010	The study followed up participants for less than 6 months
Ouyyamwongs, 2019	The study followed up participants for less than 6 months
Ovcharenko, 2020	The study followed up participants for less than 6 months
Parashis, 2016	The study followed up participants for less than 6 months
Pelegrine, 2010	There were serious doubts if the study was actually a randomized controlled trial and the authors did not answer back and clarified the doubts
Pellegrini, 2014	A histological and histomorphometrical study
Perelman-Karmon, 2012	A histological and histomorphometrical study
Pinho, 2006	The study followed up participants for less than 6 months
Poulias, 2013	The study followed up participants for less than 6 months
Rasperini, 2010	Unclear whether alveolar ridge preservation was used for participants requiring implant-related prosthodontic treatment
Sbordone, 2017	Unclear whether alveolar ridge preservation was used for participants requiring implant-related prosthodontic treatment
Scheyer, 2012	A histological study
Schneider, 2014	The study only reported the soft tissue volumetric changes
Serino, 2003	The study is not a randomized controlled trial
Shakibaie, 2013	The study is not a randomized controlled trial
Shim, 2018	The study is not a randomized controlled trial
Sisti, 2012	The study followed up participants for less than 6 months
Spinato, 2014	The study followed up participants for less than 6 months
Sun, 2019	The study followed up participants for less than 6 months
Temmerman, 2016	Unclear whether alveolar ridge preservation was used for participants requiring implant-related prosthodontic treatment
Thalmair, 2013	The study only reported the soft tissue volumetric changes
Toloue, 2012	The study followed up participants for less than 6 months
Vance, 2004	The study followed up participants for less than 6 months
Walker, 2017	The study followed up participants for less than 6 months
Wood, 2012	The study followed up participants for less than 6 months
Zadeh, 2016	Unclear whether alveolar ridge preservation was used for participants requiring implant-related prosthodontic treatment
Zhao, 2018	The study is not a randomized controlled trial

TABLE 2 CHARACTERISTICS OF THE INCLUDED STUDIES

	Barone et al., 2012	Brkovic et al., 2012	Cha et al., 2011	Fernandes et al., 2011	Festo et al., 2013	Fischer et al., 2018	Gholami et al., 2012	Hoang and Mealey, 2012
Study design	RCT (parallel group)	RCT (parallel group)	RCT (parallel group)	RCT (split-mouth)	RCT (split-mouth)	RCT (parallel group)	RCT (split-mouth)	RCT (parallel group)
Location	Lucca, Italy	Belgrade, Serbia	Seoul, South Korea	Sao Paulo, Brazil	Naples, Italy	Wurzburg, Germany	Tehran, Iran	San Antonio, Texas, USA
Number randomized (participants/ sites)	40/40	20/20	40/42	18/36	15/30	40/40	13/30	40/40
Age (years)	Range: 26 to 69	Mean age 49 ± 15 (test group A); 46 ± 13 (test group B)	Mean age 54.85 ± 8.37 (test group); 51.89 ± 12.08 (control group)	Mean age 44.0 ± 8.10 (33 to 58)	Range: 28 to 58 years	Range: 18 to 80 years	Mean age: 44.6 ± 11.4 (21 to 60)	Mean age 56.1 (29 to 76)
Smoking habits	12 (6 in each group)	4 (test group A) 5 (test group B)	NR	None	None	NR	None	None
Teeth extracted	Anterior and premolars	Canine, premolar, molar areas	Maxillary molar teeth	Maxillary anterior teeth	Premolars	Non-molar teeth	Non-molar teeth	Molars
Comparison	ARP *versus* extraction alone Test group: (n = 20 extraction sockets) xenograft (corticocancellous porcine bone)* and collagen membrane† Control group: (n = 20 extraction sockets) extraction alone	ARP *versus* ARP Test group A: (n = 11 extraction sockets) B-TCP/ C1g‡ Test group B: (n = 9 extraction sockets) B-TCP/ C1g‡ and collagen barrier§	ARP *versus* extraction alone Test group (n = 21 extraction sockets) DBBM with 10% porcine collagenI + collagen barrier§ Control group: (n = 20 extraction sockets) extraction alone	ARP *versus* ARP Test group: (n = 18 extraction sockets) ADM¶ + ABM with synthetic cell-binding peptide P-15# Control group: (n = 18 extraction sockets) ADM¶ only	ARP *versus* extraction alone Test group: (n =15 extraction sockets) corticocancellous porcine bone xenograft** mixed granules with a diameter ranging from 250 to 1000 mm + soft cortical membrane†† Control group: (n =15 extraction sockets) extraction alone	ARP *versus* extraction alone Test group A: (n = 9 extraction sockets) DBBM (500 to 1000 mm particle size)‡‡ + soft tissue punch harvested from the palate Test group B: (n = 8 extraction sockets) DBBM (500 to 1000 mm particle size)‡‡ Test group C: (n = 10 extraction sockets) DBBM (500 to 1000 mm particle size)‡‡ + resorbable collagen membrane§§ Control group: (n = 8 extraction sockets) extraction alone	ARP *versus* ARP Test group (n = 15 extraction sockets) DBBM (small particle size 0.25 mm to 1.0 mm)‖‖ + collagen barrier§ Control group: (n = 15 extraction sockets) nanocrystalline hydroxyapatite (NCHA) + collagen barrier§	ARP *versus* ARP Test group: (n = 15 extraction sockets) demineralized bone matrix, SPS between 125 mm and 710 mm in a carrier of bovine collagen and sodium alginate Control group: (n = 15 extraction sockets) demineralized bone matrix, MPS between 125 mm and 710 mm in a carrier of bovine collagen and sodium alginate + additional particles measuring approximately 2 to 4 mm in length

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	Barone et al., 2012	Brkovic et al., 2012	Cha et al., 2011	Fernandes et al., 2011	Festo et al., 2013	Fischer et al., 2018	Gholami et al., 2012	Hoang and Mealey, 2012
Surgical technique	Primary closure	Flap, primary closure for the (graft and membrane) group	Flapless, no primary closure	Flap, primary closure	Flap, primary closure	Flapless, no primary closure	Flap, primary closure	Flaps were not reflected to obtain primary closure of the wound
Type of socket	Four-wall socket	Four-wall socket	One-, two-, three- and four-wall sockets	All alveolar sockets that had buccal bone defects after extraction	Four-wall socket	Three- and four-wall socket	Four-wall socket	Four-wall socket
Duration of follow-up	Seven months until implant placement + 36 months	Nine months	Six months	Six months	Six months	Six months	Six to eight months (mean 6.9 ± 0.8 months)	Six months
Outcomes	Plaque index, gingival index, bleeding on probing, width and height of alveolar ridge, implant failure, need for additional augmentation prior to implant placement	Width and height of alveolar ridge	Width and height of alveolar ridge	Width and height of alveolar ridge	Width and height of alveolar ridge	Soft tissue volumetric analysis, need for additional augmentation at the time of implant placement	Width and height of alveolar ridge, need for additional augmentation prior to implant placement	Width and height of alveolar ridge
Method of assessment	Periodontal probe, standardized radiographs, template	Periodontal probe Caliper	Panoramic radiograph, computed tomography	Periodontal probe, template	Caliper, template	Operator reported whether additional augmentation was needed	Caliper	Periodontal probe, caliper
Sample size calculation	NR	NR	Reported	Reported	NR	Reported	NR	Reported
	Iorio-Siciliano et al., 2017	**Iorio-Siciliano et al., 2020**	**Madan et al., 2014**	**Pang et al., 2014**	**Patel et al., 2013**	**Santana et al., 2018**	**Scheyer et al., 2016**	**Serrano Mendez et al., 2017**
Study design	RCT (parallel group)	RCT (parallel group)	RCT (split-mouth)	RCT (parallel-group)	RCT (parallel-group)	RCT (parallel group)	RCT (parallel group)	RCT (parallel group)
Location	Naples, Italy	Naples, Italy	Uttar Pradesh, India	Xi'an, China	London, UK	Massachusett, USA	USA and Germany (multicenter study)	Bogota, Colombia
Number randomized (participants/ sites)	20/20	45/45	15/60	30/30	30/30	32/45	40/40	20/20
Age (years)	Mean age 38.2 ± 9.4 (test group); 40.2 ± 12.1 (control group)	Mean age 38.9 ± 10.1 (test group A); 43.6 ± 14.2 (test group B); 38.4 ± 13.2 (control group)	Range: 20 to 45	Range 22 to 47 years	Mean age 37.3 ± 11.4 (20 to 58)	Range: 34 to 52 years	Range: 18 to 70 years	Mean age 44
Smoking habits	None	None	None	None	Three	None	None	Two
Teeth extracted	Maxillary or Mandibular teeth	Single- and multi-rooted posterior teeth	Non-molar teeth	Non-molar and molar teeth	Non-molar teeth	Single-rooted teeth	Premolar and molar teeth	Non-molar teeth

(continues)

