Clinical efficacy and safety of P-15 peptide enhanced bone graft substitute in surgical bone regenerative procedures in adult maxillofacial, spine, and trauma patients

a systematic literature review

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Aims

Autologous bone graft (ABG) is considered the 'gold standard' among graft materials for bone regeneration. However, complications including limited availability, donor site morbidity, and deterioration of regenerative capacity over time have been reported. P-15 is a synthetic peptide that mimics the cell binding domain of Type-I collagen. This peptide stimulates new bone formation by enhancing osteogenic cell attachment, proliferation, and differentiation. The objective of this study was to conduct a systematic literature review to determine the clinical efficacy and safety of P-15 peptide in bone regeneration throughout the skeletal system.

Methods

PubMed, Embase, Web of Science, and Cochrane Library were searched for relevant articles on 13 May 2023. The systematic review was reported according to the PRISMA guidelines. Two reviewers independently screened and assessed the identified articles. Quality assessment was conducted using the methodological index for non-randomized studies and the risk of bias assessment tool for randomized controlled trials.

Results

After screening, 28 articles were included and grouped by surgical indication, e.g. maxillofacial procedures (n = 18), spine (n = 9), and trauma (n = 1). Published results showed that P-15 peptide was effective in spinal fusion (n = 7) and maxillofacial (n = 11), with very few clinically relevant adverse events related to P-15 peptide.

Conclusion

This systematic literature review concluded that moderate- (risk of bias, some concern: 50%) to high-quality (risk of bias, low: 46%) clinical evidence exists showing equivalent safety and efficacy in bone regeneration using a P-15 peptide enhanced bone graft substitute compared to ABG. P-15 peptide is safe and effective, resulting in rapid bone formation with a low probability of minor complications.

Bone & Joint Research

Article focus

- Clinical efficacy and safety of P-15 peptide in bone regeneration procedures.
- Systematic review on numerous clinical indications in bone regeneration procedures.

Key messages

- ABM/P-15 is effective and safe to use in multiple surgical procedures as a bone graft substitute (BGS) for bone regenerative indications.
- High-quality clinical evidence exists for equivalent safety and efficacy in bone healing using a P-15 peptide enhanced BGS compared to autologous bone graft.
- P-15 peptide is a safe and effective BGS resulting in rapid bone formation with a low probability of minor complications.

Strengths and limitations

- This is the first systematic review that considers the available evidence for the clinical efficacy and safety of P-15 peptide in multiple surgical procedures in bone regeneration.
- Studies with long-term clinical follow-up were included.
- Heterogeneity of the clinical indications, outcome measures, and bone fusion definitions resulted in reduced generalizability.

Introduction

Bone grafting procedures are increasingly common in spine surgery, tumour surgery, and trauma and maxillofacial surgical procedures.[1,2] It is estimated that 2.2 million annual bone grafting procedures are performed globally. This is predicted to rise annually by 13% along with the increased number of bone-reconstructive surgical procedures associated with an ageing population.[3]

Autologous bone graft (ABG) is considered the 'gold standard' for regenerative bone healing.[1,2,4,5] ABG is harvested from cancellous marrow and consists predominantly of inorganic calcium phosphate combined with organic type-I collagen. The type-I collagen binding domain is imperative for osteoblasts and mesenchymal stem cells (MSCs) to migrate and adhere to the bone matrix.[6] In this bone matrix, osteogenic cells, cytokines, and regulatory proteins are integrated. This would give ABG osteogenic, osteoconductive, and osteoinductive properties.[2] Nevertheless, several limitations have been reported.[2,4,5] First of all, the number of stem cells and growth factors change significantly with age, thereby diminishing the regenerative capacity of ABG.[7] Additionally, limited volume, and variations in bone quality and donor site morbidity due to harvesting, have been reported as disadvantages.[1,2,4,5]

To overcome these drawbacks, various bone graft materials and bone graft substitutes (BGS) have been developed including allograft, synthetic proteins, ceramics, and cellular-based allografts (CBAs). Limited availability and variable quality combined with lower regenerative potential and decreased fusion rates make allograft suboptimal.[8] Bone morphogenetic proteins are the most potent bone formation materials currently available for adjunctive surgical use in the clinic. These proteins, however, can have both an anabolic and catabolic effect, and can thus stimulate both osteoblast and osteoclast activities. Moreover, serious complications have been reported in the YODA trial.[9] Issues with dosage, complications, and cost-effectiveness prevent broad clinical use.

