Systematic Review / Meta-analysis

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Efficacy of bone ring grafts for the reconstruction of alveolar ridge deficiencies: a systematic review. Part II: animal trials

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Background: Bone ring (BR) grafts have been introduced to reconstruct alveolar ridge defects with simultaneous implant placement, but their clinical effectiveness remains undetermined. The aim of the current systematic review was to critically appraise evidence from animal studies regarding the effectiveness of BR grafts in alveolar ridge reconstruction and their variations under different surgical protocols.

Methods: Electronic retrieval of six databases (MEDLINE, Embase, Cochrane Library, ScienceDirect, Web of Science, and Scopus) and citation search until 11 October 2023, for animal studies on bone augmentation employing BR grafts. The outcome variables were total bone area (BA), bone volume (BV), bone-implant contact (BIC), and histology. The protocol was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and prospectively registered with PROSPERO (CRD42023453949).

Results: Ten studies were included in the qualitative analysis according to the screening criteria. Two studies demonstrated favorable bone remodeling and osseointegration of the BR with both the implant and pristine bone. A comparative study between autogenous BRs and allogenic BRs reported a higher percentage of BA and BIC at 4 months of healing, but conflicting data were observed at 8 months. Another study indicated a significant advantage of autogenous BRs over bovine and biphasic ceramic BRs in terms of BA and BIC after 5 weeks. Three studies found that using collagen membranes did not significantly affect BA, BV, or BIC when used simultaneously with autogenous BRs during implant placement. Two studies evaluated one-stage and two-stage implant placement in conjunction with BR grafts, revealing similar levels of BA, BV, and BIC except for differences in total treatment time. Furthermore, one study found that the use of mucogingival junction incision and split-thickness flap significantly reduced the incidence of wound dehiscence compared with conventional incision and flap.

Conclusions: Vertical bone augmentation surgery utilizing BR grafts with one-stage implant placement yielded histological and histomorphometric outcomes comparable to those achieved with two-stage implant placement or the additional application of collagen membrane.

Keywords: alveolar ridge reconstruction, animal study, bone augmentation, bone graft, bone ring, systematic review

Introduction

Reconstructing edentulous areas with severe bone deficiencies presents a formidable challenge for implantologists[1]. Various bone augmentation techniques, such as onlay/inlay grafting, distraction osteogenesis, and guided bone regeneration, have been documented in the literature to address inadequate bone dimensions for implant placement[2,3]. Although these procedures have demonstrated favorable outcomes in correcting alveolar ridge defects, a staged implantation approach is typically necessary after primary bone augmentation, thereby prolonging the duration of surgical treatment[4].

Bone ring (BR) graft was initially described by Fukuda *et al*.[5] as a one-staged procedure for vertical augmentation, wherein an

HIGHLIGHTS

- Bone ring (BR) graft is effective in the reconstruction of vertical bone defects, especially when applied to saddle-shaped or wall-contained defects.
- BR grafting with simultaneous implant placement did not achieve histomorphological differences compared with staged implant placement, but the former shortened the overall treatment time.
- Autogenous BRs exhibit optimal bone remodeling properties, but the usage of collagen membrane did not provide significant benefits.

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autogenous ring-shaped bone graft was secured with a simultaneously inserted dental implant. The efficacy of this technique for alveolar ridge reconstruction has been reported in several case reports[6,7] and cohort studies[8,9]. Despite the favorable osteogenic, osteoconductive, and osteoinductive properties of ring-shaped autograft[10], there are apparent drawbacks, including additional surgery, donor-site morbidity, and unpredictable graft resorption[11]. To circumvent these drawbacks, alternative biomaterials, such as allograft, xenograft, and synthetic materials, have been developed and garnered initial approval in specific clinical reports[12,13].

The limited clinical evidence, however, posed challenges in determining whether clinical outcomes were potentially affected by some surgical modalities, such as barrier membrane utilization and timing of implant placement, and whether there was a protocol that more reliably benefited bone area (BA)/volume (BV), and bone-to-implant contact (BIC). In this sense, several clinical studies have yielded pivotal evidence to drive the application and refinement of BR grafts[14,15]; however, scarce systematic reviews have consolidated these findings and offered recommendations for utilizing BRs for alveolar ridge reconstruction surgery in humans[16].

Therefore, a systematic review of the available animal studies regarding BR grafts was conducted with two specific objectives: 1) to appraise the histologic and histomorphometric performance of BR grafts for alveolar ridge reconstruction in animals; 2) to investigate the efficacy of BR grafts under various surgical protocols (e.g. membrane usage, timing of implant placement, and incision and flap design).

Materials and methods

Protocol and registration

The protocol was elaborated and registered in the International Prospective Register of Systematic Reviews (PROSPERO code: CRD42023453949, access to https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023453949). The systematic review was developed and followed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA 2020) statement[17] and Assessing the Methodological quality of Systematic Reviews (AMSTAR 2) guidelines[18].

Focus question and PIOS criteria

The focus question was developed according to the population, intervention, outcome, and study design (PIOS): 'In animals being in need of reconstruction surgery, what is the efficacy of reconstructive procedures employing the BR grafts?'

Population (P): Animals with bone defects requiring reconstruction surgery.

Intervention (I): Reconstruction surgery employing the BR grafts.

Outcomes (O): BA, BIC, BV, and histology.

Study design (S): Animal studies.

Search strategy

The authors conducted a comprehensive search for relevant studies in the MEDLINE, Embase, Cochrane Library (CENTRAL), Web of Science, Scopus, and ScienceDirect databases using the search strategy outlined in Table 1. The databases were searched from their inception until 11 October 2023. Additionally, the authors independently explored the citations of pertinent articles to identify any potentially eligible studies. During the searching phase, GraphPad (https://www.graphpad.com/quickcalcs/kappa1.cfm) was used online to assess the decision homogeneity, yielding satisfying agreement between reviews (Cohen kappa = 0.84).

