Clinical Applications of Cell-Based Approaches in Alveolar Bone Augmentation: A Systematic Review

Siddharth Shanbhag, BDS, MSc;* Vivek Shanbhag, BDS, MDS*

ABSTRACT

Background: Cell-based approaches, utilizing adult mesenchymal stem cells (MSCs), are reported to overcome the limitations of conventional bone augmentation procedures.

Purpose: The study aims to systematically review the available evidence on the characteristics and clinical effectiveness of cell-based ridge augmentation, socket preservation, and sinus-floor augmentation, compared to current evidence-based methods in human adult patients.

Materials and Methods: MEDLINE, EMBASE, and CENTRAL databases were searched for related literature. Both observational and experimental studies reporting outcomes of "tissue engineered" or "cell-based" augmentation in ≥5 adult patients alone, or in comparison with noncell-based (conventional) augmentation methods, were eligible for inclusion. Primary outcome was histomorphometric analysis of new bone formation. Effectiveness of cell-based augmentation was evaluated based on outcomes of controlled studies.

Results: Twenty-seven eligible studies were identified. Of these, 15 included a control group (8 randomized controlled trials [RCTs]), and were judged to be at a moderate-to-high risk of bias. Most studies reported the combined use of cultured autologous MSCs with an osteoconductive bone substitute (BS) scaffold. Iliac bone marrow and mandibular periosteum were frequently reported sources of MSCs. In vitro culture of MSCs took between 12 days and 1.5 months. A range of autogenous, allogeneic, xenogeneic, and alloplastic scaffolds was identified. Bovine bone mineral scaffold was frequently reported with favorable outcomes, while polylactic–polyglycolic acid copolymer (PLGA) scaffold resulted in graft failure in three studies. The combination of MSCs and BS resulted in outcomes similar to autogenous bone (AB) and BS. Three RCTs and one controlled trial reported significantly greater bone formation in cell-based than conventionally grafted sites after 3 to 8 months.

Conclusions: Based on limited controlled evidence at a moderate-to-high risk of bias, cell-based approaches are comparable, if not superior, to current evidence-based bone grafting methods, with a significant advantage of avoiding AB harvesting. Future clinical trials should additionally evaluate patient-based outcomes and the time-/cost-effectiveness of these approaches.

KEY WORDS: bone augmentation, bone grafting, stem cells

Insufficient alveolar bone volume, as a result of periodontal disease and/or resorption atrophy, often presents a clinical challenge for the placement of dental implants. The primary objective in these situations is to predictably regenerate the lost bone, so as to allow the placement of implants in restoratively and esthetically optimal positions.[1] Several approaches for alveolar bone regeneration have been proposed.[2] The most widely accepted of these are: vertical and horizontal ridge augmentation (RA) including guided bone regeneration (GBR)[3]; alveolar ridge/socket preservation (SP) following dental extraction[4]; and sinus-floor augmentation (SA) in the atrophic posterior maxilla.[5] All of these regenerative techniques mainly involve the use of autogenous bone and/or bone substitute materials with or without the additional use of barrier membranes.[6]

*Private practice, Mumbai, India

Reprint requests: Dr. Siddharth Shanbhag, Centre for Oral Rehabilitation & Implant Dentistry, 1 Laxmi Niwas, 87 Bajaj Road, Vile Parle West, Mumbai 400056, India; e-mail: sidshanbhag@gmail.com

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Although autogenous bone (AB), with its osteogenic, osteoinductive, and osteoconductive properties, is considered the "gold standard" for augmentation, its use is limited by the need for additional harvesting procedures and significant donor-site morbidity.[7] Recently, "tissue engineering" or "cell-based" approaches have been identified as promising alternatives to AB grafting.[8] "Tissue engineering" generally refers to the harvesting of multipotent stem cells from an autologous source (e.g., bone marrow) and their subsequent in vitro culture and "expansion" to provide adequate numbers for clinical application.[9] The triad of bone tissue engineering involves the combination of osteogenic progenitor *cells*, osteoinductive growth factors or *signals,* and osteoconductive *scaffolds.*[10] Therefore, the combined product can potentially replicate the properties of AB. The fourth patient-based factor critical for success is *vascularization* of the graft, which is essential for oxygenation and nutrition of the implanted cells.[11] An alternative approach to tissue engineering involves the use of fresh autologous tissue containing stem cells, for "chair side" application, without in vitro cultivation, thereby reducing additional time and cost for patients (e.g., bone marrow aspirate concentrate [BMAC®, Harvest Technologies, Munich, Germany]).[12]

Adult mesenchymal stem cells (MSCs) offer the greatest potential in tissue engineering for clinical applications – given their multipotency, (relatively) easy accessibility, and predictable in vitro isolation and culturing into desired cell types, including osteogenic progenitors.[13] Although a majority of research related to MSCs and their application has been in vitro and animal-model based, recent studies have identified in vivo human applications of MSCs for oral bone regeneration.[8,14]

The aim of the present study was to systematically review the current literature on in vivo human applications of cell-based approaches in alveolar bone augmentation; and to specifically discuss the clinical effectiveness of such approaches in vertical or horizontal RA, GBR, SP, and SA.

MATERIALS AND METHODS

Study Design

A study protocol for a narrative literature review was developed based on recommended methods.[15] The focused "PICO" question was: "what are the characteristics and effectiveness of cell-based approaches in RA, GBR, SP, and SA in human adult patients in comparison to conventional grafting procedures?" "Conventional" grafting procedures were defined as those involving the use of AB, bone substitutes, or a combination of the two.

Inclusion and Exclusion Criteria

All studies with a minimum of five human adult patients (>18 years) undergoing bone augmentation procedures involving the use of human adult MSCs in the maxilla or mandible to facilitate dental implant placement were eligible for inclusion. Studies reporting both "tissue engineered" and "chair side" or "non-cultured" cell-based approaches were eligible for inclusion. Descriptive studies (case series [$n \geq 5$] *without* a control group, controlled cohort studies [CCs]) and experimental studies (nonrandomized controlled trials [CTs] and randomized controlled trials [RCTs]) with at least 3 months follow-up were included. Study design was determined according to recent consensus.[16] Individual case reports and case series with <5 patients were excluded. Primary outcome of interest was histomorphometric analysis of the regenerated bone. Secondary outcomes were radiographic and/or histological analyses, complications, failures, patient-reported outcomes (e.g., morbidity), and implant survival rates.

Search Strategy

Electronic databases of MEDLINE (via PubMed), EMBASE, and CENTRAL were searched for relevant English-language literature up to and including March 2013. Key words such as "alveolar augmentation," "ridge augmentation," "guided bone regeneration," "bone augmentation," "bone graft," "tissue regeneration," "sinus augmentation," "sinus floor elevation," "sinus grafting," "sinus lift," "ridge preservation," "socket preservation," "cell," "stem cell," "mesenchymal stem cells," "bone marrow," "cell based," "tissue engineering," and "tissue engineered bone" were used in various combinations using Boolean operators ("OR," "AND"). Unpublished literature was searched via the Google and Google Scholar search engines. Additionally, the bibliographies of all relevant studies and review articles were searched.

Study Selection

Titles and abstracts of the search-identified studies were screened by both reviewers based on the inclusion criteria and full texts of all eligible studies were obtained. Differences in assessment of eligibility were resolved

by discussion. Full texts were independently reviewed by both authors and final inclusion was based on the aforementioned inclusion criteria.

Data Extraction

Two reviewers independently extracted data from the full texts of included articles using specially designed forms. Data were extracted on author(s), study design, nature of the augmentation procedures, any additional procedures performed, number of patients (in each group), presence of a control group, source of MSCs, culture expansion (time), growth factors, scaffolds, follow-up periods, outcome measures, main results, complications and patient morbidity. Although uncontrolled studies were reviewed, the evidence for clinical effectiveness of cell-based bone augmentation was evaluated based only on outcomes of controlled studies. Descriptive summaries of the studies were entered into tables and a qualitative synthesis of evidence was planned. Any disagreement between the reviewers at the stages of study selection and data extraction was resolved by discussion. Full texts of all abbreviations used are provided in Table 1.