There is variable evidence that demineralized bone matrix (DBM) is effective on its own, with its clinical osteoinductive capacity questioned in systematic reviews.[10,11] In certain indications, DBM is used as an extender to other bone graft materials.[8] Ceramic materials do yield good bone formation over time but at a delayed rate compared to ABGs. This is because the cellular component (osteoprogenitor cells) is not available in these products and needs to be provided by the body, a process that takes time. In attempts to improve osteogenic properties, MSCs were added to allografts, known as CBAs. Initially, promising results were found in pre-clinical in vitro models but these did not translate to successful animal studies.[12]

Recently, bioactive synthetic peptide-enhanced BGS have been developed. Synthetic peptides mimic cell binding domains of naturally occurring proteins. The peptides are absorbed on to the surface of a scaffold, resulting in a biomaterial that mimics the natural environment of bone closely.[8] Collagen comprises more than 90% of the bone matrix and is a major regulator of cell adhesion. P-15 peptide is a synthetic replicate of a 15-amino acid residue sequence (^{766}GTPGPQGIAGQRGVV^{780}) naturally found in the alpha-I chain of type I collagen.[13] P-15 mimics the properties of collagen in promoting interactions with cell surface receptors such as integrins, discoidin receptor 2, and fibronectin. Combining P-15 peptide in high density with anorganic hydroxyapatite bone minerals (ABM), a source of calcium phosphate, increases MSC and osteoblast adhesion to the ABM scaffold and improves its osteoconductivity.[13-17] This is a result of receptor-mediated binding which promotes cellular biological activation. Furthermore, ABM/P-15 stimulates bone-producing cell attachment, proliferation, and differentiation, as well as promoting intramembranous and endochondral ossification.[16,18,19] In contrast to osteoinductive proteins, relatively inexpensive osteogenic cell binding peptides retain specific biological activity without the potential risks associated with growth factors by specifically only targeting the MSC and osteoblast. ABM/P-15 may be combined with an inert carrier component to confer specific handling or delivery properties (i-FACTOR Bone Graft component proportion (w/w), ABM/P-15 particles 51.9%, sodium carboxymethylcellulose 1.5%, glycerin USP 7.0%, and water USP 39.6%).[20]

Thus, P-15 may prove to be a successful alternative to ABG. Currently, most of the evidence for P-15 as a BGS is limited to dental and spinal procedures.[21,22] A systematic overview of the clinical efficacy and safety of P-15 across procedures is currently lacking. Therefore, this systematic review aims to provide a comprehensive overview of the clinical safety and efficacy of P-15 peptide-enhanced BGS in multiple bone regeneration procedures.

Methods

Protocol registration

The study protocol for this systematic review was registered in PROSPERO under registration number CRD42022306683. This study was written in accordance with the Preferred Reporting

Items for Systematic reviews and Meta-Analyses (PRISMA)[23] statement. A completed PRISMA checklist can be found in the Supplementary Material.

Eligibility criteria

Human clinical studies investigating spinal, maxillofacial, or traumatological surgical interventions utilizing P-15 peptide-enhanced bone graft, with a minimum follow-up period of three months, were eligible for inclusion. Additionally, articles had to be available in full-text form and in the English language. Studies that considered malignancies or infections, or which were published prior to 1990, were excluded.

Information sources and research

On 13 May 2023, a search was conducted in PubMed (Medline), Embase (OVID), Web of Science (WOS), and the Cochrane library. A search string was constructed using the following MeSH terms and their synonyms, and was adapted for each database: ("General Surgery" OR "Surgical procedures, operative" OR "reconstructive surgical procedures" OR "orthopedic procedures" OR "maxillofacial surgery" OR "cervicoplasty" OR "guided tissue regeneration" OR "guided tissue regeneration, periodontal" OR "regenerative medicine" OR "bone regeneration" OR "Spine" OR "Neck" OR "Spinal Fusion" OR "Intervertebral Disc Displacement") AND ("cell-binding peptide P-15" OR "P-15 peptide enhanced bone graft" OR "synthetic peptide P-15"). The following filters were applied: clinical, comparative, randomized controlled trials, observational and multicentre studies, English language, full text, publication year from 1990 to present. The detailed search per database can be found in the Supplementary Material.

Study selection

Screening of title/abstract and subsequently full-text studies on eligibility was performed by two reviewers independently (BJS, TAH). Any disagreement was resolved by discussion or, if necessary, by a third assessor (JJCA). The online tool Rayyan.ai (USA) was used to aid the reviewers during screening. References were screened for additionally relevant articles.

Data collection process and data synthesis

A standardized Excel format was used to extract relevant data. The data extraction was independently performed by two reviewers (BJS, TAH). Discrepancies were first discussed, and disagreements were settled by a third assessor (JJCA). The following data were extracted: digital object identifier (DOI), article title, year of publication, first author, study design, level of evidence, location of implant, experimental and control groups, intervention used, and the number of participants included. When appropriate, subgroups of mean age, sex, follow-up time, initial diagnosis, inclusion and exclusion criteria, clinical measurements, radiological measurements, adverse events related to the implant and adverse events related to the intervention, funding, and conflict of interests were detailed.