Selection criteria

The inclusion criteria were as follows: 1) the animals with good general health; 2) assessment and recording of at least one specific outcome variable; 3) studies involving bone reconstruction procedures.

The exclusion criteria were as follows: 1) absence of interested outcomes; 2) published in a language other than English; 3) inappropriate study design (i.e. clinical trial, review, protocol, and conference article).

Data collection

After identifying the initial retrieved publications, two independent reviewers conducted a comprehensive screening process as follows: 1) deleted duplicate studies, 2) read the titles and abstracts, 3) reviewed full texts, and 4) determined eligibility for inclusion.

The included studies provided the following valuable data: author, year of publishing, animals, origins of BR grafts, recipient sites, intervention groups, implant placement, follow-up periods, outcomes, and main findings and conclusions. Then, unmatched information cross-checked and verified to ensure the exclusion of literature that did not meet the predefined selection criteria.

Assessment of risk of bias

The SYstematic Review Center for Laboratory Animal Experimentation (SYRCLE) risk of bias tool, developed based on the Cochrane Collaboration Risk of Bias tool, was utilized to assess the risk of bias in the included animal trials[19]. The tool encompassed six types of bias across 10 domains: selection bias (sequence generation, baseline characteristics, and allocation concealment), performance bias (random housing and blinding), detection bias (random outcome assessment and blinding), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other biases. Two independent authors evaluated these 10 items using a question-based format with response options 'yes', 'no', or 'unclear', which were interpreted as indicating 'low risk of bias', 'high risk of bias', or 'uncertain risk of bias', respectively.

Reporting quality of evidence

The Animal Research: Reporting In Vivo Experiments (ARRIVE) 2.0 checklist was employed to assess the reporting quality of animal studies[20]. The checklist comprised 21 items; each responded as '1' or '0', denoting compliance or noncompliance with the criteria, respectively.

Synthesis of data

Due to the substantial heterogeneity observed among the included studies in terms of study design, surgical protocol, and

Table 1

The search strategy used for each database

Database	Search strategy	Records
MEDLINE	(('bone regeneration'[MeSH Terms] OR ('bone augmentation'[Title/Abstract] OR 'ridge augmentation'[Title/Abstract] OR 'bone graft'[Title/Abstract])) AND ('bone ring'[Title/Abstract] OR 'ring block'[Title/Abstract] OR 'ringbone'[Title/Abstract]))	28
Embase	('bone regeneration'/exp OR 'bone augmentation'/exp OR 'ridge augmentation' OR 'bone graft'/exp OR 'bone graft') AND ('bone ring' OR 'ring block' OR 'ringbone')	40
Web of Science	('bone regeneration' OR 'bone augmentation' OR 'ridge augmentation' OR 'bone graft') AND ('bone ring' OR 'ring block' OR 'ringbone') AND (languages: English)	33
ScienceDirect	('bone regeneration' OR 'bone augmentation' OR 'ridge augmentation' OR 'bone graft') AND ('bone ring' OR 'ring block' OR 'ringbone') AND (Subject area 'Medicine and Dentistry')	71
Cochrane library (CENTRAL)	('bone regeneration' OR 'bone augmentation' OR 'ridge augmentation' OR 'bone graft') AND ('bone ring' OR 'ring block' OR 'ringbone')	6
Scopus	('bone regeneration' OR 'bone augmentation' OR 'ridge augmentation' OR 'bone graft') AND ('bone ring' OR 'ring block' OR 'ringbone') AND (LIMIT-TO (EXACTKEYWORD , 'Animals') OR LIMIT-TO (EXACTKEYWORD , 'Animal'))	28

outcome variables, a descriptive analysis was employed instead of conducting a meta-analysis.

Results

Study selection

The literature search yielded a total of 206 records, while two additional records[21,22] were identified through citation searching. After eliminating 67 duplicates, the titles and abstracts of the remaining papers were scrutinized, leading to the exclusion of another 129 records. Finally, 12 full-texts were assessed for eligibility based on the selection criteria. Among these, two articles[23,24] were excluded due to language restriction and model trial, leaving 10 animal studies[21,22,25–32] eligible for inclusion in this systematic review (Fig. 1).

Study characteristics

Among the included studies, all except for Draenert *et al.*[21]'s study were controlled trials, with the latter being a single-arm cohort study. All studies employed BR grafts with simultaneous implant placement (202 implants) for vertical bone augmentation in animals, while Nakahara *et al.*'s studies[29,30] additionally assessed the impact of staged implant placement (32 implants). Recipient sites were selected in the mandible for eight studies[22,26–32], while one each utilized the iliac bone[25] and tibia[21]. Beagle dogs served as animal models in seven studies[22,26,27,29–32], sheep in two studies[25,28], and rabbits in one study[21]. The type of BRs comprised autografts, allografts, xenografts, and biphasic ceramics, and follow-up periods ranged from one to 12 months.

Risk of bias and reporting quality within studies

Table 2 presents the results of the risk of bias assessment conducted using the SYRCLE tool for the included animal studies. None of the studies fulfilled all requirements, indicating a lack of comprehensive compliance. There is significant uncertainty and high risk associated with allocation concealment, performance bias, and detection bias due to insufficient description in these studies. Considering that the included trials adhered to a prespecified protocol and had minimal risk of baseline characteristics as well as reporting bias.

The reporting quality of the included studies was assessed according to the ARRIVE 2.0 guideline in Table 3, mainly including study design, trial procedures, results statistics, and ethical statements. None of the studies provided valid information regarding randomization, blinding, and protocol registration; however, most of the studies did report other items.

Synthesis of results

In general, a wide variability regarding study design and surgical protocol investigated, as well as parameters reported, was observed in the included studies (Table 4). All studies gave to some extent descriptive aggregate data of their results. Moreover, we transformed specific quantitative findings into means and SD to enhance the interstudy comparison.