	Iorio-Siciliano et al., 2017	Iorio-Siciliano et al., 2020	Madan et al., 2014	Pang et al., 2014	Patel et al., 2013	Santana et al., 2018	Scheyer et al., 2016	Serrano Mendez et al., 2017
Comparison	ARP *versus* extraction alone Test group: (n = 10 extraction sockets) DBBM with 10% porcine collagen‖ + collagen barrier§ Control group: (n = 10 extraction sockets) extraction alone	ARP *versus* ARP *versus* extraction alone Test group A: (n = 12 extraction sockets) DBBM with 10% porcine collagen‖ Test group B: (n = 13 extraction sockets) DBBM‖‖ + resorbable collagen membrane§ Control group: (n = 15 extraction sockets) extraction alone	ARP *versus* extraction alone Test group (n = 30 extraction sockets) resorbable polylactide and polyglycolide (PLA-PGA) sponge¶¶ Control group: (n = 30 extraction sockets) extraction alone	ARP *versus* extraction alone Test group: (n = 15 extraction sockets) DBBM‖‖ + collagen barrier§ Control group: (n = 15 extraction sockets) extraction only	ARP *versus* ARP Test group: (n = 13 extraction sockets) synthetic bone substitute Straumann bone ceramic (SBC) (granule size 400 mm to 1000 mm)## + collagen barrier§ Control group: (n =12 extraction sockets) DBBM‖‖ + collagen barrier§	ARP *versus* ARP Test group A: (n = 13 extraction sockets) mineralized ground cancellous human allograft‴ + synthetic polymeric polyethylene glycol (PEG) barrier membrane## Test group B: (n = 14 extraction sockets) DBBM‖‖ + PEG barrier membrane## Test group C: (n = 14 extraction sockets) PEG barrier membrane## (not included in the analysis)	ARP *versus* ARP Test group A (n = 21 extraction sockets) demineralized allograft††† + cross-linked bovine collagen membrane‡‡‡ Test group B: (n = 19 extraction sockets) DBBM) with 10% porcine collagen‖ + collagen barrier§	ARP *versus* ARP Test group A: (n = 10 extraction sockets) DFDB (600 to 800 mm)§§§ + Collagen barrier§ Test group B: (n = 10 extraction sockets) DBBM with 10% porcine collagen‖ + collagen barrier§
Surgical technique	Flap, no primary closure	Flap, no primary closure	Flapless, no primary closure	Flap, primary closure	Flap, no primary closure	Flap, primary closure	Flap, no primary closure	Flap, primary closure
Type of socket	Four-wall socket	Four-wall socket	Four-wall socket	Four-wall socket	Four-wall socket	Four-wall socket	Three-wall socket	Four-wall socket
Duration of follow-up	Six months	Six months	Six months	Six months	Twelve months	Six months	Six months	Six months
Outcomes	Width and height of alveolar ridge	Width and height of alveolar ridge, thickness of buccal wall	Width and height of alveolar ridge, histologic analyses	Width and height of alveolar ridge, implant stability measurements	Width and height of alveolar ridge, probing pocket depth, gingival recession, implant survival, need for additional augmentation prior to implant placement	Width and height of alveolar ridge, histologic analysis	Width and height of alveolar ridge, soft tissue inflammation, histomorphometric analysis	Width and height of alveolar ridge, histomorphometric analysis

(continues)

	Iorio-Siciliano et al., 2017	Iorio-Siciliano et al., 2020	Madan et al., 2014	Pang et al., 2014	Patel et al., 2013	Santana et al., 2018	Scheyer et al., 2016	Serrano Mendez et al., 2017
Method of assessment	Periodontal probe, caliper	Periodontal probe, caliper	Periodontal probe, computed tomography, template	Computed tomography	Periodontal probe, standardized radiograph	Periodontal probe, caliper, template	Periodontal probe, template	Periodontal probe, caliper, standardised radiograph, template
Sample size calculation	NR	Reported	NR	NR	Reported	NR	Reported	Reported

RCT: randomized controlled trial; ARP: alveolar ridge preservation; B-TCP/C1g: beta-tricalcium phosphate with type 1 collagen; DBBM: deproteinized bovine bone mineral; ADM: acellular dermal matrix; ABM: anorganic bovine bone matrix; SPS: single particle size; MPS: multiple particle size; DFDFBA: demineralized freeze-dried cortical bone allograft; NR: not reported

˙mp3, Osteobiol, Coazze, Italy

†Evolution, Osteobiol, Coazze, Italy

‡Septodent, Saint-Maur-des-Fosses, France

§Bio-Gide, Geistlich Pharma AG, Wolhusen, Switzerland

‖Bio-Oss Collagen, Geistlich Pharma AG, Wolhusen, Switzerland

¶AlloDerm, LifeCell Corporation, The Woodlands, Texas, USA

#PepGen P-15, DENTSPLY Friadent CeraMed, Lakewood, Colorado, USA

¨Gen-Os, Osteobiol, Coazze, Italy

††Lamina, Osteobiol, Coazze, Italy

‡‡Endobon, Zimmer Biomet, West Palm Beach, Florida, USA

§§OsseoGuard, Zimmer Biomet, West Palm Beach, Florida, USA

‖‖Bio-Oss, Geistlich Pharma AG, Wolhusen, Switzerland

¶¶Fisiograft, Ghimas SpA, Italy

##Straumann AG, Basel, Switzerland,

¨¨AlloGraft, OCAN 250-1000 microns; Straumann AG, Basel, Switzerland

†††OraGraft DGC, LifeNet Health Inc, Virginia Beach, Virginia, USA

‡‡‡BioMend Extend, Zimmer Dental Inc, Carlsbad, California, USA

§§§Banco de Tejidos Cosme y Damian, Bogota, Colombia

Characteristics of participants at baseline

Inclusion criteria:

- Age ≥18 years of age[115,117,119-121,123,124,127,128,130]. In one trial, an age range of 20 and 55 was specified[116];
- ≥20 teeth in both maxillary and mandibular arches[118];
- Extraction of non-molars and subsequent single-tooth implant treatment[115,116,118-121,125-128,130];
- Extraction of one or more maxillary or mandibular molars and subsequent single-tooth implant treatment[116,117,122];
- Extraction of maxillary or mandibular non-molars and molars with subsequent implant treatment[123,124];
- Extraction of premolars or molars with subsequent implant treatment[129];
- Radiographic bone height of 4 to 8 mm at the site intended for surgery[117];
- Radiographic bone height of ≥7 mm at the site intended for surgery[125];
- Full-mouth plaque and bleeding scores of less than 25%[123,124];
- Presence of at least 2 mm of keratinised tissue[123,124];
- Being in good general health[116,117,120,125,126].

Exclusion criteria:

- Patients with acute periapical or periodontal infections[116,118,120,121,124 126]. Acute endodontic lesion in the test tooth or in the neighbouring areas[127]. Teeth with small apical lesions ≤3 mm were not excluded if it was determined that the lesion could be adequately debrided after extraction[122];

- Inability to maintain adequate oral hygiene[116]. Full- mouth plaque level of more than 30%[127,130]. Periodontally compromised teeth[124]. Untreated periodontal disease[120];
- Third molars[124];
- Loss of buccal bone at the time of extraction[129,130];
- Any medical condition that contraindicated surgery[117,123,124,128];
- Compromised health that could affect the ability of the participants' tissues to heal[115,116,118,119,121,122,127,129,130]. Immunosuppressive systemic diseases[128];
- History of malignancy, radiotherapy, or chemotherapy[117,120,129];
- Pathologic condition of the maxillary sinus such as active sinusitis or cysts[117];
- Use of medications that compromise healing[126,129]. Use of intravenous bisphosphonates[120,129].
- Long-term antibiotic therapy or the need for antibiotic prophylaxis[118];
- Allergy to medications, grafting materials, or membranes used in the study[115,121,129];
- Pregnancy or lactation[116-120,122-124,126,127,129,130];
- Occlusal considerations: lack of opposing occluding dentition in the area intended for extraction[115], absence of one or two of the adjacent teeth[115,117,119,127,129,130], suitable occlusion for the planned prosthodontic treatment[116], extensive parafunctional habits or bruxism[127];
- Smoking habits: smokers[116,119,123,124,126,128,129]. Smoking more than 10 cigarettes per day[115,120,127,130]. Smoking more than 20 cigarettes[117].

Characteristics of outcome measures

Primary outcome measures:

- Changes in the bucco-lingual/palatal width of the alveolar ridge were reported in 14 trials[115-119,121-124,126-130];
- Changes in vertical height of the alveolar ridge were reported in 14 trials[115-119,122-130];
- Complications were reported in five trials[116,117,119,127,129]. The adverse events ranged from pain and swelling[119,127], moderate glazing, redness and oedema[129], partial loss of grafting material[127], membrane exposure[127], fibrous adhesion[116] to delayed healing with partial exposure of buccal plate[117]. Eleven trials reported that the procedure was uneventful[115,118,120-126,128,130];
- Need for additional augmentation prior to implant placement was reported in seven tria ls[115,117,120,121,124,127,129];
- Aesthetic outcomes of future prosthodontic rehabilitation were not assessed in any trial;
- Implant failure rate was reported in three trials[115,126,127].

Secondary outcome measures:

- Peri-implant marginal bone level changes were measured in one trial[115] using standardised intraoral radiographs;
- Changes in probing depth (PD) at teeth adjacent to the extraction site were presented in one trial[127];
- Changes in clinical attachment level (CAL) at teeth adjacent to the extraction site were not reported in any trial;
- Complications of prosthodontic rehabilitation were not reported in any trial.

Risk of bias

Four trials were judged to be at high risk of bias overall[115,116,118,124], whereas the remaining trials were judged to be at unclear risk of bias[117,119-123,125-130] (**FIG. 2**, **TABLE 3**). The random sequence generation was judged as adequate in all but three trials[126,128,129] in which the method of randomisation was unclear. In one trial[118] allocation was not concealed, while it was not clear how the allocation was concealed in 13 trials[116,117,119-123,125-130]. Allocation was adequately concealed in two trials[115,124].

It is acknowledged that there is a risk of performance bias as it is not possible to blind the surgeon or the participant to the intervention. Therefore, the assessment of blinding was limited to assessing the blinding of outcome evaluation, which is a more practical way to minimise detection bias in these trials. A blinded outcome assessor recorded the follow-up measurements in four trials[115,120,121,127]. Blinding of assessors was not clear in nine trials[117,119,122,123,125,126,128-130]. The blinding process was not attempted in three trials[116,118,124]. No withdrawals were reported in nine trials[115,116,118,119,123,125,126,129,130]. Withdrawals and exclusions occurred in seven trials[117,120-122,124,127,128].