Studies were clustered in three groups depending on the implant location: spine, trauma, and maxillofacial. Data were summarized into tables per cluster and study design. Tables were accompanied by narrative descriptions. When available, the primary outcome was percentage of fusion or defect fill. If those measurements were unavailable, change in clinical attachment level (CAL) or time until consolidation was reported.

Methodological quality assessment

Quality assessment was also conducted by two reviewers independently (BJS, TAH) using the Risk-of-Bias tool for randomized controlled trials (RoB2)[24] and the Methodological Index for Non-Randomized Studies (MINORS).[25] Comparative studies can receive a maximum ideal score of 24 points and non-comparative studies a maximum of 16 points according to the MINORS tool. Comparative studies can score high,[19-24] moderate,[13-18] or low (0 to 12). Non-comparative studies can score high,[13-16] moderate,[9-12] or low (0 to 8).[26,27]

Results

A total of 1,767 manuscripts were identified during the search. After removal of duplicates, 1,232 articles were screened on title and abstract. Subsequently, 50 full-text articles were screened on eligibility and references were checked for additional relevant articles. In total, 28 manuscripts were included (Figure 1).

Study characteristics

Articles were grouped according to intervention location: maxillofacial, spine, and trauma. Main characteristics of all included studies are summarized in Table I.

Maxillofacial procedures

Patient characteristics: A total of 18 manuscripts investigated maxillofacial application of ABM/P-15 resulting in a total population of 298 individual participants with 575 periodontal defects (Table I).[28–45] A mean 17 (2 to 33) participants and 32 (15 to 93) defects were discussed per manuscript.[28,29,44] Generally, periodontal osseous defects had either a minimal probing depth of 3 mm,[28-3437-39] a minimal residual alveolar ridge height of 1 mm,[42,43] or at least one tooth that warranted extraction and arthroplasty.[40,41,44,45]

Characteristics of interventions: Most manuscripts (n = 12) focused on maxillofacial defects utilizing flap debridement (FD) in combination with defect filling. ABM/P-15 was compared to FD,[28,32,33,37,38] platelet-rich plasma (PRP),[34] other ABM/P-15 products,[31,39] ABM alone,[29] demineralized freeze-dried bone allograft (DFDBA),[28] guided tissue regeneration (GTR),[36] coronally positioned flap,[35] or had no control group[30] (Table I). Furthermore, two papers used alveolar ridge preservation techniques where ABM/P-15 was compared to nothing[40] or to acellular dermal matrix (ADM)[41] (Table II). Another two papers employed sinus augmentation, where one study was non-controlled[43] while the other compared ABM/P-15 to BioOss and ABG.[42] Additionally, two articles used oral implants where ABM/P-15 was compared to C-graft and Puros[44] or BioOss[45] (Table I).

Defect fill and CAL gain and safety: In total, 13 of the 16 maxillofacial comparator studies reported equal or significantly improved results using ABM/P-15. Significant increase in bone formation using ABM/P-15 for treatment of periodontal osseous defects was reported when compared to DFDBA,[28] FD,[28,33,37,38] ABM,[29,30] and PRP.[34] ABM/P-15 performed similarly to GTR[36] and other forms of ABM/P-15.[31] One study showed