Risk of Bias and Quality Assessment

Risk of bias in the included studies was evaluated by both authors (as part of the data extraction process) using the Cochrane Collaboration's tool[17] for randomized trials and adaptations of previously reported criteria[4] for nonrandomized studies. Additionally, "source of funding" and "reporting of complications" in all studies was assessed. Based on the information provided in the published reports, each of these criteria was scored as either "yes," "no," or "unclear"; and based on fulfillment of these criteria, studies were judged to be at a "low," "moderate," or "high" risk of bias. Any differences in assessment between the reviewers were resolved by discussion and consensus. Finally, based on the risk of bias across studies in each group (randomized and nonrandomized), overall quality of the "body of evidence" was judged to be "high," "moderate," "low," or "very low" using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.[18]

TABLE 1 Abbreviations Used in the Text

Abbreviation	Full Text
AB	Autogenous bone
MSCs	Mesenchymal stem cells
RA	Ridge augmentation
GBR	Guided bone regeneration
SP	Socket preservation
SA	Sinus-floor augmentation
CC	Controlled cohort study
CT	Nonrandomized controlled trial
RCT	Randomized controlled trial
BMA	Bone marrow aspirate
BMAC	Bone marrow aspirate concentrate
BMSCs	Bone marrow-derived mesenchymal stem cells
PMSCs	Periosteum-derived mesenchymal stem cells
AMSCs	Alveolar bone-derived mesenchymal stem cells
DPSCs	Dental pulp stem cells
GFs	Growth factors
PRP	Platelet rich plasma
DBBM	Deproteinized bovine bone mineral
PLGA	Polylactic–polyglycolic acid copolymer
CaP	Calcium phosphate
HA	Hydroxyl-apatite
CT	Computed tomography
VEGF	Vascular endothelial growth factor
TGF-β	Transforming growth factor – beta
BMP	Bone morphogenic protein
NBF	New bone formation

RESULTS

Search Results and Study Characteristics

Of the 507 search-identified studies, 27 were finally included in the review (Figure 1; Tables 2–5). Of these, seven were related to RA,[19–25] four to SP,[24,26–28] and 21 to SA.[19,21,23,24,29–46] Three studies[19,21,23] reported outcomes of MSC-application in both SA and RA, and one study[24] in GBR, SP, and SA. One study[26] reported the outcomes of cell-based bone regeneration in mandibular third-molar extraction sockets and was categorized as an SP study. All studies related to SA reported the lateral augmentation technique, except Yamada and colleagues[35] who reported the osteotome technique. Twelve studies were uncontrolled case series. Fifteen studies included a control group (or a split-mouth design), most of which were in relation to SA ($n = 11$). Among these were eight RCTs, five CTs, and two CCs reporting on 296 patients and 454 augmentation procedures (25 RAs, 88 SPs and 341 SAs). The results are presented hereafter under two broad headings: *characteristics* of cell-based augmentation techniques (controlled and uncontrolled

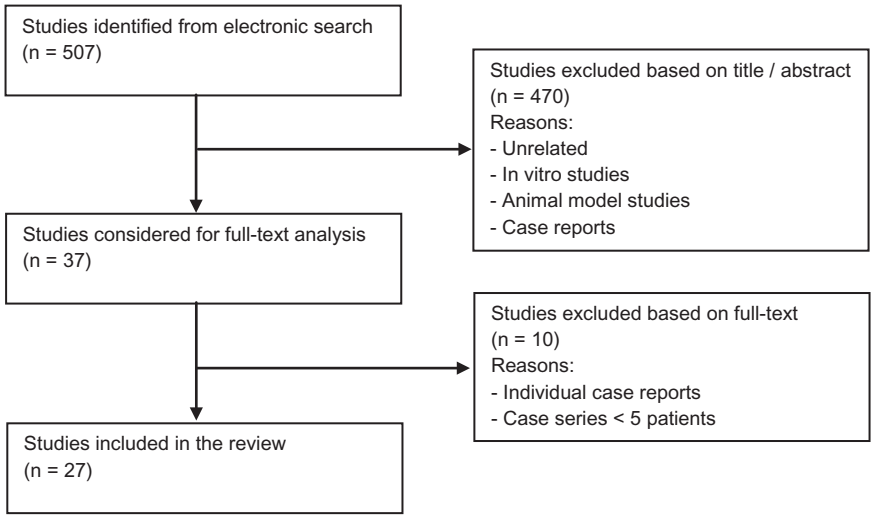

Figure 1 Flowchart for study selection (n = number of articles).

evidence; Tables 2–5) and the *effectiveness* of these techniques (controlled evidence; Tables 4 and 5) in bone regeneration.

Characteristics of Cell-Based Approaches

Cells: Sources of MSCs. All but two studies reported using autologous patient-derived adult MSCs. These two studies[32,40] reported using a commercially prepared "cellular allograft bone matrix" (Osteocel®, ACE Surgical Supply, Brockton, MA, USA) containing vital MSCs, where graft preparation included rigorous microbial and immunological testing. A majority of studies reported using autologous cultured MSCs (bone marrow-derived mesenchymal stem cells [BMSCs]) isolated from iliac crest bone marrow aspirate (BMA). Four studies reported the use of fresh autologous bone marrow,[19,22,27,45] while four others reported the use of BMAC.[41–43,45] No differences in augmentation outcomes were observed when comparing BMAC and tibial BMA, with the same scaffold.[45] Similarly, no differences were reported when comparing the BMAC ("closed", "chair side") method with the FICOLL® ("open") method of MSC isolation, using the same scaffold.[43] One study[38] reported isolating MSCs from the posterior mandibular bone marrow. Mandibular periosteum-derived MSCs (PMSCs) were frequently used.[23,36,37,39] One study each reported the use of alveolar bone-derived MSCs (AMSCs)[44] and dental pulp stem cells (DPSCs).[26] The duration between tissue harvesting and application in the studies that reported cell culture expansion, that is, the in vitro processing phase, was 12 days to 1.5 months.

Signals: Growth Factors (GFs). One research group reported the combined use of autologous platelet-rich plasma (PRP) and BMSCs for RA, GBR, and SA.[21,24,31] Two studies reported the use of PRP with allogeneic[19] or autogenous[23] bone and MSCs. Autologous serum derived from whole venous blood was commonly used as a culture medium for MSCs. Use of other individual GFs was not reported.

Scaffolds. A range of scaffolds was identified across the included studies. The choice of scaffold was based on previous in vitro and/or animal research, usually by the same group. Autologous scaffolds used were bone (maxilla,[44] mandible[23]), PRP, and/or thrombin.[21,24,31] Bone substitute scaffolds most often used were deproteinized bovine bone mineral (DBBM; Bio-Oss®, Geistlich Biomaterials AG, Wolhusen, Switzerland) – either alone[33,41–43,45] or in combination with AB.[44] Four studies reported the use of allogeneic bone scaffolds.[19,22,32,40] Other alloplastic scaffolds used were polylactic–polyglycolic acid copolymer (PLGA; OralBone®, BioTissue Technologies, Freiburg, Germany),[34,37–39] hydroxyl-apatite (HA),[20] biphasic hydroxyl-apatite/β-tricalcium phosphate (HA/β-TCP),[30] fibrin glue,[43] collagen sponge,[26] and gelatine sponge.[28]

Effectiveness of Cell-Based Approaches

Risk of Bias and Quality of Controlled Evidence. Risk of bias was evaluated separately for randomized and nonrandomized studies (Table 6). Among the randomized trials, most studies (n = 5/8) appeared to be at a

TABLE 2 Summary of Uncontrolled Studies on Ridge Augmentation (RA), Guided Bone Regeneration (GBR), and Socket Preservation (SP)

Authors	Patients/ Procedures	MSC Source Culture (Time)	Scaffold	Follow-Up	Radiographic Outcomes	Histological/ Histomorphometric Outcomes	Implant Survival/ Time
RA studies							
Filho Cerruti and colleagues[19]	32	Iliac, sternal BMA No	Allograft + A-PRP	8 months	Bone gain: width = 6 mm height = 10 mm	Good integration of scaffolds, NBF and presence of osteoblasts 1 graft failure	100% 2–4 years
Soltan and colleagues[25]	5	Iliac BMA No	Allograft	4–8 months	NR	Biopsy of one patient, 54% bone; 46% marrow NBF = 89%; allograft = 11%	100% NR
Meijer and colleagues[20]	5	Iliac BMA Yes (2 weeks)	HA	4 months	Stable bone volume	NBF in only 2 of 5 patients No NBF in 3 patients	100% 15 months
Ueda and collegues[21]	8	Iliac BMA Yes (1 month)	A-PRP + T	6 months	MBH gain = 5.00 mm	NR	100% 1 year
GBR study							
Yamada and colleagues[24]	36	Iliac BMA Yes (1 month)	A-PRP + T	5 years	NBF with little resorption BD increase from baseline to 5 years ($p < .001$)	"Good" NBF	100% 5 years
SP study							
Yamada and colleagues[24]	12	Iliac BMA Yes (1 month)	A-PRP + T	6 months	NBF with little resorption BD increase from baseline, to 5 years ($p < .001$)	"Good" NBF	NR

BMA, bone marrow aspirate; HA, hydroxyl-apatite; A-PRP, autologous platelet rich plasma; T, thrombin; MBH, mean bone height; BD, bone density measured by computed tomography; NBF, new bone formation; NR, not reported.