Effects of interventions

In total, 426 participants with 524 extraction sites were included in the analysis.

Bone grafting versus *extraction*

We found eight trials in this category: seven trials comparing xenografts *versus* extracti on[115,117,119,120,123,124,126] and one trial comparing alloplasts *versus* extraction[125].

Xenografts versus *extraction*

Changes in width and height of alveolar ridge

Meta-analyses of six trials[115,117,119,123,124,126] showed a significant reduction in the bucco-lingual/palatal width (mean difference (MD) -1.18 mm, 95% confidence interval (CI) -1.82 to -0.54; P = 0.0003, I^2 = 82%; 6 studies, 184 participants, 201 extraction sites) (**FIG. 3A**), and height of the

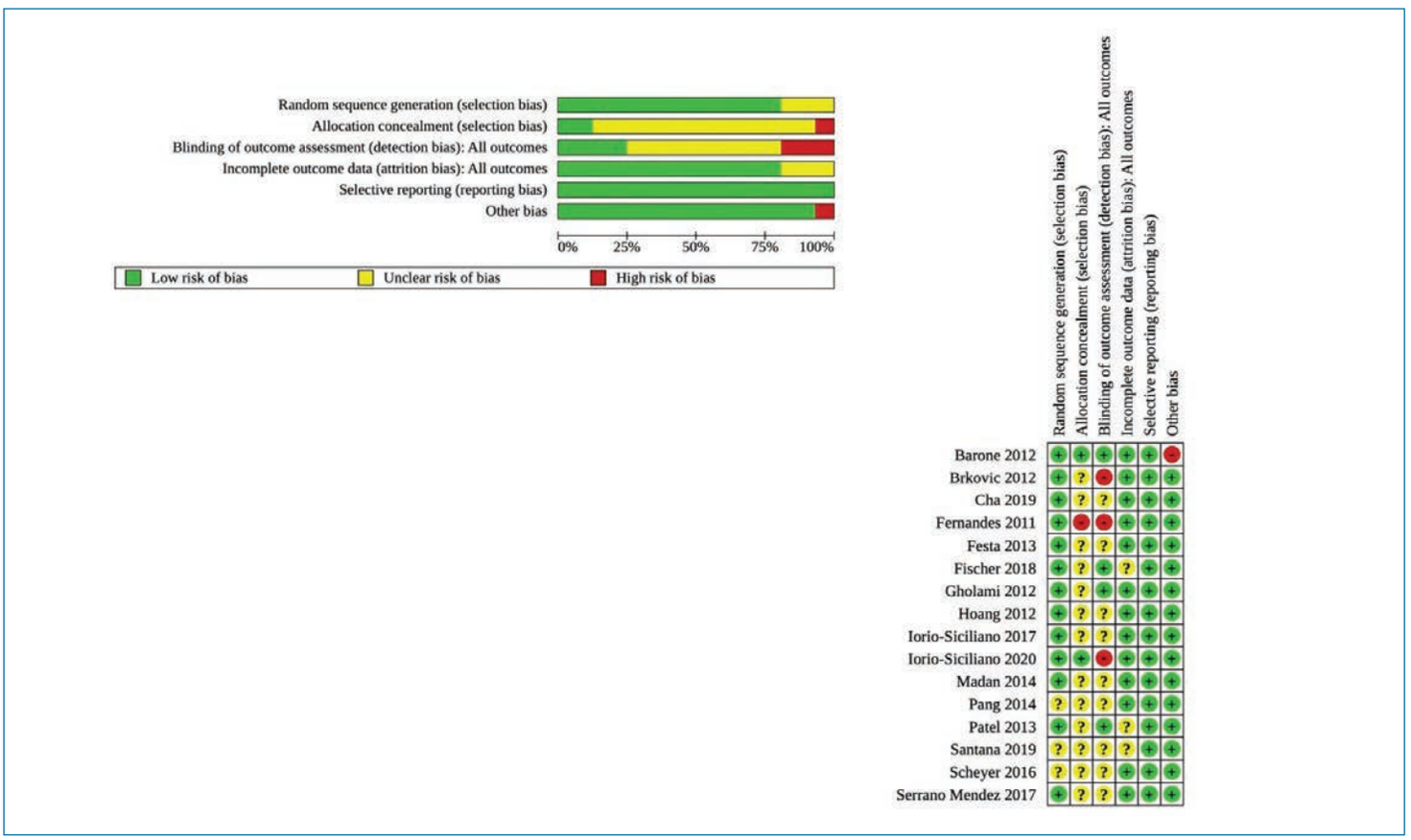


FIG. 2: *Assessment of applicability concerns and risk of bias of the included studies presented with low (green), unclear (yellow) and high (red) risk of bias.*

TABLE 3 ASSESSMENT OF RISK OF BIAS OF THE INCLUDED STUDIES

	Barone et al., 2012	Brkovic et al., 2012	Cha et al., 2019	Fernandes et al., 2011	Festo et al., 2013	Fischer et al., 2018	Gholami et al., 2012	Hoang and Mealey, 2012
Random sequence generation (selection bias)	Low risk *Reported in the article "Extraction sockets were allocated to either a test (graft material) or control (spontaneous healing) group using a computerized random allocation process"*	Low risk *The authors replied that cue cards in sealed envelopes drawn from a jar at the time of acceptance of participant into the study*	Low risk *Reported in the article "using a web-based software"*	Low risk *Reported in the article "The sites for the test and control groups were randomly selected by a coin toss"*	Low risk *Reported in the article "The test and control sites were randomly selected using a coin toss "*	Low risk *Reported in the article "Randomization was performed using a computerized randomization scheme"*	Low risk *Reported in the article "Fifteen symmetrical pairs were randomly selected using a random number table "*	Low risk *Reported in the article "Immediately preceding the start of the surgical procedure, an envelope was drawn from a stack of sealed envelopes with the name of either graft material written inside"*
Allocation concealment (selection bias)	Low risk *Reported in the article "Only one of the investigators (BO), not involved in the selection and treatment of the patients, was aware of the randomization sequence and had access to the randomisation list. The randomized codes were enclosed in sequentially numbered, identical opaque, and sealed envelopes"*	Unclear risk *No information in the article No clarifying reply*	Unclear risk *Insufficient information in the article*	High risk *The authors replied that no allocation concealment was attempted*	Unclear risk *No information in the article and the authors did not provide further information*	Unclear risk *No information in the article*	Unclear risk *No information in the article. In their response, the authors did not provide more details to clarify this issue*	Unclear risk *No information in the article.*
Blinding of outcome assessment (detection bias)	Low risk *All radiographic measurements were taken by one masked examiner*	High risk *Nothing reported in the article, but the authors replied that the nature of the appearance of the wound made it impossible to reliably blind the observer*	Unclear risk *No information in the article*	High risk *The authors replied that examiners were not blinded*	Unclear risk *No information in the article and the authors did not provide further information*	Low risk *Reported in the article "...blinded examiners performed data collection and analysis to avoid bias"*	Low risk *The horizontal ridge width was assessed blindly. The operator was blinded to the treatment groups during surgical re-entry, and the serial longitudinal sections were also coded and analysed by an examiner masked to the type of treatment*	Unclear risk *Histologic examination was conducted by masked examiners but not clear whether clinical parameters were recorded by masked examiners*

(continues)

	Barone et al., 2012	Brkovic et al., 2012	Cha et al., 2019	Fernandes et al., 2011	Festo et al., 2013	Fischer et al., 2018	Gholami et al., 2012	Hoang and Mealey, 2012
Incomplete outcome data (attrition bias)	Low risk *All data presented*	Low risk *All data presented*	Low risk *Number and reasons for withdrawals were reported. It does not seem that the lost data had affected the results. One out of the 40 participants dropped out due to personal reason following tooth extraction*	Low risk *All data presented*	Low risk *All data presented*	Unclear risk *It is not clear whether the number and reasons for withdrawals had affected the results. The trial reported 5 dropouts. Of which, 2 declined implant placement and the remaining 3 were non-compliant with the protocol*	Low risk *Number and reasons for withdrawals were reported. It does not seem that the lost data had affected the results*	Low risk *The study excluded 10 participants. Of which, 9 were non-compliant with the trial protocol and 1 withdrew from the study at the time of surgery due to large buccal and palatal dehiscence after extracting the tooth Dropouts were equal in both groups*
Selective reporting (reporting bias)	Low risk *All outcomes appear to be reported*	Low risk *All outcomes appear to be reported*	Low risk *All outcomes appear to be reported*	Low risk *All outcomes appear to be reported*	Low risk *All outcomes appear to be reported*	Low risk *All outcomes appear to be reported*	Low risk *All outcomes appear to be reported*	Low risk *All outcomes appear to be reported*
Other bias	High risk *The inclusion criteria included non-molar sites while the figures in the article showed an ARP of a molar site*	None detected	None detected	None detected	None detected	None detected	None detected	None detected

	Iorio-Siciliano et al., 2017	Iorio-Siciliano et al., 2020	Madan et al., 2014	Pang et al., 2014	Patel et al., 2013	Santana et al., 2018	Scheyer et al., 2016	Serrano Mendez et al., 2017
Random sequence generation (selection bias)	Low risk *Reported in the article "The fresh alveolar sockets were randomly assigned to the test or control group with the allocation conducted using a commercially available computer software package"*	Low risk *Reported in the article "Randomization procedure was performed by single examiner using a commercially available computer software package"*	Low risk *Reported in the article "Extraction sockets were randomly allocated for test and control groups by the toss of a coin into equal numbers"*	Unclear risk *The method of randomization was not mentioned*	Low risk *Reported in the article "The subjects were randomly assigned to the test or the control group by a computer-generated table. A balanced randomly permuted block approach was used to prepare the randomization tables in order to avoid unequal balance between the two treatments"*	Unclear risk *No information in the article*	Unclear risk *Reported in the article "Subjects were randomly assigned to either the control or test therapy in a block 1:1 ratio"*	Low risk *Reported in the article "A randomization table was created electronically in blocks of two patients"*