In the study conducted by Benlidayi *et al.*[25], a vertical bone augmentation of both 2 mm and 4 mm was designed to compare the differences between autogenous and allogeneic BRs. It was observed that after four months, the 2 mm (BA: 70.85 ± 3.51%, BIC: 75.32 ± 7.10%) and 4 mm groups (BA: 85.63 ± 3.59%, BIC: 95.76 ± 2.97%) of autogenous BRs exhibited higher values compared to the corresponding allogeneic 2 mm (BA: 54.53 ± 2.67%, BIC: 68.97 ± 11.25%) and 4 mm (BA: 66.59 ± 2.63%, BIC: 64.40 ± 4.71%) groups; however, this trend reversed at 8 months. Histologically, more bone marrow spaces in the autogenous BR area and less lamellar bone in contact with the implant were found during the observation period, while allogeneic BR was completely resorbed and replaced with mature lamellar bone.

The series of studies by Haga-Tsujimura *et al.*[26,27] investigated the impacts of a collagen membrane on bone remodeling and osseointegration of implants placed simultaneously with a BR graft at 3, 6, and 12 months. Morphological parameters (total BA) were calculated for regions of interest (ROI) of R1 (from 1 mm high at the shoulder of the implant (IS) to 5 mm below the center of the implant and 4 mm wide from the center of the implant) and R2 (from the bottom of R1 to the tip of the implant), BIC values of the two regions (linear distance from IS to the first BIC (IS-fBIC) and linear distance from the IS to the top of the surrounding bone (IS-TSB). BV values of the two areas [total around BR (V1) and under BR 5 mm (V2)] were also counted, respectively. These parameters evaluated did not exhibit any significant differences between the two groups during the observation period; however, there was a notable increase in BIC values over time for both groups. Histologically, new bone with blood vessels located near the surface of the pristine bone and around the implant was observed in both groups. However,

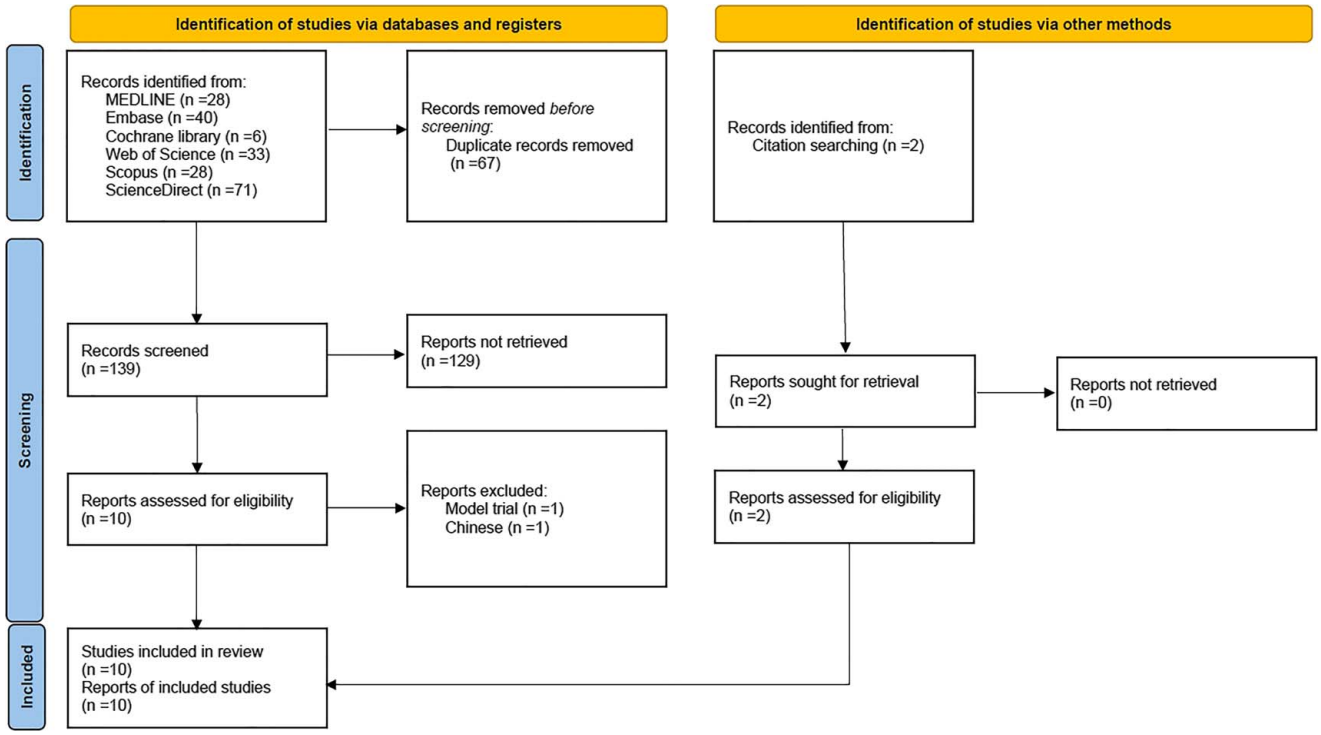

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart of the search process.

especially in the membrane group, there were fragmented loose strands of short, wave-like fibers subsequent to degradation of the collagen membrane.

Jinno *et al.*[28] assessed the disparities in bone remodeling and osseointegration of three types of BR grafts (autograft, bovine, and biphasic bone) within the augmented region of the mandible after five weeks. The results showed that autogenous bone exhibited a significantly higher percentage of BA (62.69%) compared to bovine (7.37%) and biphasic bone (5.58%); however, all three groups displayed notably low rates of BIC without reaching statistical significance. Histologically, the interface between the implant and autogenous BR found evidence of new bone formation and osteoid deposition, whereas no signs of new bone ingrowth were observed within the BR graft or at the interfaces between the implants and the BR grafts in the other two groups. The study conducted by Draenert *et al.*[21] revealed a distinct pattern of new bone ingrowth with most mature mineralization in the marginal bone area forming a mineralization triangle from the local bone surface toward the supracrestal implant surface after 1 month.