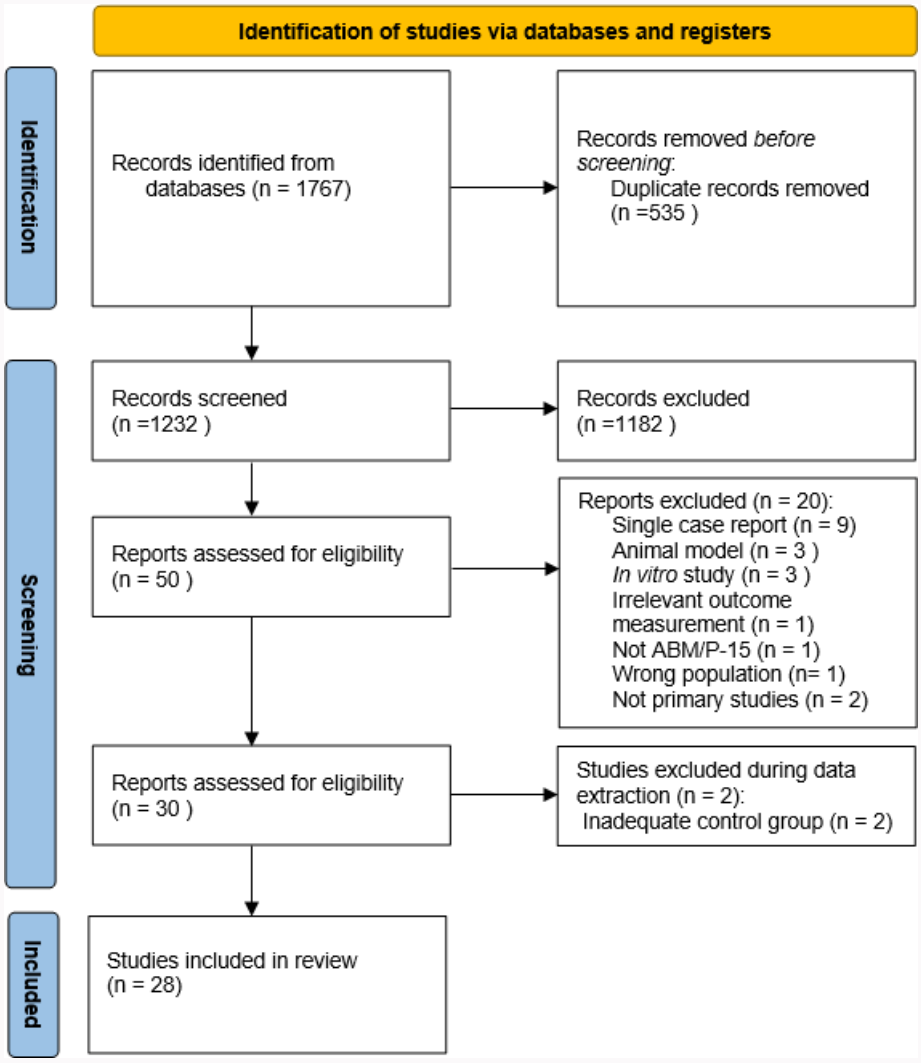

Fig. 1
Flow diagram representing the search strategy for and inclusion of studies. ABM/P-15, anorganic bovine matrix in combination with P-15 peptide.

that a mixture of ABM/P-15 (PepGen P-15) with platelet-rich fibrin (PRF) performed better than PepGen P-15 alone.[39] Two studies examining ridge preservation reported a significant decrease in bone resorption of the alveolar ridge after tooth extraction when applying ABM/P-15 compared to nothing[40] or ADM.[41] Studies assessing treatment efficacy in gingival recession treatment[35] and in furcation defects[32] reported no additional effect of using ABM/P-15. Equal performance was reported when ABM/P-15 was compared to BioOss and ABG in sinus augmentation.[42] Scarano et al[43] did find similar rates of newly formed bone, but did not perform any statistical comparisons between ABM/P-15 and other BGSs. Finally, Kohal et al[45] reported that ABM/P-15 used for implant attachment was equal to BioOss when measuring clinical defect depth at implant insertion after membrane removal but prior to the removal of test implants at two, four, six, and nine months. However, when PepGen P-15 was compared to C-graft and Puros, a significant increase in vital bone formation was reported using ABM/P-15.[44]

No complications related to ABM/P-15 were reported. Nonetheless, swelling,[42] membrane exposure,[45] tissue damage,[45] and failure of initial treatment[29] were documented as complications related to the procedure.

Spine

Patient characteristics: A total of 710 participants (range: 3 to 319) were considered in seven studies looking at spinal fusion (Table I).[46-54] The mean age ranged from 45.7[48] to 71.35[52] years. Patients underwent either cervical (n = 322)[46-49] or lumbar (n = 278)[50-54] spinal fusion utilizing ABG, ABM/P-15, or an alternative BGS. However, 33 participants undergoing cervical spinal fusion were lost to follow-up in the first year,[47] resulting in analysis of 289 participants (ABM/P-15: n = 137, ABG: n = 139).[46-49]

Characteristics of interventions: Four manuscripts reported on anterior cervical discectomy and fusion (ACDF) procedures where ABM/P-15, (i-FACTOR Peptide Enhanced Bone Graft) was compared to ABG[47-49] or nothing.[46] Additional studies compared non-instrumented,[52,54] instrumented,[53] anterior,[50] and posterior[51] lumbar interbody fusion surgeries. In these lumbar studies, ABM/P-15 was compared to rhBMP-2 and DBM,[53] allograft,[52,54] ABG,[51] or nothing.[50]

Cervical spinal fusion rates and safety: In the Arnold et al Investigational Device Exemption (IDE) clinical trial,[47] at 12 months cervical fusion was achieved in 89% (129/145) of the participants using ABM/P-15 and in 86% (121/141) of the participants using ABG. Non-inferiority of ABM/P-15

Table I. Characteristics of included studies.