(continues)

	Iorio-Siciliano et al., 2017	Iorio-Siciliano et al., 2020	Madan et al., 2014	Pang et al., 2014	Patel et al., 2013	Santana et al., 2018	Scheyer et al., 2016	Serrano Mendez et al., 2017
Allocation concealment (selection bias)	Unclear risk *No information in the article*	Low risk *Reported in the article "Allocation was performed after tooth or root extraction by opening an opaque envelope"*	Unclear risk *No information in the article*	Unclear risk *No information in the article*	Unclear risk *It is not clear whether the randomized codes were enclosed in sequentially numbered, identical, opaque, and sealed envelopes*	Unclear risk *No information in the article*	Unclear risk *No information in the article*	Unclear risk *Insufficient information in the article.*
Blinding of outcome assessment (detection bias)	Unclear risk *No information in the article*	High risk *Reported in the article "The principal investigator and co-investigators were not masked"*	Unclear risk *No information in the article*	Unclear risk *No information in the article*	Low risk *All periodontal and surgical measurements were made by a single, blinded examiner*	Unclear risk *No information in the article*	Unclear risk *No information in the article*	Unclear risk *Reported in the article "The clinical measurements were performed by a different person that was not involved in any other section of the treatments" and "The histological assessments were performed by an operator not involved in any of the other parts"*
Incomplete outcome data (attrition bias)	Low risk *All data presented*	Low risk *Number and reasons for withdrawals were reported. It does not seem that the lost data had affected the results.*	Low risk *All data presented*	Low risk *All data presented*	Unclear risk *It is not clear whether the number and reasons of withdrawals had any impact on the results and how the authors managed the dropouts*	Unclear risk *Four sites were excluded but authors did not fully clarify all the reasons for dropouts apart from some inadequate sampling for histological evaluation*	Low risk *All data presented*	Low risk *All data presented*
Selective reporting (reporting bias)	Low risk *All outcomes appear to be reported*	Low risk *All outcomes appear to be reported*	Low risk *All outcomes appear to be reported*	Low risk *All outcomes appear to be reported*	Low risk *All outcomes appear to be reported*	Low risk *All outcomes appear to be reported*	Low risk *All outcomes appear to be reported*	Low risk *All outcomes appear to be reported*
Other bias	None detected	None detected	None detected	None detected	None detected	None detected	None detected	None detected

ARP: alveolar ridge preservation

alveolar ridge (MD -1.35 mm, 95% CI -2.00 to -0.70; P < 0.0001, I2 = 87%; 6 studies, 184 participants, 201 extraction sites) (**FIG. 3B**). Both meta-analyses indicated a significant benefit for ARP using xenografts.

Complications

In one trial[117] delayed healing with partial exposure of the buccal plate at suture removal was reported by one participant in the test group. Another trial[119] reported postoperative pain and swelling without specifying the number of participants showing those symptoms.

Five trials[115,120,123,124,126] reported that the procedure was uneventful.

Need for additional augmentation prior to implant placement

A meta-analysis of four trials[115,117,120,124] showed no evidence of a significant difference that ARP with xenograft reduced the need for additional augmentation (risk ratio (RR) 0.68, 95% CI 0.29 to 1.62; P = 0.39; 4 studies, 154 participants, 156 extraction sites) (**FIG. 3C**).

Implant failure rate

One trial[115] found no evidence of a difference between the use of xenograft and extraction. Two implants failed, one in each group: one implant was not osseointegrated six months post-placement at the time of abutment connection, another implant failed and was removed as a result of mobility after 24 months of loading. Another trial[126] reported no implant failures after one-year follow-up (**FIG. 3D**).

Peri-implant marginal bone level changes

The data in relation to peri-implant marginal bone level changes were obtained from the results after seven months[115]. There were no statistically significant differences between the two groups for the marginal bone changes (**FIG. 3E**).

Other outcomes

None of the studies comparing xenografts with extraction reported on aesthetic outcomes of future prosthodontic rehabilitation, changes in probing depth (PD) and changes in clinical attachment level (CAL) at teeth adjacent to the extraction site, or prosthodontic outcomes of rehabilitation.

Alloplasts versus *extraction*

Changes in width and height of alveolar ridge

One trial[125] of split-mouth design compared resorbable polylactide and polyglycolide (PLA-PGA) sponge (Fisiograft, Ghimas SpA, Italy) with extraction alone. The study evaluated 60 non-molar extraction sites in 15 participants at six months. No dropouts were reported. After six months, statistically significant differences were detected for ridge height in favour of ARP (**FIG. 3F**).

Complications

Madan and colleagues[125] reported that the procedure was uneventful.

Other outcomes

No other primary or secondary outcomes were reported by the only trial included comparing alloplasts *versus* extraction.

Different grafting materials

We found eight trials in this category: three trials comparing allograft *versus* xenograft[128-130], two trials comparing alloplast *versus* xenograft[121,127], one trial comparing alloplast with and without membrane[116], one trial comparing allograft with and without synthetic cell-binding peptide P-15[118], and one trial comparing alloplast with different particle sizes[122].

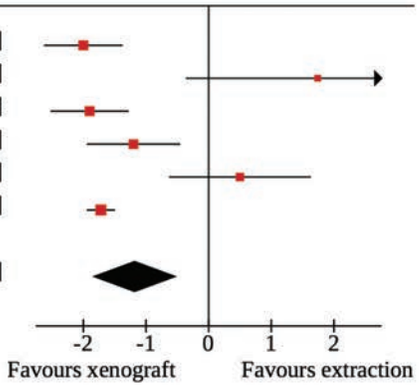
Allografts versus *xenografts*

Changes in width and height of alveolar ridge

Meta-analyses of three trials[128-130] showed no significant differences between the two groups with regard to bucco-lingual/palatal width (MD -0.40 mm, 95% CI -1.13 to 0.34; P = 0.29, I^2 = 82%; 3 studies, 87 participants, 87 extraction sites; **FIG. 4A**), and height of the alveolar ridge (MD -0.45 mm, 95% CI -1.48 to 0.58; P = 0.39, I^2 = 56%; 2 studies, 60 participants, 60 extraction sites; **FIG. 4B**).

Study or Subgroup	MD	SE	Xenograft Total	Extraction Total	Weight	Mean Difference IV, Random, 95% CI
Barone 2012	-2	0.32	20	20	19.3%	-2.00 [-2.63 , -1.37]
Cha 2019	1.74	1.0733	21	20	6.7%	1.74 [-0.36 , 3.84]
Festa 2013 (1)	-1.9	0.318	15	15	19.4%	-1.90 [-2.52 , -1.28]
Iorio-Siciliano 2017	-1.2	0.3808	10	10	17.9%	-1.20 [-1.95 , -0.45]
Iorio-Siciliano 2020	0.5	0.5779	25	15	13.6%	0.50 [-0.63 , 1.63]
Pang 2014	-1.72	0.1157	15	15	23.0%	-1.72 [-1.95 , -1.49]
Total (95% CI)			**106**	**95**	**100.0%**	**-1.18 [-1.82 , -0.54]**

Heterogeneity: Tau² = 0.45; Chi² = 27.38, df = 5 (P < 0.0001); I² = 82%
Test for overall effect: Z = 3.62 (P = 0.0003)
Test for subgroup differences: Not applicable

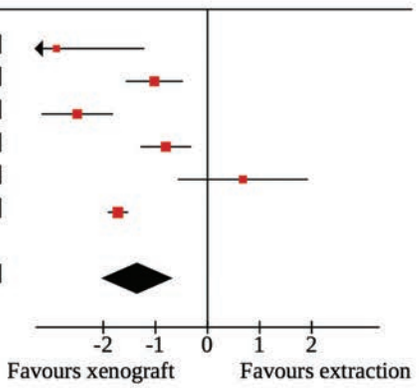


Footnotes
(1) For split-mouth trials the number of participants is double-counted.

3A

Study or Subgroup	MD	SE	Xenograft Total	Extraction Total	Weight	Mean Difference IV, Random, 95% CI
Barone 2012	-2.9	0.86	20	20	8.9%	-2.90 [-4.59 , -1.21]
Cha 2019	-1.02	0.2794	21	20	19.3%	-1.02 [-1.57 , -0.47]
Festa 2013 (1)	-2.5	0.35	15	15	17.9%	-2.50 [-3.19 , -1.81]
Iorio-Siciliano 2017	-0.8	0.25	10	10	19.8%	-0.80 [-1.29 , -0.31]
Iorio-Siciliano 2020	0.68	0.6364	25	15	12.2%	0.68 [-0.57 , 1.93]
Pang 2014	-1.72	0.0989	15	15	21.9%	-1.72 [-1.91 , -1.53]
Total (95% CI)			**106**	**95**	**100.0%**	**-1.35 [-2.00 , -0.70]**

Heterogeneity: Tau² = 0.49; Chi² = 37.61, df = 5 (P < 0.00001); I² = 87%
Test for overall effect: Z = 4.09 (P < 0.0001)
Test for subgroup differences: Not applicable

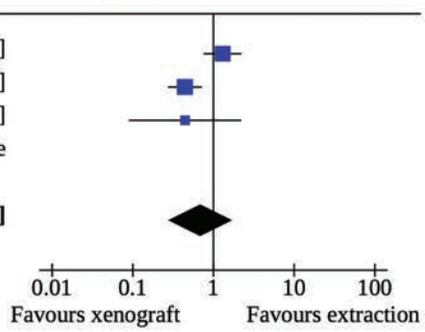


Footnotes
(1) For split-mouth trials, the number of participants is double-counted.