The series of studies by Nakahara *et al.*[29,30] compared the bone remodeling and osseointegration performance of implants placed in a single-staged compared to a two-staged procedure using BR grafts. Throughout the observation period, both groups exhibited similar percentages of BA and BIC values in the ROI (aligns with Haga-Tsujimura *et al.*'s labeling method[26,27]). However, the BV of BR was greater in the one-staged than in the two-staged group, reaching the significance at 6 months of the osseointegration period ($P = 0.002$). Histologically, favorable consolidation of the BR with the pristine bone and implant through the ingrowth of blood vessels and new bone was observed in both groups; however, the consolidation process in the two-stage group was more advanced than that in the one-stage group and relatively more lines representing cortical bone remodeling were located within the new bone.

Two studies conducted by Yu *et al.*[22,32] investigated the bone remodeling of autogenous BRs with one-stage implant placement, as well as the impact of different incision designs on preventing wound dehiscence. In the first study[32], a significantly higher BV ratio (91.11 ± 0.02) was observed in the BR group compared to the control group without BR grafting (88.38 ± 2.34), as determined by micro-computed tomography scanning. Histologically, new bone formation was observed at the interface between BR and implant in the BR group. In the second study[22], the incidence of wound dehiscence was significantly lower in the mucogingival junction incision group (16.7%) compared to the alveolar crest incision group (75%). The buccolingual section of micro-CT scanning revealed favorable osseointegration between autogenous BRs and implants in both groups. However, vertical bone loss was higher at wound dehiscence sites, particularly on the buccal side.

Discussion

Summary of evidence

The literature search yielded a total of 10 studies, of which nine were comparative studies, and one was a one-cohort study including 59 animals and 234 implants placed following vertical ridge augmentation.

The findings of the current systematic review demonstrated that: 1) feasibility of BR grafts for vertical augmentation was achieved, albeit utilizing different sources[25,28]; 2) histological and histomorphometric similarity between BR grafts performed

Table 2
The risk of bias through SYRCLE tool

	Selection bias		Performance bias			Detection bias		Attrition bias		Reporting bias	Other
SYRCLE tool for risk of bias	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding	Random outcome assessment	Blinding	Incomplete data outcome		Selective outcome reporting	Other sources of bias
Benlidayi *et al.* 2018[25]	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	HIGH	UNCLEAR		UNCLEAR	LOW
Draenert *et al.* 2012[21]	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	UNCLEAR	LOW		UNCLEAR	UNCLEAR
Haga-Tsujimura *et al.* 2018[26]	UNCLEAR	LOW	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	LOW		LOW	LOW
Haga-Tsujimura *et al.* 2023[27]	UNCLEAR	LOW	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	LOW		LOW	LOW
Jinno *et al.* 2018[28]	LOW	LOW	UNCLEAR	UNCLEAR	HIGH	HIGH	HIGH	UNCLEAR		LOW	LOW
Nakahara *et al.* 2016[29]	UNCLEAR	LOW	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR		LOW	LOW
Nakahara *et al.* 2017[30]	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	UNCLEAR	UNCLEAR		LOW	LOW
Nakahara *et al.* 2020[31]	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR		LOW	LOW
Yu *et al.* 2020[22]	HIGH	LOW	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	HIGH	LOW		LOW	LOW
Yu *et al.* 2021[32]	LOW	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW		LOW	LOW

with either one-stage or two-stage implant placement, but a shorter treatment duration in the former option[29,30]; 3) the use of a membrane did not result in superior BA, BIC, and BV gain compared to augmentation without a membrane[26,27]; 4) absence of the healing cap or occurrence of wound dehiscence negatively affected bone remodeling of BR grafts with pristine bone and implants[22,26,29,30]; 5) employing mucogingival junction incision and split-thickness flap effectively reduced the incidence of wound dehiscence[22].

Histology and histomorphometry

The qualitative and quantitative data pertaining to the BR grafts were elucidated by employing tissue sectioning and micro-CT scanning. The histological sections are suitable for distinguishing specific details on the implant surface, such as cells, non-mineralized osteoid, and soft tissue. Micro-CT, which is utilized for detecting mineralized tissue, is more appropriate for analyzing the preservation of BR primarily composed of cortical bone and evaluating bone formation surrounding implants during later stages of healing. This systematic review demonstrated the beneficial effect of BR grafts for enhancing BA and BV, albeit with variations in the selection of ROI among studies. The general observation of the included studies also supported the finding that there was a definite increase in peri-implant bone within the area of the grafted BR.

From the perspective of histology, the structure of the BR surrounding the implant elicited distinct manifestations of bone remodeling. Throughout the healing process, new bone trabeculae gradually infiltrated the pores within the BR[21,32]. On the outer side of the BR, a connection was established between the pristine bone and implant surface through newly formed mineralized tissue, resulting in a mineralized triangle from the local bone surface toward the supracrestal implant surface[21]. Notably, autogenous bone exhibited accelerated marginal bone mineralization and lamellar bone formation, whereas allogeneic, bovine-derived, or biphasic ceramic materials showed delayed processes[28].

The histomorphometry varies among different types of BRs. In the study by Benlidayi *et al.*[25], a reversal in the trend of autograft and allograft was observed at 4 and 8 months in BA. This can be attributed to a more noticeable absorption of autograft around nonloaded implants during this period, while allograft was replaced by mature lamellar bone, resulting in an overall increase in BA. Another study[28] with a shorter follow-up period of only 5 weeks demonstrated that autogenous BR exhibited superior capacity for bone remodeling and volume maintenance compared to slow resorptive bovine bone and biphasic ceramics because of the presence of cells and growth factors conducive to bone regeneration in autogenous bone. Interestingly, this study reported relatively low BIC values, ranging from 8.79% for biphasic ceramic to 15.77% for autogenous bone, which was notably lower compared to other studies. Understandably, after only 5 weeks of healing, immature and nonlamellar new bone was observed at the interface between the BR and the implant, even when autogenous BRs were used, not to mention the limited osteogenesis potential of bovine bone and biphasic ceramics.