Author, year	Study design	Country	Defect sites (patients, n)	Surgical intervention	Experimental group	Comparator group	Follow-up, mths	Defect characteristics
Periodontal osseous defects								
Yukna et al, 1998[28]	RCT	USA	93 (n = 31) S. M.	FD with defect filling	ABM/P-15	DFDBA and FD	6 to 7	3 intrabony defects ≥ 3 mm deep, of the 1-wall, 2-wall, wide 3-wall, and combination type of bone loss
Yukna et al, 2000[29]	RCT	USA	66 (n = 33) S. M.	FD with defect filling	ABM/P-15	ABM	6 to 7	At least two advanced periodontal intrabony defects ≥ 3 mm deep, of the 1-wall, 2-wall, wide 3-wall, and combinations
Yukna et al, 2002[30]	Follow-up study	USA	25 (n = 25)	FD with defect filling	Baseline ABM/ P-15	3 year follow-up ABM/P-15	36	Intrabony defects ≥ 3 mm deep, of the 1-wall, 2-wall, wide 3-wall, and combination type of bone loss
Matos et al, 2007[31]	RCT	Portugal	47 (n = 19) S. M.	FD with defect filling	Hydrogel ABM/ P-15	Particulate ABM/ P-15	6	2 non-adjacent periodontal intrabony defects with an intraosseous component ≥ 3 mm and PD ≥ 6 mm
Eto et al, 2007[32]	RCT	Brazil	24 (n = 12) S. M.	Furcation defects	ABM/P-15	FD	6 to 7	Two class II furation defects, horizontal PD > 3 mm, in contralateral lower molars, and no restorations or caries in the area
Kasaj et al, 2008[33]	RCT	Germany	26 (n = 26)	FD alone/defect filling	ABM/P-15	FD alone	12	Infrabony defect with PD ≥ 6 mm and radiological depth of the defect ≥ 3 mm
Pradeep et al, 2009[34]	RCT	India	28 (n = 14) S. M.	FD with filling	PRP+ ABM/P-15	PRP	9	Paired, contralateral interproximal intrabony defects ≥ 4 mm deep, distance alveolar crest (AC) and defect base (DB), with an interproximal probing depth ≥ 5 mm following phase I therapy (scaling and root planning) in vital, asymptomatic first and second molars without furcation involvement
Nazareth nd Cury, 2011[35]	RCT	Brazil	30 (n = 15) S. M.	Gingival recession treatment	CPF+ ABM/P-15	CPF	6	Bilateral miller class I Gingival recession defects (≥ 2 mm depth), involving maxillary canine or premolar teeth (depth difference between L-R ≤ 2 mm)
Queiroz et al, 2013[36]	RCT	Brazil	30 (n = 15) S. M.	Intraosseous defect treatment	ABM/P-15	GTR	6	Generalized aggressive periodontitis
Fatima et al, 2015[37]	RCT	India	20 (n = 10) S. M.	FD with filling	ABM/P-15	FD	9	Bilateral moderate to severe (> 6 mm) periodontal osseous defects
Mishra et al, 2019[38]	RCT	India	40 (n = 20) S. M.	FD with filling	ABM/P-15	FD	6	One pair of bilateral deep interproximal infrabony periodontal defects with a PPD of ≥ 5 mm and radiological evidence of angular bone loss ≥ 3 mm at baseline
Goyal et al, 2020[39]	RCT	India	24 (n = 12) S. M.	Intraosseous defect treatment	PepGen P-15	PepGen P-15:PRF 50:50	3 to 6	Bilateral intraosseous defects in contralateral arch with PPD ≥ 5 mm
Ridge preservation								
Neiva et al, 2008[40]	RCT	USA	24 (n = 24)	Alveolar ridge preservation	ABM/P-15 putty	No substance	4	One maxillary premolar tooth requiring extraction and arthroplasty by dental implant, residual extraction sockets with < 80% bone loss in all dimensions
Fernandes et al, 2011[41]	RCT	Brazil	36 (n = 18) S. M.	Extraction and ridge preservation	ABM/P-15	ADM	6	At least 2 hopeless, single-rooted, and non-adjacent teeth in the maxilla in need for extraction