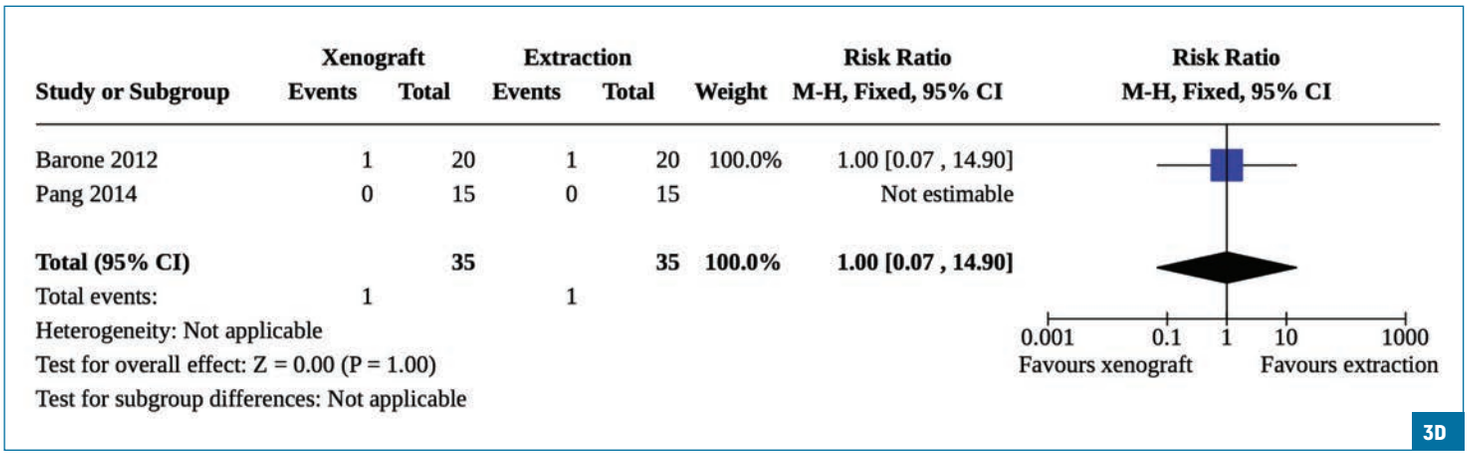
3B

Study or Subgroup	Xenograft Events	Xenograft Total	Extraction Events	Extraction Total	Weight	Risk Ratio M-H, Random, 95% CI
Barone 2012	13	20	10	20	40.3%	1.30 [0.75 , 2.24]
Cha 2019	9	21	20	20	41.7%	0.44 [0.27 , 0.72]
Fischer 2018	3	27	2	8	18.0%	0.44 [0.09 , 2.21]
Iorio-Siciliano 2020	0	25	0	15		Not estimable
Total (95% CI)		**93**		**63**	**100.0%**	**0.68 [0.29 , 1.62]**
Total events:	25		32			

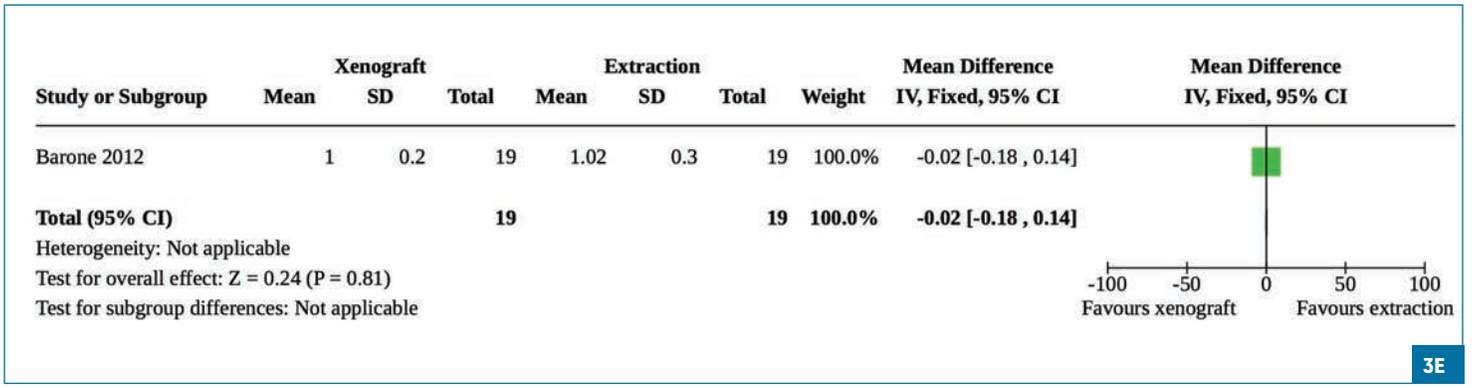
Heterogeneity: Tau² = 0.41; Chi² = 8.74, df = 2 (P = 0.01); I² = 77%
Test for overall effect: Z = 0.86 (P = 0.39)
Test for subgroup differences: Not applicable



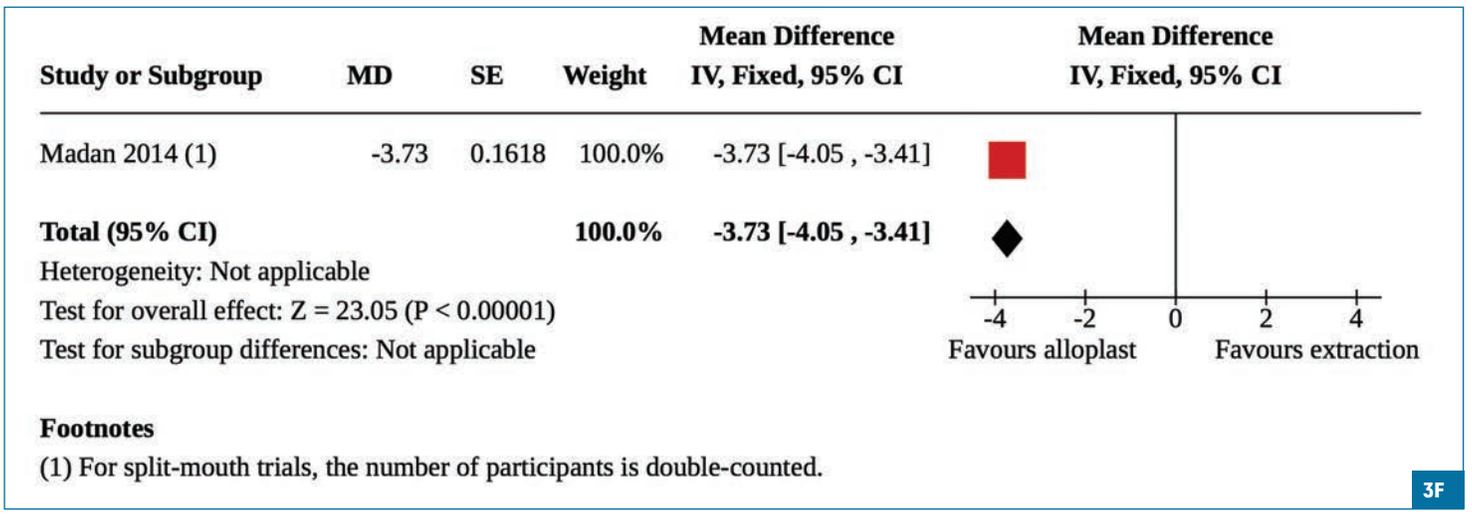
3C



3D



3E



3F

FIGS. 3A-F: *Comparison: alveolar ridge preservation (ARP)* versus *extraction alone*
Outcomes: xenograft versus *extraction alone: changes in width of alveolar ridge (mm) (A); xenograft* versus *extraction alone: changes in height of alveolar ridge (mm) (B); xenograft* versus *extraction alone: need for additional augmentation prior to implant placement (C); xenograft* versus *extraction alone: implant failures (D); xenograft* versus *extraction alone: peri-implant marginal bone level changes (E); alloplast* versus *extraction alone: changes in height of alveolar ridge (mm) (F).*
SE: standard error; IV: inverse variance; CI: confidence interval; τ: Kendall tau; z: z test

Complications

One trial[129] reported moderate glazing, redness and oedema, while two trials[128,130] reported there were no adverse events.

Need for additional augmentation prior to implant placement

Only one trial[129] reported that additional bone augmentation procedure was required for three sites in the allograft group, while none of the sites in the xenograft required additional augmentation procedure before implant placement. No statistically significant difference was shown between the two groups (RR 6.36, 95% CI 0.35 to 115.73; P = 0.21; 1 study, 40 participants, 40 extraction sites; **FIG. 4C**).

Other outcomes

None of the trials under this comparison reported on aesthetic outcomes of future prosthodontic rehabilitation, implant failure rate, peri-implant marginal bone level changes, changes in probing depth and changes in clinical attachment level at teeth adjacent to the extraction site, or prosthodontic outcomes of rehabilitation.

Alloplasts versus *xenografts*

Changes in width and height of alveolar ridge

Meta-analysis of two studies[121,127] showed that there were no statistically significant differences for changes in width and height of the alveolar ridge, with mean differences of -0.31 mm (95% CI -0.66 to 0.04; P = 0.08, I2 = 73%; 2 studies, 37 participants, 55 extraction sites; **FIG. 4D**) and -0.60 mm (95% CI -1.27 to 0.07; P = 0.08; 1 study, 25 participants, 25 extraction sites; **FIG. 4E**), respectively.

Complications

One trial[127] reported pain, swelling, membrane exposure, and partial loss of grafting material, while the other trial[121] reported that the procedure was uneventful.