In general, the healing period for BR grafts with simultaneous implant placement has been deemed reliable, with autografts requiring a minimum of 6 months and nonautografts

Table 3

Assessment of reporting quality within studies through ARRIVE 2.0 guideline

ARRIVE criteria	Benlidayi *et al.* 2018[25]	Draenert *et al.* 2012[21]	Haga-Tsujimura *et al.* 2018[26]	Haga-Tsujimura *et al.* 2023[27]	Jinno *et al.* 2018[28]	Nakahara *et al.* 2016[29]	Nakahara *et al.* 2017[30]	Nakahara *et al.* 2019	Yu *et al.* 2020[22]	Yu *et al.* 2021[32]
Study design	1	1	1	1	1	1	1	1	1	1
Sample size	1	1	1	1	1	1	1	1	0	1
Inclusion and exclusion criteria	1	1	1	0	1	1	1	1	1	1
Randomization	0	0	0	0	0	0	0	1	0	0
Blinding	0	0	0	0	0	0	0	0	0	0
Outcome measures	1	1	1	1	1	1	1	1	1	0
Statistical methods	1	1	1	1	1	1	1	1	1	1
Experimental animals	1	1	1	1	1	1	1	1	1	1
Experimental procedures	1	1	1	1	1	1	1	1	1	1
Results	1	1	1	1	1	1	1	1	1	1
Abstract	1	1	1	1	1	1	1	1	1	1
Background	1	1	1	1	1	1	1	1	1	1
Objectives	1	1	1	1	1	1	1	1	1	1
Ethical statement	1	1	1	1	1	1	1	1	1	1
Housing and husbandry	1	0	1	0	0	1	1	1	1	1
Animal care and monitoring	1	1	1	1	1	1	1	1	1	1
Interpretation/ scientific implications	1	1	1	1	1	1	1	1	1	1
Generalizability/ translation	1	1	0	1	1	1	1	1	1	1
Protocol registration	0	0	0	0	0	0	0	0	0	0
Data access	1	1	1	1	1	1	1	1	1	1
Declaration of interests	1	1	1	0	1	1	1	1	1	1

necessitating at least 8 months[25]. Although several previous clinical trials have adhered to this protocol to some extent[8,15], further investigation is still needed to establish more specific guidelines regarding the healing timeline for different types of BR grafts.

Use of collagen membrane

Due to the high biocompatibility and transmembrane angiogenic potential of collagen membranes, it is a common practice to incorporate its use for preventing soft tissue ingrowth and stabilizing the augmented space during bone augmentation[33,34]. However, three included studies have revealed that augmentation without membrane coverage did not yield significant differences in terms of BA, BV, and BIC[26,27,31]. These unexpected results can be attributed to several possible reasons: 1) The cortical layer of the BR may exhibit more excellent resistance to tissue ingrowth and resorption compared to collagen membranes[31]; 2) The difference in the presence of collagen membranes might not have been detected employing small sample size[26]; 3) Placement of collagen membranes may further increase soft tissue tension and thus contributing to wound dehiscence[26]. To clarify, collagen membranes have been found to have no detrimental influence on the processes of bone remodeling and osseointegration, consistent with previous findings in other bone augmentation surgeries[35,36]. During the initial healing period, the collagen membrane may impede invasion and infiltration of cellular components involved in tissue organization; however, over time, its collagen and fibrous tissue will gradually undergo metabolism after integration into the matrix[26,27].

Feasibility of one-staged implant placement

Previously, it was believed that simultaneously placed implants might impede the BR graft remodeling process, while the two-staged placement of implants was deemed more secure[4]. Nevertheless, Nakahara *et al*.'s histological analyses revealed progressive and complete revascularization as well as remodeling of nonvital bone in both groups throughout the follow-up period[29,30]. Significantly, simultaneous implant placement did not impede the regenerative capacity of BR, suggesting that single-staged implant placement using BR can be considered equally efficient as the two-staged technique. It is worth noting; however, that these two studies employed acute saddle-type bone defects in the mandibular region of beagle dogs, which facilitates the initial angiogenesis of the BR graft and enhances vascular and progenitor cell migration into the bone[29,37,38]. When considering implant placement in a noncontained atrophic bone defect with a BR graft, caution should be exercised when interpreting the performance between the one-stage and two-stage.

Table 4

The characteristics of the included animal studies

Author	Animals	Origins of BR grafts	Recipient sites	Intervention groups	Implant placement	Follow-up periods
Benlidayi *et al.* 2018[25]	Four sheeps	Autogenous BRs from the iliac bone	VA in the iliac bone	G1) 2 mm VA with autogenous BR + collagen membrane; G2) 4 mm VA with autogenous BR + collagen membrane	16, one-staged	4, 8 months
		Allogeneic BRs (Maxgraft; Botiss Dental)		G3) 2 mm VA with allogeneic BR + collagen membrane; G4) 4 mm VA with allogeneic BR + collagen membrane	16, one staged	
Draenert *et al.* 2012[21]	Six chinchilla rabbits	Cylindrical porcine BRs	VA in the tibia	Cylindrical porcine BRs	12, one staged	1 month
Haga-Tsujimura *et al.* 2018[26]	Six beagle dogs	Autogenous BRs from the calvaria	VA in the mandible	G1) Autogenous BR + collagen membrane	12, one staged	3, 6 months
				G2) Autogenous BR	12, one staged	
Haga-Tsujimura *et al.* 2023[27]	Three beagle dogs	Autogenous BRs from the calvaria	VA in the mandible	G1) Autogenous BR + collagen membrane	6, one staged	12 months
				G2) Autogenous BR	6, one staged	
Jinno *et al.* 2018[28]	Six sheeps	Autogenous BRs from the mandibular ramus	VA in the mandible	G1) Autogenous BR	6, one staged	5 weeks
		Bovine BRs (Bio-Oss Collagen, Geistlich)		G2) Bovine BR	6, one staged	
		Resorbable biphasic ceramic BRs (Cerament Bone Void Filler, Bone Support AB)		G3) Resorbable biphasic ceramic BR	6, one staged	
Nakahara *et al.* 2016[29]	Eight beagle dogs	Autogenous BRs from the calvaria	VA in the mandible	G1) Autogenous BR + collagen membrane	16, one staged	3, 6 months
				G2) Autogenous BR + collagen membrane	16, two staged (6 months)	
Nakahara *et al.* 2017[30]	Eight beagle dogs	Autogenous BRs from the calvaria	VA in the mandible	G1) Autogenous BR + collagen membrane	16, one staged	3, 6 months
				G2) Autogenous BR + collagen membrane	16, two staged (6 months)	
Nakahara *et al.* 2020[31]	Six beagle dogs	Autogenous BRs from the calvaria	VA in the mandible	G1) Autogenous BR + collagen membrane	12, one staged	3, 6 months
				G2) Autogenous BR	12, one staged	
Yu *et al.* 2020[22]	Six beagle dogs	Autogenous BRs from lower buccal edge of the first molar	VA in the mandible	G1) Mucogingival junction incision + split-thickness flap elevation + autogenous BR	12, one staged	3 months
					12, one staged	