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Author, year	Study design	Country	Defect sites (patients, n)	Surgical intervention	Experimental group	Comparator group	Follow-up, mths	Defect characteristics
Sinus augmentation								
Degidi et al, 2004[42]	Comparative	Italy	33 (n = 7) S. M.	Maxillary sinus augmentation	ABM/P-15	Bio-Oss and ABG	6	Presence of maxillary partial (unilateral or bilateral) edentulism involving the premolar or molar areas and presence of a residual alveolar ridge height between 1 and 4 mm
Scarano et al, 2006[43]	Performance	Italy	16 (n = 16)	Sinus augmentations	PepGen P-15	N/A	36	Maxillary partial edentulism involving the premolar/molar areas and the presence of 3 to 5 mm crestal bone between the sinus floor and alveolar ridge
Other								
Thompson et al, 2006[44]	Comparative	USA	15 (n = 2) S. M.	Implant	PepGen P-15	C-Graft and Puros	4	Teeth for extraction were not restorable because of advanced decay/periodontal disease; 4 to 5 wall defects
Kohal et al, 2015[45]	RCT	Germany	23 (n = 24)	Oral implant	ABM/P-15	BioOss	2, 4, 6, 9	Need of an implant-retained overdenture in the mandible due to unacceptable retention of their complete dentures caused by severe atrophy of their jaws
Cervical spine								
Maharaj et al, 2016[46]	Prospective cohort	Australia	3 (n = 3)	ACDF procedure	ABM/P-15 i-FACTOR	N/A	9	Patients having a revision ACDF on a background of a previous fused ACDF using ABG with the revision procedure performed using an available bone graft substitute
Arnold et al, 2016[47]	RCT	North America	319 (n = 319)	Instrumented ACDF procedure	ABM/P-15 i-FACTOR	ABG	12	Degenerated/dark C3-C7 disc on MRI, decreased disc height compared with adjacent levels on radiological film, CT or MRI, disc herniation on CT or MRI; failed to gain adequate relief from at least 6 weeks of nonoperative treatment
Arnold et al, 2018[48]	Follow-up study	North America	319 (n = 319)	Instrumented ACDF procedure	ABM/P-15	ABG	24	See Arnold et al, 2016[47]
Arnold et al, 2023[49]	Follow-up study	North America	152 (n = 152)	Instrumented ACDF procedure	ABM/P-15	ABG	72	See Arnold et al, 2016[47]
Lumbar spine								
Mobbs et al, 2014[50]	Prospective	Australia	142 (n = 110) One level: 80 Two levels: 27 Three levels: 3	Anterior lumbar interbody fusion surgery (ALIF)	ABM/P-15	N/A	15 to 43	Radiological presence of DDD with back pain and no radiculopathy, DDD with back pain and radiculopathy, spondylolisthesis (degenerative or isthmic), adjacent-segment degeneration, scoliosis; and, failed union of a posterior fusion
Lauweryns and Raskin, 2015[51]	RCT	Belgium	45 (n = 40) One level: 24 Two levels: 14 Three levels: 1	PLIF	ABM/P-15	ABG	6, 12, 24	Presence of disc pathology, spinal stenosis, maximum grade 1 isthmic or degenerative spondylolisthesis, and revision of nonunion, adjacent level degeneration, or post-discectomy revision between L2 and S1

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Author, year	Study design	Country	Defect sites (patients, n)	Surgical intervention	Experimental group	Comparator group	Follow-up, mths	Defect characteristics
			Four levels: 1					
Jacobsen et al, 2020[52]	RCT	Denmark	240 (n = 98) ABM/P-15 One level: 70 Two levels: 56 Allograft One level: 82 Two levels: 32	Non-instrumented lumbar fusion surgery	ABM/P-15	Allograft	24	Severe reduction of walking ability due to spinal stenosis, a minimum score of 7 on Konno's "History of Examination Characteristics", Central spinal stenosis on 1 to 2 levels with spondylolisthesis verified by MRI and lateral standing radiographs, completion of a minimum of 3 months of non-surgical therapy with little or no effect
Sathe et al, 2022[53]	Retrospective comparative	South Korea	140 (n = 140) ABM/P-15: 46 rhBMP-2: 44 DBM: 50	ILIF	ABM/P-15	rhBMP-2, DBM	> 6	Lumbar degenerative disorders with instability/spondylolisthesis wherein fusion was deemed necessary
Andresen et al, 2024[54]	Follow-up study	Denmark	Clinical outcome: 83 (n = 83) Fusion: 58 (n = 58)	Non-instrumented lumbar fusion surgery	ABM/P-15	Allograft	60	See Jacobsen et al, 2020[52]
Trauma								
Gomar et al, 2007[55]	Pilot case series	Spain	22 (n = 22)	Internal fixation	ABM/P-15	N/A	Monthly until consolidation	Failure of previous surgical fracture treatment, with loss of internal fixation, or lack of consolidation after at least 6 months from initial treatment

Characteristics of included studies that investigated ABM/P-15 in maxillofacial procedures, spine, or trauma. Studies are grouped by treatment location.
ABG, autologous bone graft; ABM/P-15, anorganic bone mineral combined with P-15 peptide; ACDF, anterior cervical discectomy and fusion; ADM, acellular dermal matrix; CAL, clinical attachment level; CPF, coronally positioned flap; DBM, demineralized bone matrix; DDD, degenerative disc disease; DFDBA, demineralized freeze-dried bone allograft; FD, flap debridement; GTR, guided tissue regeneration; ILIF, instrumented lumbar interbody fusion; N/A, not applicable; PD, probing depth; PLIF, posterior lumbar interbody fusion; PPD, probing pocket depth; PRF, platelet-rich fibrin; PRP, platelet-rich plasma; RCT, randomized controlled trial; rhBMP2, recombinant human bone morphogenetic protein 2; S.M., split mouth study.

Table II. Results for studies researching anorganic hydroxyapatite bone minerals (ABM)/P-15 in maxillofacial, spine, and traumatological procedures.