Need for additional augmentation prior to implant placement

The meta-analysis included two trials[121,127] and showed no evidence of a difference (RR 1.09, 95% CI 0.65 to 1.83; P = 0.75, I^2 = 0%; 2 studies, 37 participants, 55 extraction sites; **FIG. 4F**).

Implant failure rate

One trial[127] reported that none of the implants failed after 12 months of loading (**FIG. 4G**).

Changes in probing depths (PD) at teeth adjacent to the extraction site

Meta-analyses showed no differences in PDs at the neighbouring teeth between the test groups. Only one trial[127] reported the changes in PD at teeth adjacent to the extraction sites (MD -0.30 mm, 95% CI -0.61 to 0.01; P = 0.06; 1 study, 25 participants, 25 extraction sites; **FIG. 4H**).

Other outcomes

None of the included studies reported on aesthetic outcomes of future prosthodontic rehabilitation, peri-implant marginal bone level changes, changes in CAL at teeth adjacent to the extraction site, and prosthodontic outcomes of rehabilitation.

Alloplasts with and without membrane

Changes in width and height of alveolar ridge

One trial[116] of parallel-group design compared beta-tricalcium phosphate with type I collagen (β-TCP/C1g) (Septodont, Saint-Maur-des-Foses, France) *versus* β-TCP/C1g and barrier membrane (Bio-Gide, Geistlich Pharma AG, Wolhusen, Switzerland). Twenty participants enrolled in this study with each participant contributing to either non-molar or molar extraction site. All the sites healed uneventfully with no signs of inflammation. Significant reductions in the alveolar ridge height and width and height in the non-membrane group were observed (**FIGS. 4I, 4J**).

Complications

Fibrous adhesions at the cervical part of previously preserved sockets were observed in two participants[116].

Other outcomes

None of the trials reported on any other primary or secondary outcomes of this review.

Allografts with and without synthetic cell-binding peptide P-15

Changes in width and height of alveolar ridge

One trial[118] of split-mouth design compared acellular dermal matrix (ADM) (AlloDerm, LifeCell Corporation, The Woodlands, Texas, USA), anorganic bovine bone matrix (ABM) with synthetic cell-binding peptide P-15 (PepGen P-15, Dentsply Friadent CeraMed, Lakewood, Colorado, USA) *versus* ADM only. A total of 18 participants (36 maxillary anterior extraction sockets) completed the study with no postoperative complications. A reduction in alveolar ridge width in the allograft with synthetic cell- binding peptide P-15 group was observed, however, no statistically significant differences were found between the two groups in terms of ridge height (**FIGS. 4K, 4L**).

Complications

Fernandes and colleagues[118] reported that the procedure was uneventful.

Other outcomes

Fernandes and colleagues[118] did not report on any other primary or secondary outcomes of this review.

Alloplasts with different particle sizes

Changes in width and height of alveolar ridge

One trial[122] of parallel-group design including 30 participants (30 extractions sites) compared demineralised bone matrix, single particle size (SPS) between 125 μm and 710 μm in a carrier of bovine collagen and sodium alginate *versus* demineralised bone matrix multiple particle size (MPS) between 125 μm and 710 μm in a carrier of bovine collagen and sodium alginate. No statistically significant differences were found between the two groups in terms of ridge width and height (**FIGS. 4M, 4N**).

Complications

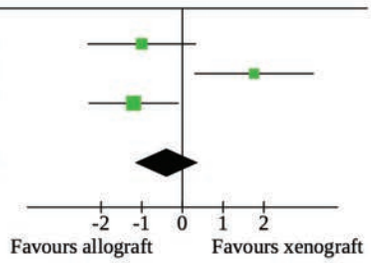
Hoang and Mealey[122] reported that the procedure was uneventful.

Other outcomes

Hoang and Mealey[122] did not report on any other primary or secondary outcomes of this review.

Study or Subgroup	Allograft Mean	SD	Total	Xenograft Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Santana 2019	1.5	1.9	13	2.5	1.6	14	30.5%	-1.00 [-2.33 , 0.33]
Scheyer 2016	-4.95	2.65	21	-6.71	2.07	19	25.1%	1.76 [0.29 , 3.23]
Serrano Mendez 2017	1.4	1.1	10	2.6	1.4	10	44.4%	-1.20 [-2.30 , -0.10]
Total (95% CI)			**44**			**43**	**100.0%**	**-0.40 [-1.13 , 0.34]**

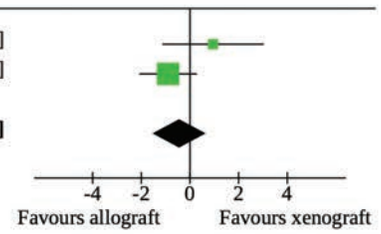
Heterogeneity: Chi² = 11.13, df = 2 (P = 0.004); I² = 82%
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable



4A

Study or Subgroup	Allograft Mean	SD	Total	Xenograft Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Scheyer 2016	-5.29	3.73	21	-6.24	2.98	19	24.4%	0.95 [-1.13 , 3.03]
Serrano Mendez 2017	-0.5	1.4	10	0.4	1.3	10	75.6%	-0.90 [-2.08 , 0.28]
Total (95% CI)			**31**			**29**	**100.0%**	**-0.45 [-1.48 , 0.58]**

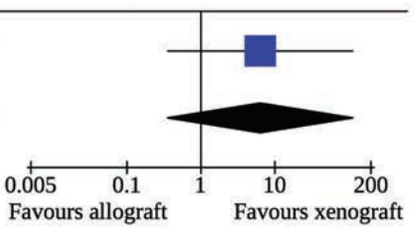
Heterogeneity: Chi² = 2.29, df = 1 (P = 0.13); I² = 56%
Test for overall effect: Z = 0.85 (P = 0.39)
Test for subgroup differences: Not applicable



4B

Study or Subgroup	Allograft Events	Total	Xenograft Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Scheyer 2016	3	21	0	19	100.0%	6.36 [0.35 , 115.73]
Total (95% CI)		**21**		**19**	**100.0%**	**6.36 [0.35 , 115.73]**
Total events:	3		0			

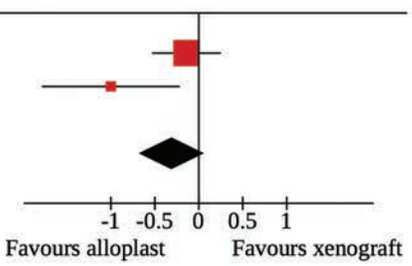
Heterogeneity: Not applicable
Test for overall effect: Z = 1.25 (P = 0.21)
Test for subgroup differences: Not applicable



4C

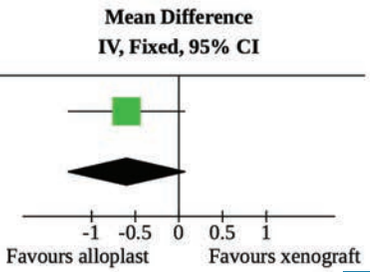
Study or Subgroup	MD	SE	Alloplast Total	Xenograft Total	Weight	Mean Difference IV, Fixed, 95% CI
Gholami 2012 (1)	-0.14	0.2	15	15	80.0%	-0.14 [-0.53 , 0.25]
Patel 2013	-1	0.4	13	12	20.0%	-1.00 [-1.78 , -0.22]
Total (95% CI)			**28**	**27**	**100.0%**	**-0.31 [-0.66 , 0.04]**

Heterogeneity: Chi² = 3.70, df = 1 (P = 0.05); I² = 73%
Test for overall effect: Z = 1.74 (P = 0.08)
Test for subgroup differences: Not applicable



Footnotes
(1) For split-mouth trials the number of participants is double-counted.

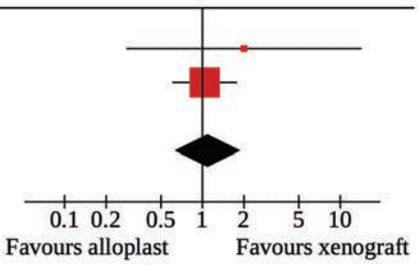
4D



Study or Subgroup	Alloplast Mean	SD	Total	Xenograft Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Patel 2013	-0.4	1	13	0.2	0.7	12	100.0%	-0.60 [-1.27 , 0.07]
Total (95% CI)			**13**			**12**	**100.0%**	**-0.60 [-1.27 , 0.07]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.75 (P = 0.08)
Test for subgroup differences: Not applicable

4E

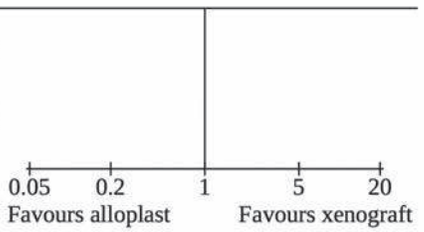


Study or Subgroup	log[RR]	SE	Alloplast Total	Xenograft Total	Weight	Risk Ratio IV, Fixed, 95% CI
Gholami 2012 (1)	0.693	1.002	15	15	7.1%	2.00 [0.28 , 14.25]
Patel 2013	0.037	0.276	13	12	92.9%	1.04 [0.60 , 1.78]
Total (95% CI)			**28**	**27**	**100.0%**	**1.09 [0.65 , 1.83]**

Heterogeneity: Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.75)
Test for subgroup differences: Not applicable

Footnotes
(1) For split-mouth trials the number of participants is double-counted.