Table 4

(*Continued*)

Author	Animals	Origins of BR grafts	Recipient sites	Intervention groups	Implant placement	Follow-up periods
				G2) Alveolar crest incision + buccal and lingual full-thickness flap elevation + autogenous BR		
Yu *et al.* 2021[32]	Six beagle dogs	Autogenous BRs from lower buccal edge of the first molar	VA in the mandible	G1) Autogenous BR	12, one staged	3 months
				G2) -	12, one staged	

Author	Total BA	BIC	BV	Histological examination	Main findings and conclusions
Benlidayi *et al.* 2018[25]	G1) Autogenous 2 mm: • 4 months: 70.85 ± 3.51% • 8 months: 53.58 ± 3.21% G2) Autogenous 4 mm: • 4 months: 85.63 ± 3.59% • 8 months: 72.41 ± 5.09% G3) Allogeneic 2 mm: • 4 months: 54.53 ± 2.67% • 8 months: 66.55 ± 2.64% G4) Allogeneic 4 mm: • 4 months: 66.59 ± 2.63% • 8 months: 70.98 ± 4.19%	G1) Autogenous 2 mm: • 4 months: 75.32 ± 7.10% • 8 months: 52.95 ± 5.28% G2) Autogenous 4 mm: • 4 months: 95.76 ± 2.97% • 8 months: 89.45 ± 9.06% G3) Allogeneic 2 mm: • 4 months: 68.97 ± 11.25% • 8 months: 73.39 ± 4.19% G4) Allogeneic 4 mm: • 4 months: 64.40 ± 4.71% • 8 months: 83.25 ± 10.59%		G1) Autogenous 2 mm: 4 months: Favorable bone regeneration in the coronal part of the implant but bone marrow spaces in the BR area. Ÿ8 mo: Larger bone marrow spaces in the BR area and the narrower area of the bone trabeculae and the less lamellar bone in contact with the implant. G2) Autogenous 4 mm: Ÿ4 months: The bone graft was well consolidated to the recipient bone. The implant surface was almost completely in contact with bone in the BR area. Ÿ8 mo: Thick bone trabeculae and more bone marrow space in the BR area. High amounts of lamellar bone to implant contact G3) Allogeneic 2 mm: Ÿ4 months: Allograft did not resorb completely with the development of lamellar bone in the allograft BR area at 4 months; Ÿ4 months: Allograft BR Completely resorbed and replaced with mature lamellar bone. Thick bone trabeculae in the BR area and the new bone consolidated to the recipient bone. G4) Allogeneic 4 mm: Ÿ4 months: Partial resorption of the allograft. Some bone islands into the allograft. Lamellar bone fusion between the allograft and the recipient bone. Ÿ8 months: Allograft BR completely resorbed and replaced with mature lamellar bone. Higher bone consolidation to the recipient bone and the amount of BIC	• G1 and 2 showed higher values than G3 and 4 in terms of BA and BIC after 4 months. • G3 and 4 showed higher BA and BIC values than G1 and 2 after 8 months. • Allogeneic BR looks promising in augmentation of surgically created vertical bone defects around implants after 8 months of healing
Draenert *et al.* 2012[21]				Bony healing in the BR scaffolds with immature lamellar cancellous bone tissue ingrowth following the trabecular structure. Most mature bone with advanced mineralization was observed in the marginal bone triangle between supracrestal rough implant body and the horizontal, marginal, crestal bone	Vertical bone augmentation using xenogeneic BR results in good bony ingrowth of scaffold and osseointegration of the dental implant
Haga-Tsujimura *et al.* 2018[26]	G1) • 3 months: 44 ± 5.165% (R1), 14.90 ± 5.578% (R2)	G1) IS-fBIC: • 3 months: -1.75 ± 0.73 mm		G1) Ÿ3 months: The membrane remnants. New immature bone facing the remnants of the collagen membrane. The majority of bone tissue close to the implant was new bone.	• No significant effects of membrane placement or healing period on the total area of the bone and BIC • The disruption of soft tissue was a frequent complication	