TABLE 3 Summary of Uncontrolled Studies on Sinus Augmentation (SA)

Authors	Patients (Procedures) RRH (mm)	MSC Source Culture (Time)	Scaffold	Follow-Up	Radiographic Outcomes	Histological/ Histomorphometric Outcomes	Implant Survival/ Time
Schimming and Schmelzeisen[29]	27 (41) ≤3 mm	Periosteum Yes (7.5 weeks)	PLGA fleece + bovine- T	3 months	NBF with little resorption	In 18 patients: mineralized trabecular bone and osteocytes with remnants of PLGA In 8 patients: no new bone formation and connective tissue replacement	97.14% 3 months
Filho Cerruti and collegues[19]	32 (NR) NR	Iliac, sternal BMA No	Allograft + A-PRP	8 months	MBH gain = 9–15 mm	Good integration of scaffolds, NBF and presence of osteoblasts 1 graft failure	100% 2–4 years
Shayesteh and colleagues[30]	6 (10) ≤3 mm	Iliac BMA Yes (1 month)	HA/β-TCP (60:40)	3 months	MBH gain = 8.58 mm	Mean NBF = 41.34%	93% 4 months
Ueda and colleagues[21]	6 (8) ≤5 mm	Iliac BMA Yes (1 month)	A-PRP + T	2–5 years	MBH gain = 8.70 mm	NR	100% 2–5 years
Yamada and colleagues[31]	12 (16) 2–10 mm	Iliac BMA Yes (1 month)	A-PRP + T	2–6 years	MBH gain = 8.80 mm	NR	100% 2–6 years
McAllister and colleagues[32]	5 (NR) ≤6 mm	Allogeneic bone No	Allograft	3–5 months	NR	Mean NBF = 33% (range 22–40%) Mean residual graft = 6% (range 3–7%)	NR
Fuerst and colleagues[33]	12 (22) 2 mm	Iliac, chin bone Yes (1 month)	DBBM (Bio-Oss®)	6 months 1 year	At 1 year, graft volume reduction = 39.24% ($p < .001$)	At 6 months, Mean NBF = 17.9 ± 4.6% Mean DBBM = 19.4 ± 10.1%	96% 6 months
Trautvetter and colleagues[34]	10 (17) ≥4 mm	Periosteum Yes (7–8 weeks)	PLGA (OralBone®)	6 months	MBH gain = 7.30 mm	Mature bone with osteocytes embedded in trabecular bone; No remnants of biomaterial and no formation of connective tissue	100% 5 years
Yamada and colleagues[24]	39 (NR) NR	Iliac BMA Yes (1 month)	A-PRP + T	5 years	NBF with little resorption BD increase from baseline to 5 years ($p < .001$)	"Good" NBF	100% 5 years
Yamada and colleagues[35] (osteotome SA)	8 (23) 4–11 mm	Iliac BMA Yes (1.5 months)	A-PRP + T	3 months 6 months	MBH gain at 3 months = 8.20 mm at 6 months = 8.00 mm	NR	100% 1 year

RRH, residual ridge height in mm; BMA, bone marrow aspirate; HA/β-TCP, biphasic hydroxyl-apatite β-tricalcium phosphate; A-PRP, autologous platelet rich plasma; T, thrombin; DBBM, deproteinized bovine bone mineral; PLGA, polylactic–polyglycolic acid copolymer; MBH, mean bone height; BD, bone density measured by computed tomography; NBF, new bone formation; NR, not reported.

TABLE 4 Summary of Controlled Studies on Ridge Augmentation (RA) and Socket Preservation (SP)

Authors	Design Patients (Procedures)	Cell-Based (Test) Group: MSC Source Culture (Time)	Cell-Based (Test) Group: Scaffold (Patients/ Procedures)	Control Group (Patients/ Procedures)	Follow-Up	Radiographic Outcomes	Histological/ Histomorphometric Outcomes	Implant Survival/ Time
RA studies								
da Costa and colleagues[22]	RCT 10 (10)	Iliac BMA No	Allograft (5/5)	Solely allograft (5/5)	6 months	MBW gain (mm): test > control (4.6 ± 1.43 vs 2.15 ± 0.47; $p = .002$)	NBF (%): test > control (60.7 ± 16.18 vs 41.4 ± 12.5; $p = .019$)	NR
Nagata and colleagues[23]	CC NR	Periosteum Yes (6 weeks)	AB (mandible) + A-PRP (14/15)	Solely AB (mandible) (NR)	4 months	NR	ALP and TRAP activity of regenerated bone: test > control ($p < .05$, $p < .001$) Recruitment of osteoblasts and osteoclasts: test > control	NR
SP studies								
Kaigler and colleagues[28]	RCT 24 (24)	Iliac BMA Yes (12 days)	Gelatine sponge (12/12)	Solely gelatine sponge (12/12)	6 weeks 12 weeks	Bone fill (%) at 6 weeks: test > control (78.9 vs 55.3; $p = .01$) Bone fill (%) at 12 weeks: test = control (80.1 vs 74.6; $p = .28$)	NBF (%) at 6 weeks: test > control (28.8 ± 9.1 vs 19.6 ± 4.2; $p = .09$) NBF (%) at 12 weeks: test = control (35.2 ± 8.9 vs 35.1 ± 3.2; $p = .49$)	100% 1 year
Pelegrine and colleagues[27]	RCT 13 (30)	Iliac BMA No	None (7/15)	Blood clot (6/15)	6 months	NR	Mean NBF (%): test = control (45.47 ± 7.21 vs 42.87 ± 11.33; $p = .36$)	NR
d'Aquino and colleagues[26]	SM-CT 17 (34)	Dental pulp Yes (3 weeks)	Collagen sponge (17/17)	Solely collagen sponge (17/17)	3 months	NBF: test > control ("faster")	Test sites: well-organized and vascularized bone Control sites: immature fibrous bone and evidence of bone absorption	—

RCT, randomized controlled trial; SM-RCT, split-mouth RCT; CT, controlled trial; CC, controlled cohort study; BMA, bone marrow aspirate; A-PRP, autologous platelet rich plasma; T, thrombin; AB, autogenous bone; MBW, mean bone width; NBF, new bone formation; NR, not reported.

TABLE 5 Summary of Controlled Studies on Sinus Augmentation (SA)

Authors	Design Patients (SAs) RRH (mm)	Cell-Based (Test) Group		Control Group (Patients/SAs)	Follow-Up	Radiographic Outcomes	Histological/ Histomorphometric Outcomes	Implant Survival/ Time
		MSC Source Culture (Time)	Scaffold (Patients/SAs)					
Rickert and colleagues[41]	SM-RCT 11 (22) ≤3 mm	Iliac BMAC No	DBBM (Bio-Oss®) + A-T (11/11)	AB (mandible) + Bio-Oss® (30:70) (11/11)	3–4 months	NR	Median NBF (%): test > control (17.7 ± 7.3 vs 12.0 ± 6.6; $p = .026$) Bio-Oss: test = control ($p = .722$) Marrow space: test = control ($p = .859$)	NR
Sauerbier and colleagues[42]	Part SM-RCT 26 (45) ≤4 mm	Iliac BMAC No	Bio-Oss® + A-T (25/34)	AB (mandible) + Bio-Oss® (30:70) (11/11)	3–4 months	Augmented bone volume (ml) test > control (1.74 ± 0.69 vs 1.33 ± 0.62; $p = .02$)	Mean NBF (%): test = control (12.6 ± 1.7 vs 14.3 ± 1.8; $p = .333$) Bio-Oss (%): test > control (31.3 ± 2.7 vs 19.3 ± 2.5; $p < .001$) Marrow space: test > control by 3.3% ($p = .137$)	NR
Hermund and colleagues[44,46]	RCT 20 (20) ≤3 mm	Tuberosity bone Yes (1 month)	AB (maxilla) + Bio-Oss® (1:1) (10/10)	AB (maxilla) + Bio-Oss® (1:1) (10/10)	4 months 2.5 years	MBH reduction (%) over 2.5 years: test = control (10 vs 13; $p = .18$)	No overall difference between groups in median (95% CI) NBF (%) (30 [23–40] vs 25 [21–37]; $p = .41$)	100% 2.5 years
Kühl and colleagues[45] (a)	SM-RCT 6 (12) ≤3 mm	Tibia BMA No	Bio-Oss® (6/6)	Solely Bio-Oss® (6/6)	2 weeks 6 months	Volume reduction (%): test = control (20.45 ± 13.51 vs 15.20 ± 8.37; $p = .249$)	NR	NR
Kühl and colleagues[45] (b)	SM-RCT 7 (14) ≤3 mm	Iliac BMAC No	Bio-Oss® (7/7)	Solely Bio-Oss® (7/7)	2 weeks 6 months	Volume reduction (%): test = control (16.59 ± 3.41 vs 21.50 ± 9.43; $p = .990$)	NR	NR
Gonshor and colleagues[40]	Part SM-RCT 14 (21) ≤6 mm	Allogeneic bone No	Allograft (14/14)	Solely allograft (7/7)	3–4 months	NR	Median NBF (%): test > control (32.5 ± 6.8 vs 18.3 ± 10.6; $p = .003$) Residual allograft (%): control > test (25.8 ± 13.4 vs 4.9 ± 2.4; $p = .002$)	NR