Author, year	Study design	Defect sites (patients, n)	Outcomes	Primary outcomes, mean (SD)			Adverse events	
Periodontal osseous defects				**Experimental**	**Comparator**	**Significance**	**Experimental**	**Comparator**
Yukna et al, 1998[28]	RCT	93 (n = 31) S. M.	Defect fill (%)	72.3 (23.3)	DFDBA: 51.4 (34.7) FD: 40.3 (29.9)	p < 0.05	Retreatment: 3%	Retreatment: DFDBA: 26% DEBR: 29%
Yukna et al, 2000[29]	RCT	66 (n = 33) S. M.	Defect fill (%)	72.9 (23.3)	ABM: 50.6 (26.9)	p = 0.001	No	No
Yukna et al, 2002[30]	Follow-up	25 (n = 25)	Vertical CAL (mm)	5.4 (1.9)	3 year FU: 3.8 (1.6)	p < 0.05	No	No
Matos et al, 2007[31]	RCT	47 (n = 19) S. M.	CAL difference (mm)	Hydrogel ABM/P-15: 4.47 (1.13)	Particulate ABM/P-15: 5.13 (1.61)	p = 0.09	No	No
Eto et al, 2007[32]	RCT	24 (n = 12) S. M.	Difference vertical CAL (mm)	11.1 (2.1)	FD: 11.6 (3.3)	p = 0.69	No	No
Kasaj et al, 2008[33]	RCT	26 (n = 26)	CAL difference (mm)	-3.9 (1.7)	FD: -1.8 (1.0)	p = 0.001	No	No
Pradeep et al, 2009[34]	RCT	28 (n = 14) S. M.	Radiological defect fill (%)	58.14 (12.43)	PRP: 43.81 (8.85)	p < 0.05	No	No
Nazareth and Cury, 2011[35]	RCT	30 (n = 15) S. M.	CAL (mm)	1.93 (0.44)	CPF: 2.13 (1.15)	p = 0.42	No	No
Queiroz et al, 2013[36]	RCT	30 (n = 15) S. M.	CAL (mm)	1.87 (0.94)	GTR: 2.09 (0.88)	p = 0.495	No	No
Fatima et al, 2015[37]	RCT	20 (n = 10) S. M.	Radiological defect fill (mm)	3.75 (0.98)	FD: 1.86 (0.76)	p < 0.001	No	No
Mishra et al, 2019[38]	RCT	40 (n = 20) S. M.	Defect resolution (%)	50.06	FD: 16.73	p < 0.001	No	No
Goyal et al, 2020[39]	RCT	24 (n = 12) S. M.	Difference in defect volume gain (%)	37.83 SD 15.5	PepGen P-15: PRF: 58.08 (18.14)	p = 0.008	No	No
Ridge preservation								
Neiva et al, 2008[40]	RCT	24 (n = 24)	Bone density	2.08 (0.65)	No substance: 3.33 (0.65)	p = 0.03	NM	NM
Fernandes et al, 2011[41]	RCT	36 (n = 18) S. M.	Bone resorption	2.53 (1.81)	ADM: 3.40 (1.39)	p = 0.049	No	No
Sinus augmentation								
Degidi et al, 2004[42]	Comparative	33 (n = 7) S. M.	Newly formed bone (%)	38.8 (3.2)	BioOss: 36.7 (3.3) ABG: 32.2 (2.5)	p = 0.360	Moderate swelling	Moderate swelling

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(*Continued*)

Author, year	Study design	Defect sites (patients, n)	Outcomes	Primary outcomes, mean (SD)			Adverse events	
Scarano et al, 2006[43]	Performance	16 (n = 16)	Newly formed bone (%)	37 (2.3)	N/A	N/A	No	No
Other								
Thompson et al, 2006[44]	Comparative	15 (n = 2) S. M.	Vital bone (%)	24 (8)	Puros: 6 (2) C-Graft: 2 (1)	p < 0.05	No	No
Kohal et al, 2015[45]	RCT	23 (n = 24)	Clinical defect depth (mm)	0.66 (0.24)	BioOss: 0.69 SD 0.24	p = 0.87	Tissue damaged during implant removal: 3	Tissue damaged during implant removal: 1
Cervical spine			**Outcomes**	**Test**	**Control**	**Significance**	**Test**	**Control**
Maharaj et al, 2016[46]	Prospective cohort	3 (n = 3)	Fusion	3/3	-	NM	NM	NM
Arnold et al, 2016[47]	RCT	319 (n = 319)	Fusion (%) (non-inferiority)	129/145 (88.97%)	ABG: 121/141 (85.82%)	Non inferiority: p = 0.0004	Axial pain: 39.13 Residual radiculopathy: 19.25 Dysphagia: 19.25 New radiculopathy: 10.56 New intractable neck pain: 4.35 Any: 138/165 (83. 64%)	Axial pain: 36.85 Residual radiculopathy: 18.42 Dysphagia: 19.74 New radiculopathy: 18.42 New intractable neck pain: 10.53 Any: 127/154 (82.47%)
Arnold et al, 2018[48]	Follow-up	319 (n = 319)	Fusion (%)	144/148 (97.30%)	ABG: 136/144 (94.44%)	p = 0.2195	Axial pain: 44.72% Residual radiculopathy: 21.12% Dysphagia: 19.25% New radiculopathy: 13.66% Reoperation: (3.73%) Superficial infection: 6 Any: 153/161 (95.03%)	Axial pain: 42.11% Residual radiculopathy: 20.39% Dysphagia: 19.74% New radiculopathy: 25.0% Reoperation: 16 (8.44%) Superficial infection: 0 Any: 137/151 (90.73%)
Arnold et al, 2023[49]	Follow-up	152 (n = 152)	Fusion (%) (non-inferiority)	103/104 (99.00%)	ABG: 109/111 (98.20%)	Non inferiority: p < 0.0001	Temporary dysphagia: 23 (21.70%) Radiological adjacent segment degeneration: 34 (32.1%) Secondary surgery: 20 (18.90%) Neurological success: 70 (95.9%) Subsidence of allograft ring: 2 (2.08%)	Temporary dysphagia: 25 (21.9%) Radiological adjacent segment degeneration: 35 (30.70%) Secondary surgery: 23 (20.20%) Neurological success: 70 (93.70%)
Lumbar spine								
Mobbs et al, 2014[50]	Prospective	142 (n = 110)	Fusion at 12 and 24 months (%)	One-level: 82%, 98% Two-level: 70%, 81% Three-level: 66.66%, 100%	N/A	N/A	Retrograde ejaculation: 4 Postoperative haematoma: 1, Incisional hernia: 1	