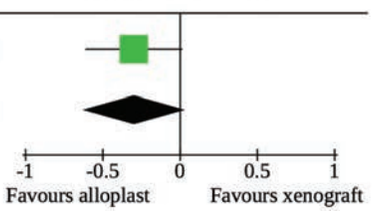
4F



Study or Subgroup	Alloplast Events	Total	Xenograft Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Patel 2013	0	13	0	12		Not estimable
Total (95% CI)		**13**		**12**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

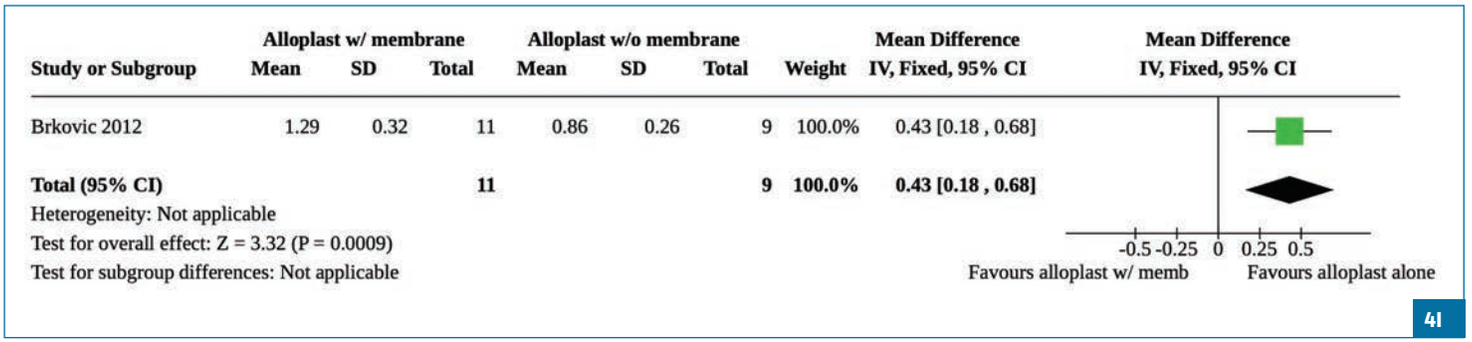
4G



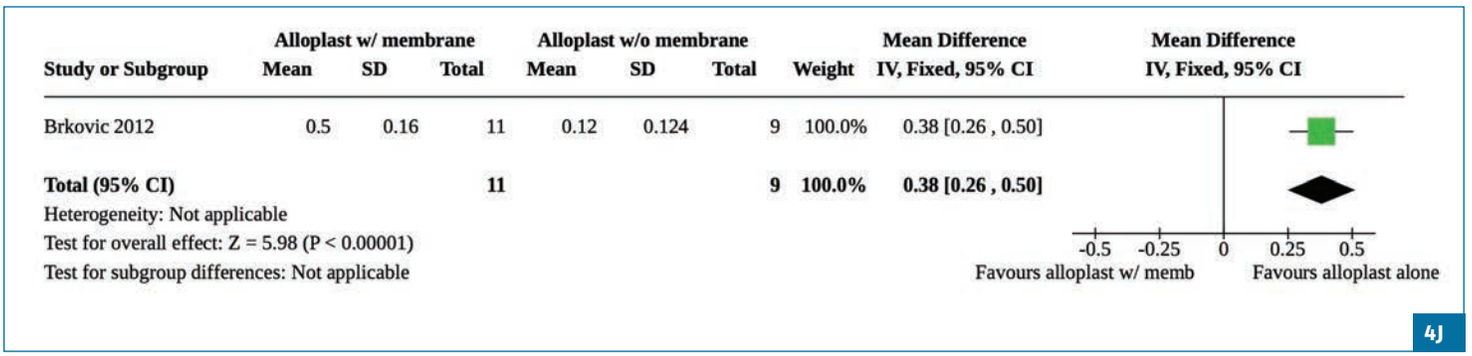
Study or Subgroup	Alloplast Mean	SD	Total	Xenograft Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Patel 2013	0	0.4	13	0.3	0.4	12	100.0%	-0.30 [-0.61 , 0.01]
Total (95% CI)			**13**			**12**	**100.0%**	**-0.30 [-0.61 , 0.01]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.87 (P = 0.06)
Test for subgroup differences: Not applicable

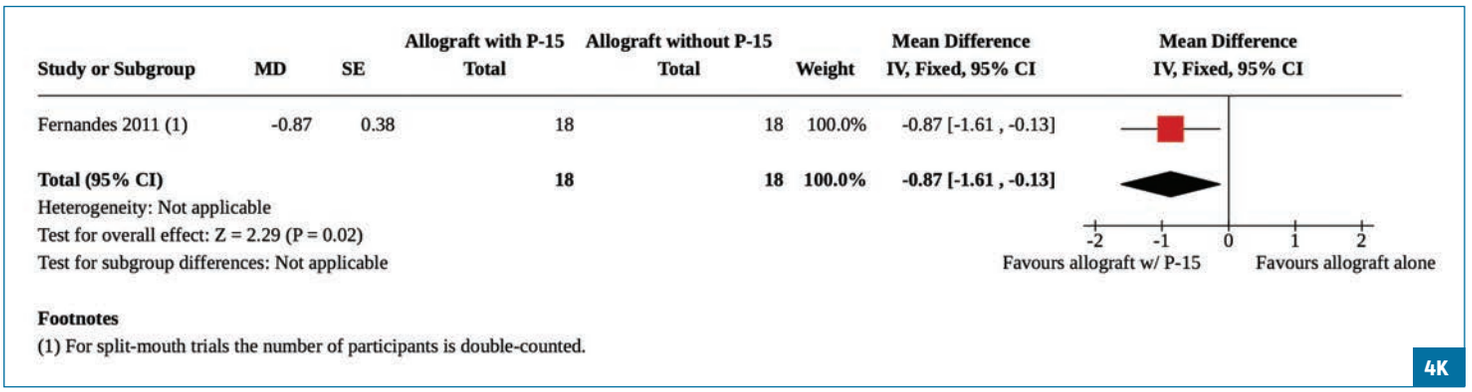
4H


Alloplast w/ membrane
Alloplast w/o membrane
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Brkovic 2012 1.29 0.32 11 0.86 0.26 9 100.0% 0.43 [0.18 , 0.68]
Total (95% CI) 11 9 100.0% 0.43 [0.18 , 0.68]
Heterogeneity: Not applicable
Test for overall effect: Z = 3.32 (P = 0.0009)
Test for subgroup differences: Not applicable
-0.5 -0.25 0 0.25 0.5
Favours alloplast w/ memb
Favours alloplast alone

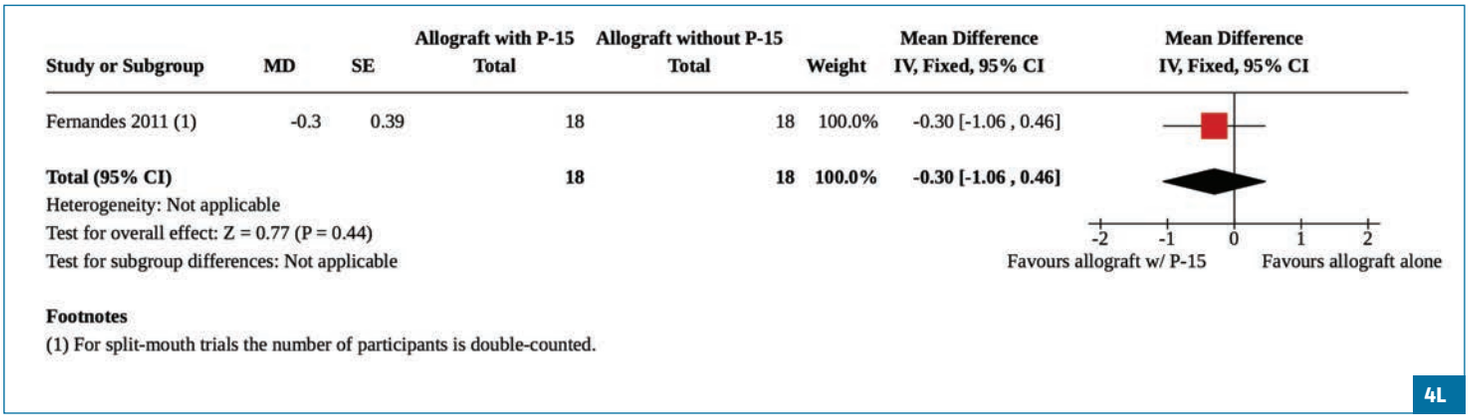
4I


Alloplast w/ membrane
Alloplast w/o membrane
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Brkovic 2012 0.5 0.16 11 0.12 0.124 9 100.0% 0.38 [0.26 , 0.50]
Total (95% CI) 11 9 100.0% 0.38 [0.26 , 0.50]
Heterogeneity: Not applicable
Test for overall effect: Z = 5.98 (P < 0.00001)
Test for subgroup differences: Not applicable
-0.5 -0.25 0 0.25 0.5
Favours alloplast w/ memb
Favours alloplast alone