Sauerbier and colleagues[43]	CT 11 (18) ≤3 mm	Iliac BMA (FICOLL) Yes (NR)	Bio-Oss® + fibrin glue (4/6)	Iliac BMAC + Bio-Oss® + A-T (7/12)	3 months	NR	Estimated (90% CI) NBF (%): test = control [15.5 (8–22) vs 19.9 (10–29); $p = .39$] Bio-Oss: control > test ($p = .019$) Marrow space: test > control ($p = .01$)	NR
Mangano and colleagues[38]	SM- CT 5 (10) NR	Mandible BM Yes (6 weeks)	PLGA (OralBone®) (5/5)	HA (5/5)	6 months	MBH gain (mm): test = 6.47 ± 1.39 control = 9.14 ± 1.19 BD (HU): test = 192.76 control = 820.65	Mean NBF (%): control > test (54.65 ± 21.17 vs 37.32 ± 19.59; p = NR)	NR
Zizelmann and colleagues[37]	CT 20 (31) ≤5 mm	Periosteum Yes (NR)	OralBone® (10/14)	AB (iliac crest) (10/17)	3 months	Volume reduction: test = 90%, control = 29% BD: test = 152 HU control = 266–551 HU	NR	NR
Springer and colleagues[36]	CT 11 (17) NR	Periosteum Yes (3 weeks)	Collagen matrix (8/12)	Bio-Oss® (3/5)	6–8 months	Sufficient quantity of mineralized tissue	Median (range) NBF (%): test > control (38 [30–51] vs 25 [22–26]; $p = .01$)	100% 38 months
Voss and colleagues[39]	CC 76 (113) ≤5 mm	Periosteum Yes (8 weeks)	OralBone® (35/50)	AB (iliac crest) (41/63)	6 months >24 months	"Good" NBF no signs of resorption	Infections and graft failure: test > control group	90.67% vs 99.45% 2 years
Nagata and colleagues[23]	CC NR ≤2 mm	Periosteum Yes (6 weeks)	AB (mandible) + A-PRP (≥50%) (15/18)	Solely AB (mandible) (NR)	4 months 1 year	Volume reduction 3 months to 1 year: test = control (~70%)	ALP and TRAP activity of regenerated bone tissue: test > control ($p < .05$, $p < .001$) Recruitment of osteoblasts and osteoclasts: test > control	NR

RCT, randomized controlled trial; SM-RCT, split-mouth RCT; CT, controlled trial; SM-CT, split-mouth CT; CC, controlled cohort study; RRH (mm), residual ridge height in mm; BM, bone marrow; BMA, bone marrow aspirate; BMAC, bone marrow aspirate concentrate; A-PRP, autologous platelet rich plasma; T, thrombin; AB, autogenous bone; DBBM, deproteinized bovine bone mineral; PLGA, polylactic–polyglycolic acid copolymer; HA, hydroxyl-apatite; MBH, mean bone height; BD, bone density measured by computed tomography; NBF, new bone formation; NR, not reported; 95% CI, 95% confidence interval.

TABLE 6 Assessment of Risk of Bias and Overall Quality of Evidence across the Included Controlled Studies

Study	Assessment Criteria									
Randomized	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data Addressed	Free of Selective Reporting	Free of Other Bias	Industry Funding	Complications†	Estimated Risk of Bias	Quality of Evidence (GRADE)
RA										
da Costa and colleagues[22]	No	No	No	Unclear	Unclear	No	No	Unclear	High	Low to moderate
SP										
Pelegrine and colleagues[27]	No	No	No	Yes	Yes	Unclear	Unclear	No	Moderate	
Kaigler and colleagues[28]	Yes	Unclear	Yes*	Yes	Yes	Unclear	Unclear	No	Moderate	
SFA										
Rickert and colleagues[41]	Yes	Unclear	Yes*	Yes	Yes	Unclear	Yes	No	Moderate	
Sauerbier and colleagues[42]	Yes	Unclear	No	Yes	Yes	Unclear	Yes	No	Moderate	
Gonshor and colleagues[40]	Yes	Unclear	No	Yes	Unclear	Unclear	Yes	Unclear	High	
Hermund and colleagues[44,46]	Yes	Unclear	Yes*	Yes	Yes	Unclear	No	No	Moderate	
Kühl and colleagues[45]	No	No	No	Yes	Unclear	Unclear	Yes	Unclear	High	
Nonrandomized	**Comparable Groups**	**Inclusion, Exclusion Criteria Defined**	**Blinding**	**Adequate Follow-Up**	**Adequate Outcome Assessment**	**Reasons for Loss of Follow-Up**	**Industry Funding**	**Complications†**	**Estimated Risk of Bias**	**Quality of Evidence (GRADE)**
RA										
Nagata and colleagues[23]	Unclear	No	No	Unclear	Yes	Unclear	No	Yes	High	Very low to low
SP										
d'Aquino and colleagues[26]	Yes‡	Unclear	No	Unclear	Unclear	No	No	Unclear	High	
SFA										
Springer and colleagues[36]	Unclear	No	No	Yes	Yes	N/A	Unclear	No	High	
Zizelmann and colleagues[37]	Unclear	No	No	Yes	Yes	N/A	Unclear	Yes	High	
Mangano and colleagues[38]	Yes‡	Yes	No	Yes	Yes	N/A	No	No	Moderate	
Sauerbier and colleagues[43]	Yes	Yes	No	Yes	Yes	N/A	Yes	No	Moderate	
Voss and colleagues[39]	Unclear	No	No	Yes	Yes	N/A	Unclear	Yes	High	

*Although clinicians were not blinded to the procedure, outcome assessors were blinded to test/control groups.
†Complications (in cell-based group): Yes = some complications reported, No = no complications reported, Unclear = no information regarding complications.
‡Split-mouth studies.
GRADE, Grades of Recommendation, Assessment, Development and Evaluation; N/A, not applicable.

moderate risk of bias (range: moderate to high), while most nonrandomized studies ($n = 5/7$) were judged to be at a high risk of bias (range: moderate to high). Based on these assessments, the overall quality of the "body of evidence" for clinical effectiveness of cell-based bone augmentation using the GRADE approach was judged to be low (range: very low to moderate); the recommended interpretation for which is "further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate".[18]

Outcomes of Controlled Studies. All studies reported radiographic (conventional or computed tomographic), histological, and/or histomorphometric (percentage of new bone formation) outcomes. For histological assessments, bone core biopsies of the augmented sites were obtained at the time of implant placement after a specified healing period (range 6 weeks to 8 months).

RA and GBR – Histological/Histomorphometric Outcomes: Nagata and colleagues[23] reported significantly greater alkaline phosphatase and tartrate resistant acid phosphatase activity of regenerated bone tissue in the test (PMSCs + AB + PRP) compared with control sites (AB alone), 4 months after RA ($p < .001$), suggesting greater recruitment of both osteoblasts and osteoclasts to the regenerating bone tissue in the test sites. da Costa and colleagues[22] reported significantly greater new bone formation 6 months after RA using an allograft mixed with autologous BMA compared with RA with solely allograft (60.7 ± 16.18% vs 41.4 ± 12.5%; $p = .019$).

Radiographic Outcomes: One study[22] reported significantly greater increase in mean bone width 6 months after RA. with an allograft mixed with autologous BMA compared with RA with solely allograft (4.6 ± 1.43 mm vs 2.15 ± 0.47 mm; $p = .002$).