	• 6 months: 37.83 ± 12.47% (R1), 22.25 ± 10.04% (R2)	• 6 months: -2.13 ± 0.995 mm IS-TSB: • 3 months: -0.33 ± 0.733 mm • 6 months: -1.18 ± 0.913 mm		Ÿ6 mo: Sparse membrane fibers existed as fragmented loose strands of short, wave-like fibers. The bone spaces of various sizes with vessels sprinkled over the surrounding bone and perforated the grafted bone	
	G2) • 3 months: 52.32 ± 3.33% (R1), 11.52 ± 1.993% (R2) • 6 months: 61.94 ± 11.74% (R1), 13.83 ± 4.108% (R2)	G2) IS-fBIC: • 3 months: -1.08 ± 0.2 mm • 6 months: -0.12 ± 0.93 mm IS-TSB: • 3 months: -0.29 ± 0.555 mm • 6 months: 0.15 ± 0.665 mm		G2) Ÿ3 months: New bone containing vessels and labeled bone surrounding vessels around the grafted bone. The new bone with blood vessels closely faced the implant surface. Ÿ6 months: The block of cortical bone graft still appeared to maintain the volume. The grafted bone was well consolidated to the pristine bone via a new bone, with slightly less active bone remodeling around the grafted bone and around the implant	
Haga-Tsujimura *et al.* 2023[27]	G1) 43.94 ± 13.27% (R1), 15.71 ± 6.16% (R2)	G1) • IS-FBIC: -2.00 ± 1.23 mm • IS-TSB: -1.20 ± 0.83 mm	G1) V1: 71.68 ± 24.86 mm^3, V2: 144.54 ± 16.89 mm^3	G1) Membrane remnants with the new bone underneath. The surrounding bone was mature with new bone near the bone surface and near blood vessels	The BV and percentages of total BA and BIC within the BR were slightly higher in the G1 than in G2 ($P > 0.05$). Membrane application did not contribute to the performance of the BR after a 12 months healing period
	G2) 42.69 ± 17.94% (R1), 20.45 ± 5.81% (R2)	G2) • IS-FBIC: -2.05 ± 1.63 mm • IS-TSB: -1.54 ± 1.18 mm	G2) V1: 71.39 ± 37.02 mm^3, V2: 126.09 ± 24.19 mm^3	G2) The new bone with the blood vessels was located near the surface of the bone as well as around the implant	
Jinno *et al.* 2018[28]	G1) 62.69%	G1) 15.77%		G1) Ring-shape bone was integrated to residual bone. New bone and osteoid were observed between the implant and ring-shaped bone block	• G1 showed a statistically higher percentage of BA compared with G2 and G3. • BIC showed low values, and there were no statistical differences between groups. • Autogenous cortical bone blocks are superior in maintaining the volume around dental implants using the BR technique, compared with deproteinized bone block and resorbable biphasic calcium sulfate and hydroxyapatite block
	G2) 7.37%	G2) 11.29%		G2, G3) New bone formation between the ring-shape material block and the residual bone. No new bone formations between the implants facing the ring-shape biomaterial block	
	G3) 5.58%	G3) 8.79%			
Nakahara *et al.* 2016[29]	G1) • 3 mo: 69.47 ± 4.235% (R1), 36.46 ± 9.843% (R2) • 6 months: 68.11 ± 3.85% (R1), 10.38 ± 1.08% (R2)		G1) • 3 mo: 124.4118 ± 26.5899 mm^3 (R1*), 4.1974 ± 6.4127 mm^3 (R2*), 128.6092 ± 29.7222 mm^3 (RT) • 6 months:	G1) BR graft was well consolidated to the pristine bone; blood vessels grew from the pristine bone into the BR toward the implants	• No differences were observed for all morphometric parameters in BR from 3 to 6 months of osseointegration in both groups; • Single-staged implant placement may be potentially useful to shorten an overall treatment period

Table 4

(*Continued*)

Author	Animals	Origins of BR grafts	Recipient sites	Intervention groups	Implant placement	Follow-up periods
			158.6455 ± 27.876 mm^3 (R1*), 12.4473 ± 8.3671 mm^3 (R2*), 171.0928 ± 33.7486 mm^3 (RT)			
	G2) • 3 months:74.87 ± 5.54% (R1), 26.53 ± 13.5% (R2) • 6 months: 66.67 ± 5.34% (R1), 11.55 ± 2.545% (R2)		G2) • 3 months: 110.0242 ± 25.4783 mm^3 (R1*), 0.2606 ± 0.5493 mm^3 (R2*), 110.2848 ± 25.8278 mm^3 (RT) • 6 mo: 136.8208 ± 23.15948 mm^3 (R1*), 1.7758 ± 1.6196 mm^3 (R2*), 138.5966 ± 24.2295 mm^3 (RT)	G2) The superior border of bone rings showed signs of minor resorption. Cortical bone graft remodeling were located within the newly formed bone, especially toward the pristine bone. Bone consolidation to the pristine bone in control group was advanced		
Nakahara *et al.* 2017[30]		(G1) IS-fBIC: • 3 months: 73.28 ± 12.22% • 6 months: 65.27 ± 14.56% IS-TSB: • 3 months: 75.29 ± 12.15% • 6 months: 58.11 ± 20.44% (G2) IS-fBIC: • 3 months: 70.44 ± 11.67% • 6 months: 62.29 ± 11.25% IS-TSB: • 3 months: 75.64 ± 24.28% • 6 months: 51.63 ± 34.67%		G1) 3 mo: Intensive bone remodeling. Active remodeling around the residual bone graft and around implant, but not within the graft bone. Ÿ6 months: The border between the residual graft and newly formed bone was less visible. The extent of trabecular bone deposited onto the implant surface increased, reaching the apical portion on the implant G2) Ÿ3 months: Advanced osseointegration. The newly formed bone was facing the implant surface, with little residual bone remained. Ÿ6 mo: The volume of the residual bone further decreased with the surrounding bone composed mainly of newly formed lamellar bone	• Two groups of implants performed similarly in BR and in native bone throughout the observation period. • In terms of osseointegration, both techniques are likely equally efficient in the present defect model	
Nakahara *et al.* 2020[31]		G1) ¶ • 3 mo: R1: 67.61 (38.72–84.49) %	G1) ¶ 3 mo: R1: 110.49 (50.06~145.07) mm^3		• Membranes were not a significant negative factor for BV, but for BIC. • Absence of healing caps impaired BV and BIC.	