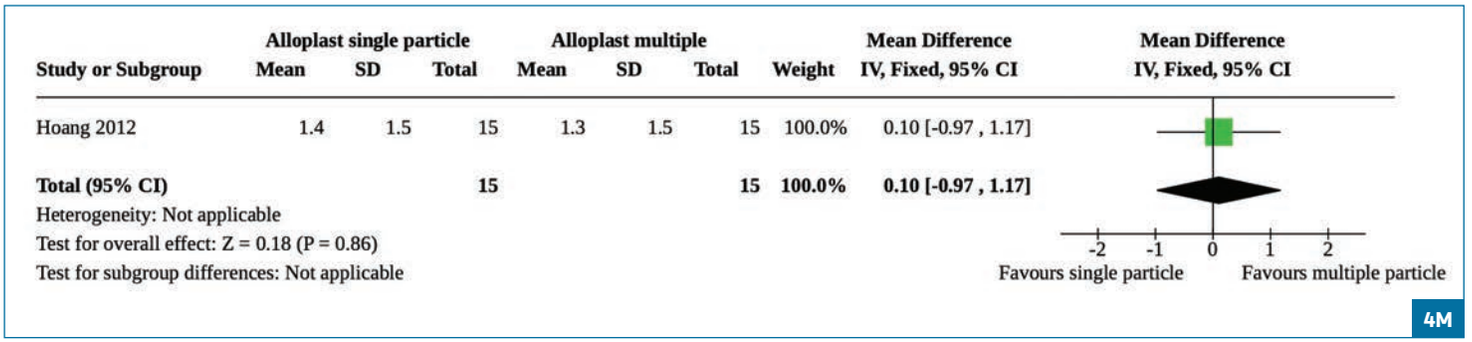
4J

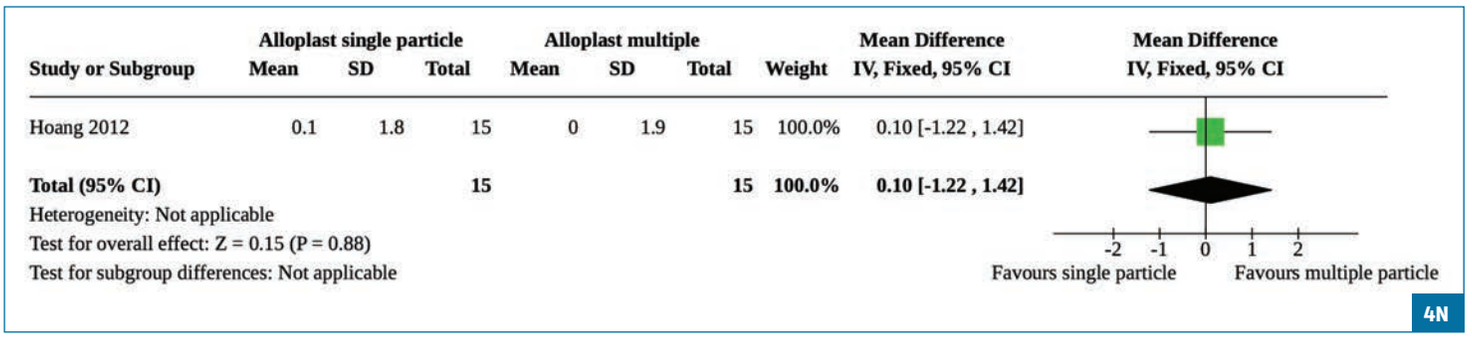

Allograft with P-15
Allograft without P-15
Mean Difference
Mean Difference
Study or Subgroup MD SE Total Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Fernandes 2011 (1) -0.87 0.38 18 18 100.0% -0.87 [-1.61 , -0.13]
Total (95% CI) 18 18 100.0% -0.87 [-1.61 , -0.13]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.29 (P = 0.02)
Test for subgroup differences: Not applicable
-2 -1 0 1 2
Favours allograft w/ P-15
Favours allograft alone
Footnotes
(1) For split-mouth trials the number of participants is double-counted.

4K


Allograft with P-15
Allograft without P-15
Mean Difference
Mean Difference
Study or Subgroup MD SE Total Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Fernandes 2011 (1) -0.3 0.39 18 18 100.0% -0.30 [-1.06 , 0.46]
Total (95% CI) 18 18 100.0% -0.30 [-1.06 , 0.46]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable
-2 -1 0 1 2
Favours allograft w/ P-15
Favours allograft alone
Footnotes
(1) For split-mouth trials the number of participants is double-counted.

4L





FIGS. 4A-N: *Comparison: different grafting materials for alveolar ridge preservation (ARP)*
Outcomes: allograft versus *xenograft: changes in width of alveolar ridge (mm) (A); allograft* versus *xenograft: changes in height of alveolar ridge (mm) (B); allograft* versus *xenograft: need for additional augmentation prior to implant placement (C); alloplast* versus *xenograft: changes in width of alveolar ridge (mm) (D); alloplast* versus *xenograft: changes in height of alveolar ridge (mm) (E); alloplast* versus *xenograft: need for additional augmentation prior to implant placement (F); alloplast* versus *xenograft: implant failures (G); alloplast* versus *xenograft: changes in probing pocket depth at teeth adjacent to the extraction site (mm) (H); alloplast with membrane* versus *alloplast without membrane: changes in width of alveolar ridge (mm) (I); alloplast with membrane* versus *alloplast without membrane: changes in height of alveolar ridge (mm) (J); allograft with P-15* versus *allograft without P-15: changes in width of alveolar ridge (mm) (K); allograft with P-15* versus *allograft without P-15: changes in height of alveolar ridge (mm) (L); alloplast single particles* versus *alloplast multiple particles: changes in width of alveolar ridge (mm) (M); alloplast single particles* versus *alloplast multiple particles: changes in height of alveolar ridge (mm) (N).*
SE: standard error; IV: inverse variance; CI: confidence interval; τ: Kendall tau; z: z test

DISCUSSION

Summary of main results

The question of whether ARP does maintain valuable alveolar ridge bone following extractions is relevant to current "state of the art" recommendations for prosthodontically-driven implant placement, with enhanced aesthetic outcomes. This applies whether delayed or immediate placement techniques are followed and regardless of the loading protocol used. A follow-up period of six months or more was considered suitable in this review to allow for most of the vertical and horizontal resorption of socket walls to occur, in order to provide a better understanding of the role of ARP in implant site development.

Quality of evidence

The certainty of the evidence for ARP interventions when compared with extraction or with another ARP intervention was considered to be very low to low. Four out of 16 trials were judged to be at high risk of bias, largely due to lack of allocation concealment and blinding of outcome assessors. Twelve trials were judged to be at unclear risk of bias. As most of the studies failed to clarify the method of allocation concealment, one may question whether the

participants might have been treated differently if the allocation of the participants was concealed from the operators. In exploring other potential sources of bias, authors were contacted to clarify inclusion criteria which only included non-molar sites, while the figures showed an ARP of molar site[115].

It is acknowledged that all trials were judged to be at high risk of performance bias but blinding of participants and personnel was not considered as one of the main domains for assessing risk of bias in this review as neither participants nor personnel could be blinded to the intervention. However, we considered the blinded assessment of outcomes because having a blinded examiner to assess the outcomes is possible in these trials, particularly when the assessment is based on radiographic or cast analysis in which the examiner can be unaware of the interventions. Moreover, blinding the outcome assessor may eliminate the detection bias as measurements are made on a very narrow scale of millimetres which may have a significant effect on the results. In this context, 12 out of 16 trials were judged to be at unclear or high risk of bias in this domain.

In some instances, the information provided by the publications was not sufficient to reliably assess the quality of the trial. Some corresponding authors provided us with additional information that clarified the trials and allowed us to include them in the present review. This emphasises the importance of clearly reporting the results, including any attempt to conceal the allocation, along with dropouts and the reasons for exclusions, as recommended by CONSORT guidelines.

Applicability of evidence

When ARP was compared to extraction alone, the inclusion of new trials further supported the use of ARP techniques to minimise changes in ridge width and height as well as the need for additional augmentation procedures. When different grafting materials for ARP were compared, new trials were included in a subgroup that compared allografts to xenografts. The variety of grafting materials and the limited number of participants per subgroup analysis did not provide any strong evidence on the use of a specific ARP technique. In addition, the small number of participants increased the risk of overestimation of intervention effects[131].

No sensitivity analysis was attempted due to the small number of included studies. The fact that over 100 trials were initially selected and considered eligible for further scrutinization highlights the growing number of trials in this field of implant dentistry. However, most studies did not meet the selection criteria of this review and therefore further studies with sufficient follow-up period are still needed. The influence of commercial funding and industry support remains an important factor that may increase the number of trials and introduce additional new materials for ARP that would potentially inflate heterogeneity further across the included trials in future reviews.

Agreements and disagreements with other systematic reviews

The present review included all the RCTs available to date. The interaction of many variables and the lack of long-term data mean that it is not possible to determine whether the reduced loss in alveolar ridge height and width achieved by ARP is likely to improve implant treatment outcomes. Several systematic reviews[11-13,15-18,37,132-139] were published on this topic, with almost half published in the last five years. They were not based on the most reliable clinical trials, and pooled different study designs, grafting materials, and therapeutic approaches in one comparison group against extraction alone. Nevertheless, they concluded that ARP may improve bone dimensions compared with extraction alone, but again questioned the long-term effects of ARP on implant success and peri-implant tissues.

Unlike other systematic reviews, Cochrane Reviews adopt stringent methodology in preparing protocols and reviews that go through internal and external thorough reviewing process prior to publication. In the current update of this Cochrane Review, we followed our original protocol by conducting a rigorous search strategy to identify only randomised trials and limiting our comparison groups to one ARP method or technique to minimise heterogeneity amongst included studies. Nevertheless, a small number of studies was analysed in many comparisons with general lack of long-term follow-up of implant outcomes.

There is general agreement that ARP may considerably enhance the site following extraction for future implant placement particularly when xenografts are compared to extraction alone. When different materials are compared in the absence of a control group of extraction alone, it is still premature to conclude which material is superior to others and whether barrier membranes provide any additional benefit.

CONCLUSIONS

ARP techniques may minimise the loss of ridge width and height under ideal conditions in non-molar four-wall sockets, following extraction, but the evidence is very uncertain. There is a general agreement that implants can be placed six months after ARP, following a delayed placement procedure. However, there was no evidence that ARP would improve implant or prosthodontic success. There is also a lack of evidence of any significant differences in the need for additional augmentation at the time of implant placement. There are more trials to suggest that xenografts (one of the most studied materials) showed successful short-term ARP in terms of minimising loss of ridge width and height. However, clinicians should interpret the findings of this review with caution as the certainty of the evidence remains very low to low with all included studies judged to be at unclear or high risk of bias. It is still not clear which ARP technique provides more predictable results. However, there is an indication that the need for primary closure is not warranted.

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