SP – Histological/Histomorphometric Outcomes: Pelegrine and colleagues[27] reported no significant differences in sockets augmented with BMA or those allowed to heal only with a blood clot (45.47 ± 7.21% vs 42.87 ± 11.33%; $p = .36$) after 6 months. Kaigler and colleagues[28] reported no significant differences in the ratio of "regenerated bone area to tissue area" (%) between the test (BMSCs in gelatine sponge) and control sites (sponge alone) at 6 weeks (28.8 ± 9.1% vs 19.6 ± 4.2%; $p = .09$) and 12 weeks (35.2 ± 8.9% vs 35.1 ± 3.2%; $p = .49$). d'Aquino and colleagues[26] reported well-organized and vascularized bone with a lamellar architecture surrounding Haversian channels in test sites (DPSCs in collagen sponge) after 3 months; compared with control sites (sponge alone) which demonstrated immature bone, incomplete Haversian channels and evidence of bone resorption.

Radiographic Outcomes: d'Aquino and colleagues[26] and Kaigler and colleagues[28] reported "significantly" better radiographic bone regeneration in test than control sites up to 3 months postoperatively. Kaigler and colleagues[28] reported greater radiographic bone fill (%) of the extraction defect in the test group after 6 weeks (78.9% vs 55.3%; $p = .01$), but similar results in the two groups after 12 weeks (80.1% vs 74.6%; $p = .28$).

SA – Histomorphometric Outcomes: In a split-mouth CT, Mangano and colleagues[38] reported lesser mean regenerated bone in the test (BMSCs + PLGA; 37.32 ± 19.59%) than control sites (calcium phosphate alone; 54.65 ± 21.17%), 6 months after SA in five patients. Two RCTs compared SA using either BMAC with Bio-Oss (test) or AB with Bio-Oss (control).[41,42] Rickert and colleagues[41] reported significantly greater new bone formation in the test (17.7 ± 7.3%) than control sites (12.0 ± 6.6%; $p = .026$); while Sauerbier and colleagues[42] identified no significant differences between the groups (12.6 ± 1.7% vs 14.3 ± 1.8%; $p = .333$) 3 to 4 months after SA. However, remnant Bio-Oss was significantly greater in the test group of the latter study (31.3 ± 2.7% vs 19.3 ± 2.5%; $p < .0001$). A third RCT[44] reported no significant differences in the ratio of augmented bone-density to pristine bone-density, between the test (AMSCs + AB/Bio-Oss; 0.48) and control groups (AB/Bio-Oss alone; 0.73; $p = .63$), 4 months after SA.

Radiographic Outcomes: Sauerbier and colleagues[42] reported significantly greater augmented bone volume in test (BMAC + Bio-Oss; 1.74 ± 0.69 ml) than control SA sites (AB + Bio-Oss; 1.33 ± 0.62 mL; $p = .02$) after 3 to 4 months. Hermund and colleagues[44] observed no significant differences between cell-based (AMSCs + AB + Bio-Oss) and control groups (AB + Bio-Oss) in graft height reduction over 2.5 years (10% vs 13%;

$p = .18$). A more recent RCT[45] found no significant differences in the graft-volume reductions 6 months after SA with solely Bio-Oss or Bio-Oss supplemented with tibial BMA or iliac BMAC. Nagata and colleagues[23] reported approximately 70% reduction in graft volume of SA sites after 1 year, with no significant differences between the test (PMSCs + AB + PRP) and control groups (AB alone, $p > .05$). Zizelmann and colleagues[37] reported graft volume reduction as high as 90% in the test (PMSCs + PLGA) compared with 29% in control SA sites (solely AB) after 3 months.

Complications and Patient Morbidity. Most studies reported an uneventful clinical course with no major complications either during the harvesting of MSCs, or the augmentation procedure. Harvesting of MSCs, both extra-oral and oral, was reported to be well tolerated by patients with minimal morbidity. Minor procedural complications such as wound dehiscence and sinus membrane perforations occurred, but healed uneventfully with standard treatments.

In one study, harvesting of mandibular retromolar bone resulted in inferior alveolar nerve injury in one patient and infection of the site in two patients, both of which healed with standard care.[42] Filho Cerruti and colleagues[19] reported the failure of one SA graft (infection) and one RA graft (nonintegration) using BMA in allograft scaffolds. Three other studies reported no major complications using a cellular-allograft matrix[32,40] or allogeneic bone scaffold.[22] Three studies reported significantly unfavorable outcomes 3 months after SA with PMSCs in PLGA-scaffolds, which necessitated secondary augmentation procedures.[29,37,39] Kaigler and colleagues[28] reported a greater need for secondary grafting procedures after SP (during implant placement) to compensate for implant thread exposure, in extraction sites augmented with collagen sponge alone compared with sites augmented with collagen sponge and BMSCs.

Implant Survival. Implant "survival" in most studies reporting this outcome was defined as the presence of a clinically functional and successfully osseointegrated fixture, without mobility or signs of infection.

Uncontrolled studies: Four studies reported 100% implant survival 1 to 5 years after RA and 11 studies reported 93% to 100% implant survival up to 5 years after SA, using cell-based approaches.

Controlled studies: One RCT[28] reported 100% implant survival in both groups, 1 year after conventional and cell-based SP. Another RCT[44] reported two implant failures (89.47% survival) during the healing period after cell-based SA, but 100% survival of the remaining implants up to 2.5 years. Voss and colleagues[39] reported lower implant survival in the cell-based SA group (90.67%) than the control (AB) group (99.45%) after at least 24 months. No studies reported significant differences in long-term implant survival between cell-based and conventional augmentation methods.

DISCUSSION

Although AB is considered the "gold standard" for regeneration, its use is limited by the need for additional harvesting procedures and significant donor-site morbidity.[47] Allogeneic bone grafts are associated with the risk of infection, disease transmission, and immune-rejection, while osteoconductive bone substitutes (xenografts, alloplasts) require extended healing times (5–9 months) for optimal bone formation.[48,49] Therefore, the goal of regenerative science is to identify minimally invasive techniques using biomaterials which possess the osteogenecity of AB, but avoid the need for harvesting and prolonged healing periods. Tissue-engineered and cell-based approaches have been identified as "platinum standard" alternatives[50] which fulfill the aforementioned criteria and can provide patients with "personalised autologous bone grafts".[51]

From a clinical viewpoint, large-scale application of cell-based regenerative approaches can be envisaged if a ready, reliable, and reproducible source of autologous stem cells is identified, that is, the cells should be "readily" accessible with minimal invasiveness and patient morbidity; should possess the ability to be "reliably" isolated and cultured in vitro into desired cell types including osteogenic progenitors; and should be "reproducible" for use in multiple clinical indications. In this regard, adult MSCs offer the greatest potential for cell-based bone regeneration.[13]

BMSCs are reportedly the most widely investigated and used adult MSCs.[51] BMSCs, combined with various scaffolds, were also used in a majority of studies included in this review. Patients' iliac crest was the most frequently reported source for autologous BMSCs and the harvesting procedure was generally well tolerated.

All studies, using autologous BMSCs for RA, GBR, SP, and SA reported favorable outcomes. However, Meijer and colleagues[20] could identify de novo bone formation (osteogenesis) in only one of five patients after RA with BMSCs in an HA scaffold. The authors attributed the unfavorable outcome to possibly insufficient vascularization of the graft, which might have led to cell death soon after implantation. Recently, the addition of angiogenic growth factors such as vascular-endothelial growth factor (VEGF) to the MSC-scaffold construct has been proposed to promote early vascularization of the graft.[52]

BMAC is a recognized method for isolating the mononuclear fraction of cells (MNC) from autologous bone marrow.[43] Bone marrow MNC mainly consist of stem cells of two lineages – hematopoietic (HSCs) and nonhematopoietic mesenchymal or stromal stem cells (MSCs). Concentration of MSCs, capable of osteogenic differentiation, in bone marrow is reported to be limited and therefore in vitro isolation and "culture expansion," to reach a "clinically significant" number, is recommended prior to clinical application.[53] During this procedure the MSCs can also be directed toward differentiating into desired lineages, for example, osteoblasts. However, the procedure requires a highly sterile "Good Manufacturing Practice" facility and involves significantly added time and costs.[53] BMAC is reported to be a time- and cost-effective "chair side" method to predictably isolate MNC including MSCs in sufficient numbers for clinical application in bone regeneration.[12,43] These findings were supported by two RCTs in our review, which reported greater[41] or comparable[42] bone formation in sinuses augmented with BMAC and Bio-Oss compared with those with AB and Bio-Oss.