	R2: 59.47 (48.97–83.37) % • 6 months: R1: 56.97 (28.43–95.19) % R2: 72.33 (59.54–76.66)% G2) ¶ • 3 months: R1: 80.20 (68.93–92.88) % R2: 64.24 (46.45–68.36) % • 6 months: R1: 81.69 (44.13–90.869) % R2: 69.34 (44.32–76.636) %	R2: 118.70 (72.57~166.65) mm^3 6 mo: R1: 65.89 (18.65~105.48) mm^3 R2: 141.04 (116.48–160.75) mm^3 G2) ¶ 3 months: R1: 97.78 (71.05–138.52) mm^3 R2: 112.48 (92.69–138.64) mm^3 6 mo: R1: 93.88 (61.80–135.32) mm^3 R2: 125.26 (113.45–153.00) mm^3		• Loss of healing caps and exposure negatively affected BV and BMD within 2 mm below the implant shoulder.
Yu *et al.* 2020[22]			ŸIn the group without wound dehiscence, the BRs and implants had osseointegrated together well, and new bone was visible at the interface between the BR and the implant; ŸIn the group with wound dehiscence, bone resorption was obvious at the upper edge of the implant, but the residual BR was still integrated with the implant and the base alveolar bone	• In wound dehiscence samples, severe bone loss, 2.47 ± 0.17 mm, was found on the buccal side of the BR. • The use of a mucogingival junction incision and split-thickness flap design can effectively prevent first-stage wound dehiscence
Yu *et al.* 2021[32]		G1) $91.11 \pm 0.02\%$ G2) $88.38 \pm 2.34\%$	G1) The BRs and implants osseointegrated together well, and new bone, which was dyed red, was visible at the interface between the BR and the implant G2) No obvious bone resorptions or osteoclast cells	Autogenous BR grafts with simultaneous implant placement can survive in a local vertical bone defect with little bone resorption and good osseointegration

BR, bone ring; VA, vertical augmentation; BA, bone area; BIC, bone-to-implant contact; BV, bone volume; BMD, Bone mineral density; R1, areas of the BR around implants; R2, areas of the BR around pristine bone; R1*, below the implant shoulder; R2*, above the implant shoulder; RT, total bone volume; V1, total around BR; V2, under BR 5mm; ¶, medians (minimum-maximum).

Design of incision and flap

Wound dehiscence, occurring in up to 75% of animal studies, represents the most prevalent complication[22]. Notably, sites of wound dehiscence displayed significant premature resorption of grafts and alveolar ridge, even when protected by a collagen membrane. Potential factors contributing to this complication include sharp edges of BR grafts, bulging of healing caps formed by membrane screws, and additional placement of collagen membranes[26,29,30]. Nevertheless, an overlooked factor is the impact of incision and flap design on wound healing outcomes. The conventional incisions and flaps employed included mid-ridge incision and full-thickness buccal mucosal flap elevation[27,28,31]. However, the complete resolution of challenges associated with releasing soft tissue tension for closure of protruded BR grafts has been rarely addressed.

In this context, Yu *et al*.[22] introduced a novel incision and flap design, opting for the incision at the mucogingival junction and elevating the split-thickness flap to the lingual side while extending the underlying flap containing the periosteum and muscle fibers to the buccal periosteum. This innovative approach offers several advantages, including passive extension of the vestibular sulcus, alleviation of buccinator muscle tension, and increased grafting space. Remarkably, this protocol significantly reduced wound dehiscence rates from 75% with conventional designs to 16.7%. Notably, the biological behaviors of this design are based on the mandibular anatomy of beagle dogs, which differs from humans. Therefore, further verification through clinical trials is necessary for the advantages of the protocol of the incision and flap.

Strengths and limitations

The strengths of this systematic review include the registration of its a priori protocol in PROSPERO, its comprehensive literature retrieval, its thorough reporting of results, the utilization of the SYRCLE tool and ARRIVE 2.0 guideline for assessing the quality of animal evidence, and the transparent provision of study data. Furthermore, as an integral part of this systematic review (Part II), a comprehensive evaluation of all available animal studies was conducted to investigate the efficacy of BR grafts in alveolar ridge reconstruction, building upon previous research findings (Part I).

The methodological and clinical heterogeneity in the identified studies imposes certain limitations on our findings. Firstly, although efforts have been made to convert histomorphometric data into means and SD for facilitating interstudy comparisons, there is a lack of alignment between the target regions and observation periods of tissue sections and CT scans. Secondly, the protocols of animal studies included assessing the efficacy of BR grafts, evaluating the value of collagen membranes, comparing the effects of implant placement in different stages, and examining differences in outcomes between mucogingival junction incision with split-thickness flap versus conventional incision with full-thickness flap, suggesting that standardized application guidelines for BR grafts are still in an exploratory stage with a lack of consensus. Third, identified animal trials reported predominantly on small sample sizes, potentially introducing small-study effects and increasing the risk of reporting bias[39].

Conclusions

Based on the findings from animal studies, BR grafts have demonstrated efficacy in reconstructing vertical bone defects. Favorable bone remodeling and osseointegration of the BR graft with both the pristine bone and implant are observed when applied in saddle-shaped or wall-contained defects. Simultaneous implant placement not only achieves histomorphological similarity to the second-stage process but also reduces the overall treatment duration. While the use of collagen membrane may not confer significant benefits, it could potentially increase soft tissue tension during wound closure; thus, alleviating tension through edge grinding of the BR and optimizing incision and flap design is recommended.

Ethical approval

For this study, ethical approval was not required.

Consent

Informed consent was not required for this systematic review.

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Author contribution

G.J.M. and Z.R.M.: writing – original draft preparation; Z.Z.L. and Y.P.X.: methodology and data curation; X.X. and Y.Z.F.: formal analysis, validation, and visualization; G.J.M.: writing – review and editing and project administration.

Conflicts of interest disclosures

The authors of this work have nothing to disclose.

Research registration unique identifying number (UIN)

The systematic review was registered in PROSPERO (register number: CRD42023453949).
Link: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023453949.

Guarantor

The guarantor of this study is Dr Jiaming Gong.

Data availability statement

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Presentation

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