Use of MSCs from the mandibular periosteum (PMSCs) was also frequently reported. Although several in vitro and animal studies have confirmed the osteogenic potential of PMSCs, harvesting is reported to be invasive and the quantity of tissue required for predictable regeneration is unknown.[54] Only one study each reported the use of alveolar (tuberosity) bone cells (AMSCs)[44] and DPSCs[26] for SA and SP, respectively. Moreover, no studies reported the use of gingival or mucosal stem cells, both of which have been reported to possess a high potential for osteogenic differentiation.[55,56]

Two studies reported the successful use of a cellular-allograft matrix prepared from cadaveric bone containing vital MSCs (Osteocel), suggesting the potential for application of adequately processed and secured allogeneic MSCs in bone augmentation.[32,40] This could eliminate the need for bone marrow biopsy and other tissue harvesting which might add to the procedural burden and induce some patient morbidity.[32,57]

Another essential component of tissue engineering is the scaffold used to deliver MSCs to the regeneration site. The scaffold should provide a supporting framework for cell colonization, migration, growth, differentiation, and ultimately growth of the regenerating tissue.[58] Requirements of an ideal scaffold are reported to be: (1) biocompatibility and osteoconductivity; (2) mechanical properties similar to host bone; (3) sufficient porosity to allow vascular in-growth; and (4) predictable in vivo resorbability.[59] A range of autologous, allogeneic, xenogeneic, and alloplastic scaffolds was reported across the included studies. DBBM (Bio-Oss) was used as a scaffold for MSCs in five controlled SA studies with favorable outcomes – indicating that it provides adequate osteoconductivity, porosity for vascular in-growth, and stability for cell proliferation.[60] On the other hand, PLGA scaffolds yielded less than favorable outcomes in three studies.[29,37,39] Mangano and colleagues[38] reported that the rapid resorption rate of PLGA scaffolds did not provide the mechanical stability to promote cellular activity, and highlighted the need for scaffold-material development. However, the "ideal" scaffold material and MSC-scaffold combination remains to be found. A trend toward the development of polymer–ceramic "composite" scaffold materials has recently been identified, and the addition of various GFs (VEGF, TGF-β, BMP, etc.) to enhance the regeneration potential of scaffolds by inducing osteogenesis and vascularization has been suggested.[59]

Although clinical evidence for the use of GFs and PRP in alveolar augmentation is limited, the addition of these products is reported to accelerate bone regeneration by enhancing angiogenesis, and inducing cell proliferation and differentiation.[61–63] Although supplementation of graft materials with GFs was not reported in any of the included studies, most studies used BMA as a source for MSCs – which is also recognized as a rich source of GFS, especially VEGF, TGF-β, and BMP.[64] Only one study[23] reported the combination of PMSCs, AB, and PRP to have a significantly superior osteogenic response in the regeneration sites compared with the use of solely AB. However, the efficacy of PRP

or GF addition to cell-based constructs remains to be determined in future RCTs.

Because the primary outcome in most controlled studies was assessment of short-term bone regeneration, only three studies reported comparative implant survival data. No significant differences were observed in the short-term (1–3 years) survival of implants placed in cell-based and conventionally augmented sites. However, uncontrolled studies reported values ranging from 93% to 100% (3 months to 6 years) after cell-based augmentation, which are comparable with survival rates after conventional grafting procedures.[65,66]

Another outcome of interest in the review was the rate of complications and patient morbidity associated with cell-based grafting. Most studies included a statement regarding the occurrence or absence of complications in their study groups (Table 6). No major complications or adverse events were reported in relation to either the harvesting (including BM aspiration) or the use of MSCs, although no studies explicitly reported the method of assessing complications (patient reported or clinician reported). Graft failure was reported in some studies but was mainly attributed to properties of the scaffold material (e.g., rapid resorption of PLGA).

Effectiveness of Cell-Based Approaches: Summary of Evidence

The effectiveness of bone regeneration techniques can be best evaluated using a controlled study design, ideally with a "gold standard" (AB) control group and "gold standard" (histomorphometric) comparison of outcomes.[67,68] Recent analyses of histomorphometric data have identified a comparable proportion of new bone formation using solely AB or a combination of AB and bone substitutes (e.g., Bio-Oss), when allowing for a healing period of 5 to 9 months.[48,49,69]

Supplementing bone substitutes with MSCs and/or GFs is hypothesized to accelerate new bone formation (NBF) by replicating the properties of AB, allowing early implant placement. In our review, nine controlled studies compared histomorphometric "new bone formation" of cell-based and conventional grafting procedures (Table 7). SA with BMAC in Bio-Oss resulted in significantly greater[41] or comparable[42] NBF compared to a combination of AB and Bio-Oss, after 3 to 4 months. The effect was attributed to the presence of native MSCs in the BMAC. However, the addition of AMSCs to the combination of AB and Bio-Oss failed to demonstrate a significant benefit.[44] Therefore, it may be hypothesized that the addition of MSCs can improve the regenerative potential of Bio-Oss but will have little additional effect on a combination of AB and Bio-Oss. However, a significant advantage of the cell-based approach is avoiding the need for AB harvesting.

Another important factor in bone augmentation, especially SA, is the volumetric stability of the graft over time.[70] The addition of Bio-Oss to AB is reported to provide additional stability, as augmentation with solely AB is characterized by unpredictable resorption.[69] Fuerst and colleagues[33] reported a 39.24% reduction in graft volume 1 year after SA with bone MSCs and Bio-Oss, which is comparable to the resorption rate of AB + Bio-Oss. Sauerbier and colleagues[42] reported significantly greater bone volume in sinuses augmented with Bio-Oss supplemented with BMAC compared to augmentation with AB and Bio-Oss, after 3 to 4 months. However, a more recent RCT[45] found no significant differences in graft volume reductions 6 months after SA with solely Bio-Oss or Bio-Oss supplemented with tibial BMA or iliac BMAC. Therefore, it can be hypothesized that the addition of BMAC or BMSCs to Bio-Oss may not alter its resorption rate but may improve its short-term (3–6 months) volume stability in comparison with a combination of AB and Bio-Oss. However, future well-designed RCTs are required to confirm these findings in the long term.

CONCLUSIONS

The following conclusions are based on the reviewed evidence from 15 controlled studies involving few patients, considerable heterogeneity, and a moderate-to-high risk of bias, and must therefore be interpreted with caution.

1. Alveolar bone augmentation using cultured autologous adult MSCs, or noncultured tissues containing MSCs (e.g., BMA or BMAC), in combination with osteoconductive bone substitute scaffolds (e.g., Bio-Oss) appears to be safe, predictable, and comparable with current evidence-based grafting methods (e.g., AB + Bio-Oss) in terms of clinical effectiveness (bone regeneration).
2. A significant advantage of this approach is the avoidance of AB harvesting.

TABLE 7 Summary of Histomorphometric Outcomes from the Included Controlled Studies

Cell-Based (Test) Group	Control Group	Design	Patients (Procedures)	Follow-Up	Results	NBF (%) Test vs Control	Estimated Risk of Bias
RA							
BMA + Allograft	Solely allograft	RCT[22]	10 (10)	6 months	Mean ± SD	60.7 ± 16.1 vs 41.4 ± 12.5*	High
SP							
BMSCs + Gelatine sponge	Solely gelatine sponge	RCT[28]	24 (24)	6 weeks	Mean ± SD	28.8 ± 9.1 vs 19.6 ± 4.2	Moderate
				12 weeks		35.2 ± 8.9 vs 35.1 ± 3.2	
BMA	Blood clot	RCT[27]	13 (30)	6 months	Median ± SD	45.4 ± 7.2 vs 42.8 ± 11.3	Moderate
SFA							
MSCs in Allograft	Solely allograft	RCT[40]	14 (21)	3–4 months	Median ± SD	32.5 ± 6.8 vs 18.3 ± 10.6*	High
BMAC + DBBM	AB + DBBM	RCT[41]	11 (22)	3–4 months	Median ± SD	17.7 ± 7.3 vs 12.0 ± 6.6*	Moderate
BMAC + DBBM	AB + DBBM	RCT[42]	26 (45)	3–4 months	Mean ± SD	12.6 ± 1.7 vs 14.3 ± 1.8	Moderate
AMSCs + AB + DBBM	AB + DBBM	RCT[44]	20 (20)	4 months	Median (95% CI)	30 (23–40) vs 25 (21–37)	Moderate
BMSCs + DBBM	BMAC + DBBM	CT[43]	11 (18)	3 months	Estimated value (90% CI)	15.5 (8–22) vs 19.9 (10–29)	Moderate
PMSCs + Collagen matrix	DBBM	CT[36]	11 (17)	6–8 months	Median (range)	38 (30–51) vs 25 (22–26)*	High
BMSCs + PLGA	HA	CT[38]	5 (10)	6 months	Mean ± SD	37.3 ± 19.5 vs 54.6 ± 21.1	Moderate

*Statistically significant difference ($p < .05$).

RCT, randomized controlled trial; CT, controlled trial; BMA, bone marrow aspirate; BMAC, bone marrow aspirate concentrate; AB, autogenous bone; DBBM, deproteinized bovine bone mineral; PLGA, polylactic–polyglycolic acid copolymer; HA, hydroxyl-apatite; NBF, histomorphometric new bone formation; SD, standard deviation; 95% CI, 95% confidence interval.

3. Bone marrow appears to be the most "ready" and "reliable" source of MSCs for bone regeneration. BMAC seems to be a feasible alternative to avoid additional time and costs associated with in vitro cell culture. Periosteum, alveolar bone, and dental pulp represent potential intraoral MSC sources.
4. DBBM (Bio-Oss) appears to be a reliable scaffold to deliver and support MSCs. The efficacy of PLGA scaffolds has been questioned due to a rapid resorption rate.
5. Addition of PRP to the cell-scaffold construct may enhance bone regeneration. The role of growth factors, especially BMP and VEGF, is unknown, although early vascularization of the graft is reported to be critical for cell survival and success.
6. The comparative evidence for other outcomes such as long-term volumetric graft stability and implant/restoration survival between cell-based and noncell-based approaches is presently insufficient.
7. Future well-designed and adequately powered RCTs should evaluate the long-term efficacy and patient-based outcomes (morbidity, time-/cost-effectiveness) of cell-based approaches for alveolar bone regeneration, in relation to existing evidence-based methods.

REFERENCES

1. Chiapasco M, Casentini P, Zaniboni M. Bone augmentation procedures in implant dentistry. Int J Oral Maxillofac Implants 2009; 24 (Suppl):237–259.
2. Tonetti MS, Hämmerle CH. Advances in bone augmentation to enable dental implant placement: Consensus Report of the Sixth European Workshop on Periodontology. J Clin Periodontol 2008; 35:168–172.
3. Esposito M, Grusovin MG, Felice P, Karatzopoulos G, Worthington HV, Coulthard P. Interventions for replacing missing teeth: horizontal and vertical bone augmentation techniques for dental implant treatment. Cochrane Database Syst Rev 2009; 4:CD003607. DOI: 10.1002/14651858.CD003607.pub4
4. Horváth A, Mardas N, Mezzomo LA, Needleman IG, Donos N. Alveolar ridge preservation. A systematic review. Clin Oral Investig 2012; 17:341–363.
5. Esposito M, Grusovin MG, Rees J, et al. Interventions for replacing missing teeth: augmentation procedures of the maxillary sinus. Cochrane Database Syst Rev 2010; 3: CD008397. DOI: 10.1002/14651858.CD008397
6. Jensen SS, Terheyden H. Bone augmentation procedures in localized defects in the alveolar ridge: clinical results with different bone grafts and bone-substitute materials. Int J Oral Maxillofac Implants 2009; 24 (Suppl):218–236.
7. Nkenke E, Stelzle F. Clinical outcomes of sinus floor augmentation for implant placement using autogenous bone or bone substitutes: a systematic review. Clin Oral Implants Res 2009; 20 (Suppl 4):124–133.
8. Khojasteh A, Behnia H, Dashti SG, Stevens M. Current trends in mesenchymal stem cell application in bone augmentation: a review of the literature. J Oral Maxillofac Surg 2012; 70:972–982.
9. Egusa H, Sonoyama W, Nishimura M, Atsuta I, Akiyama K. Stem cells in dentistry – Part II: clinical applications. J Prosthodont Res 2012; 56:229–248.
10. Oppenheimer AJ, Mesa J, Buchman SR. Current and emerging basic science concepts in bone biology: implications in craniofacial surgery. J Craniofac Surg 2012; 23:30–36.
11. Bouhadir KH, Mooney DJ. Promoting angiogenesis in engineered tissues. J Drug Target 2001; 9:397–406.
12. Jäger M, Herten M, Fochtmann U, et al. Bridging the gap: bone marrow aspiration concentrate reduces autologous bone grafting in osseous defects. J Orthop Res 2011; 29:173–180.
13. Hynes K, Menicanin D, Gronthos S, Bartold PM. Clinical utility of stem cells for periodontal regeneration. Periodontol 2000 2012; 59:203–227.
14. Mangano FG, Tettamanti L, Sammons RL, et al. Maxillary sinus augmentation with adult mesenchymal stem cells: a review of the current literature. Oral Surg Oral Med Oral Pathol Oral Radiol 2013; 115:717–723. DOI: 10.1016/j.oooo.2012.09.087
15. Higgins JPT, Green S, eds. 2011. Cochrane handbook for systematic reviews of interventions version 5.1.0 The Cochrane Collaboration, 2011. http://www.cochranehandbook.org. (Accessed March 1, 2013).
16. Tonetti M, Palmer R. Clinical research in implant dentistry: study design, reporting and outcome measurements: consensus report of Working Group 2 of the VIII European Workshop on Periodontology. J Clin Periodontol 2012; 39 (Suppl 12):73–80.
17. Higgins JP, Altman DG, Gøtzsche PC, et al.; Group CBM; Group CSM. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343:d5928.
18. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011; 64:401–406.
19. Filho Cerruti H, Kerkis I, Kerkis A, et al. Allogenous bone grafts improved by bone marrow stem cells and platelet growth factors: clinical case reports. Artif Organs 2007; 31:268–273.
20. Meijer GJ, de Bruijn JD, Koole R, van Blitterswijk CA. Cell based bone tissue engineering in jaw defects. Biomaterials 2008; 29:3053–3061.

21. Ueda M, Yamada Y, Kagami H, Hibi H. Injectable bone applied for ridge augmentation and dental implant placement: human progress study. Implant Dent 2008; 17:82–90.
22. da Costa CE, Pelegrine AA, Fagundes DJ, Simoes MeJ, Taha MO. Use of corticocancellous allogeneic bone blocks impregnated with bone marrow aspirate: a clinical, tomographic, and histomorphometric study. Gen Dent 2011; 59:e200–e205.
23. Nagata M, Hoshina H, Li M, et al. A clinical study of alveolar bone tissue engineering with cultured autogenous periosteal cells: coordinated activation of bone formation and resorption. Bone 2012; 50:1123–1129.
24. Yamada Y, Nakamura S, Ito K, et al. Injectable bone tissue engineering using expanded mesenchymal stem cells. Stem Cells 2013; 31:572–580.
25. Soltan M, Smiler D, Prasad HS, Rohrer MD. Bone block allograft impregnated with bone marrow aspirate. Implant Dent 2007; 16:329–339.
26. d'Aquino R, De Rosa A, Lanza V, et al. Human mandible bone defect repair by the grafting of dental pulp stem/progenitor cells and collagen sponge biocomplexes. Eur Cell Mater 2009; 18:75–83.
27. Pelegrine AA, da Costa CE, Correa ME, Marques JF. Clinical and histomorphometric evaluation of extraction sockets treated with an autologous bone marrow graft. Clin Oral Implants Res 2010; 21:535–542.
28. Kaigler D, Pagni G, Park CH, et al. Stem cell therapy for craniofacial bone regeneration: a randomized, controlled, feasibility trial. Cell Transplant 2012; 22:767–777. DOI: 10.3727/096368912X652968
29. Schimming R, Schmelzeisen R. Tissue-engineered bone for maxillary sinus augmentation. J Oral Maxillofac Surg 2004; 62:724–729.
30. Shayesteh YS, Khojasteh A, Soleimani M, Alikhasi M, Khoshzaban A, Ahmadbeigi N. Sinus augmentation using human mesenchymal stem cells loaded into a beta-tricalcium phosphate/hydroxyapatite scaffold. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008; 106:203–209.
31. Yamada Y, Nakamura S, Ito K, et al. Injectable tissue-engineered bone using autogenous bone marrow-derived stromal cells for maxillary sinus augmentation: clinical application report from a 2-6-year follow-up. Tissue Eng Part A 2008; 14:1699–1707.
32. McAllister BS, Haghighat K, Gonshor A. Histologic evaluation of a stem cell-based sinus-augmentation procedure. J Periodontol 2009; 80:679–686.
33. Fuerst G, Strbac GD, Vasak C, et al. Are culture-expanded autogenous bone cells a clinically reliable option for sinus grafting? Clin Oral Implants Res 2009; 20:135–139.
34. Trautvetter W, Kaps C, Schmelzeisen R, Sauerbier S, Sittinger M. Tissue-engineered polymer-based periosteal bone grafts for maxillary sinus augmentation: five-year clinical results. J Oral Maxillofac Surg 2011; 69:2753–2762.
35. Yamada Y, Nakamura S, Ueda M, Ito K. Osteotome technique with injectable tissue-engineered bone and simultaneous implant placement by cell therapy. Clin Oral Implants Res 2013; 24:468–474.
36. Springer IN, Nocini PF, Schlegel KA, et al. Two techniques for the preparation of cell-scaffold constructs suitable for sinus augmentation: steps into clinical application. Tissue Eng 2006; 12:2649–2656.
37. Zizelmann C, Schoen R, Metzger MC, et al. Bone formation after sinus augmentation with engineered bone. Clin Oral Implants Res 2007; 18:69–73.
38. Mangano C, Piattelli A, Mangano A, et al. Combining scaffolds and osteogenic cells in regenerative bone surgery: a preliminary histological report in human maxillary sinus augmentation. Clin Implant Dent Relat Res 2009; 11 (Suppl 1):e92–102.
39. Voss P, Sauerbier S, Wiedmann-Al-Ahmad M, et al. Bone regeneration in sinus lifts: comparing tissue-engineered bone and iliac bone. Br J Oral Maxillofac Surg 2010; 48:121–126.
40. Gonshor A, McAllister BS, Wallace SS, Prasad H. Histologic and histomorphometric evaluation of an allograft stem cell-based matrix sinus augmentation procedure. Int J Oral Maxillofac Implants 2011; 26:123–131.
41. Rickert D, Sauerbier S, Nagursky H, Menne D, Vissink A, Raghoebar GM. Maxillary sinus floor elevation with bovine bone mineral combined with either autogenous bone or autogenous stem cells: a prospective randomized clinical trial. Clin Oral Implants Res 2011; 22:251–258.
42. Sauerbier S, Rickert D, Gutwald R, et al. Bone marrow concentrate and bovine bone mineral for sinus floor augmentation: a controlled, randomized, single-blinded clinical and histological trial – per-protocol analysis. Tissue Eng 2011; 17:2187–2197.
43. Sauerbier S, Stricker A, Kuschnierz J, et al. In vivo comparison of hard tissue regeneration with human mesenchymal stem cells processed with either the FICOLL method or the BMAC method. Tissue Eng Part C Methods 2010; 16:215–223.
44. Hermund NU, Stavropoulos A, Donatsky O, et al. Reimplantation of cultivated human bone cells from the posterior maxilla for sinus floor augmentation. Histological results from a randomized controlled clinical trial. Clin Oral Implants Res 2012; 23:1031–1037.
45. Kühl S, Payer M, Kirmeier R, Wildburger A, Wegscheider W, Jakse N. The influence of bone marrow aspirates and concentrates on the early volume stability of maxillary sinus grafts with deproteinized bovine bone mineral – first results of a RCT. Clin Oral Implants Res 2013. DOI: 10.1111/clr.12101
46. Hermund NU, Donatsky O, Nielsen H, Clausen C, Holmstrup P. Long-term changes in graft height after

sinus floor augmentation with mesenchymal stem cells in a randomised clinical trial: radiographic evaluation with a minimum followup of 2.5 years. J Dent Med Med Sci 2012; 2:5–14.
47. Rogers GF, Greene AK. Autogenous bone graft: basic science and clinical implications. J Craniofac Surg 2012; 23:323–327.
48. Handschel J, Simonowska M, Naujoks C, et al. A histomorphometric meta-analysis of sinus elevation with various grafting materials. Head Face Med 2009; 5:12.
49. Rickert D, Slater JJ, Meijer HJ, Vissink A, Raghoebar GM. Maxillary sinus lift with solely autogenous bone compared to a combination of autogenous bone and growth factors or (solely) bone substitutes. A systematic review. Int J Oral Maxillofac Surg 2012; 41:160–167.
50. Soltan M, Smiler DG, Gailani F. A new "platinum" standard for bone grafting: autogenous stem cells. Implant Dent 2005; 14:322–325.
51. Bhumiratana S, Vunjak-Novakovic G. Concise review: personalized human bone grafts for reconstructing head and face. Stem Cells Transl Med 2012; 1:64–69.
52. Nguyen LH, Annabi N, Nikkhah M, et al. Vascularized bone tissue engineering: approaches for potential improvement. Tissue Eng Part B Rev 2012; 18:363–382.
53. Lucarelli E, Donati D, Cenacchi A, Fornasari PM. Bone reconstruction of large defects using bone marrow derived autologous stem cells. Transfus Apher Sci 2004; 30:169–174.
54. Nishimura M, Takase K, Suehiro F, Murata H. Candidates cell sources to regenerate alveolar bone from oral tissue. Int J Dent 2012; 2012:857192.
55. Tomar GB, Srivastava RK, Gupta N, et al. Human gingiva-derived mesenchymal stem cells are superior to bone marrow-derived mesenchymal stem cells for cell therapy in regenerative medicine. Biochem Biophys Res Commun 2010; 393:377–383.
56. Treves-Manusevitz S, Hoz L, Rachima H, et al. Stem cells of the lamina propria of human oral mucosa and gingiva develop into mineralized tissues in vivo. J Clin Periodontol 2013; 40:73–81.
57. Ryan JM, Barry FP, Murphy JM, Mahon BP. Mesenchymal stem cells avoid allogeneic rejection. J Inflamm (Lond) 2005; 2:8.
58. Hutmacher DW, Schantz JT, Lam CX, Tan KC, Lim TC. State of the art and future directions of scaffold-based bone engineering from a biomaterials perspective. J Tissue Eng Regen Med 2007; 1:245–260.
59. Bose S, Roy M, Bandyopadhyay A. Recent advances in bone tissue engineering scaffolds. Trends Biotechnol 2012; 30:546–554.
60. Herten M, Rothamel D, Schwarz F, Friesen K, Koegler G, Becker J. Surface- and nonsurface-dependent in vitro effects of bone substitutes on cell viability. Clin Oral Investig 2009; 13:149–155.
61. Jung RE, Thoma DS, Hammerle CH. Assessment of the potential of growth factors for localized alveolar ridge augmentation: a systematic review. J Clin Periodontol 2008; 35:255–281.
62. Arora NS, Ramanayake T, Ren YF, Romanos GE. Platelet-rich plasma in sinus augmentation procedures: a systematic literature review: Part II. Implant Dent 2010; 19:145–157.
63. Del Fabbro M, Bortolin M, Taschieri S, Weinstein RL. Effect of autologous growth factors in maxillary sinus augmentation: a systematic review. Clin Implant Dent Relat Res 2013; 15:205–216.
64. Smiler DG, Soltan M, Soltan C, Matthews C. Growth factors and gene expression of stem cells: bone marrow compared with peripheral blood. Implant Dent 2010; 19:229–240.
65. Clementini M, Morlupi A, Canullo L, Agrestini C, Barlattani A. Success rate of dental implants inserted in horizontal and vertical guided bone regenerated areas: a systematic review. Int J Oral Maxillofac Surg 2012; 41:847–852.
66. Cabezas-Mojón J, Barona-Dorado C, Gómez-Moreno G, Fernández-Cáliz F, Martínez-González JM. Meta-analytic study of implant survival following sinus augmentation. Med Oral Patol Oral Cir Bucal 2012; 17:e135–e139.
67. Farré-Guasch E, Prins HJ, Overman JR, et al. Human maxillary sinus floor elevation as a model for bone regeneration enabling the application of one-step surgical procedures. Tissue Eng Part B Rev 2013; 19:69–82.
68. Iwaniec UT, Wronski TJ, Turner RT. Histological analysis of bone. Methods Mol Biol 2008; 447:325–341.
69. Jensen T, Schou S, Stavropoulos A, Terheyden H, Holmstrup P. Maxillary sinus floor augmentation with Bio-Oss or Bio-Oss mixed with autogenous bone as graft: a systematic review. Clin Oral Implants Res 2012; 23:263–273.
70. Klijn RJ, van den Beucken JJ, Bronkhorst EM, Berge SJ, Meijer GJ, Jansen JA. Predictive value of ridge dimensions on autologous bone graft resorption in staged maxillary sinus augmentation surgery using Cone-Beam CT. Clin Oral Implants Res 2012; 23:409–415.