(*Continued*)

(*Continued*)

Author, year	Study design	Defect sites (patients, n)	Outcomes	Primary outcomes, mean (SD)			Adverse events	
				Total: 78.2%, 92.9%			Postoperative deep vein thrombosis or prolonged ileus: 5	
Lauweryns and Raskin, 2015[51]	RCT	45 (n = 40)	Fusion at 6, 12, 24 months (%)	97.73%, 97.78%, 95.56%	ABG: 59.09%, 82.22%, 93.33%	For 6 and 12 months: $p < 0.01$	Graft migration: 48%	Graft migration: 14%
Jacobsen et al, 2020[52]	RCT	98 (n = 98)	Fusion (%)	Test 63/126 (50%)	Allograft: 23/114 (20%)	24 months: $p < 0.001$	No	No
Sathe et al, 2022[53]	Retrospective comparative	140 (n = 140)	Fusion (%), mean time to fusion in months (SD)	Fusion: 97.8% Time: 4.05 (2.01)	rhBMP2: Fusion: 93.2% Time: 10 (4.28). DMB: Fusion: 98% Time: 9.44 (3.49)	12 months: $p < 0.001$	Cage subsidence: 21.7% Infection: 1	Cage subsidence rhBMP2: 30.2% DBM: 14% Infection: rhBMP2: 1 DBM: 3
Andresen et al, 2024[54]	Follow-up	Clinical outcome (questionnaire): 83 (n = 83) Fusion (CT-scan): 58 (n = 58)	Fusion (%), clinical outcomes	16/28 (57.1%)	Allograft: 9/30 (30%)	60 months: $p = 0.037$	Questionnaire: Wound discharge: 3 (6.1%) Drain production: 120.3 (SD75.5) Infection within 3 months: 1 (2.3%) Reoperations: 6 (14.0%) CT-Evaluation: Bone migration: 1 (3.6%) Calcified haematoma: 1 (3.6%) Osteolysis in adjacent vertebra: 0 Ectopic bone formation: 0	Questionnaire: Wound discharge: 5 (12.2%) Drain production: 200.3 (SD 161.3) Infection within 3 months: 1 (2.5%) Reoperations: 8 (20.0%) CT-Evaluation: Bone migration: 0 Calcified haematoma: 0 Osteolysis in adjacent vertebra: 0 Ectopic bone formation: 0
Trauma								
Gomar et al, 2007[55]	Pilot case series	22 (n = 22)	Consolidation	Consolidation: 20/22	N/A	N/A	Lost to follow-up before consolidation: 1 Retreatment: 1 Poor healing: 1	

Results of included studies that investigated ABM/P-15 in maxillofacial, spine, or traumatological procedures. Studies are grouped by treatment location.
$p < 0.05$ indicates statistical significance.
ABG, autologous bone graft; ABM, anorganic bone matrix mineral; ABM/P-15, anorganic bone minerals combined with P-15 peptide; CAL, clinical attachment level; CPF, coronally positioned flap; DBM, demineralized bone matrix; DEBR, open flap debridement; DFDBA, demineralized freeze-dried bone allograft; FD, flap debridement; FU, follow-up; GTR, guided tissue regeneration; ILIF, instrumented lumbar interbody fusion; N/A, not applicable; NM, not mentioned; PLIF, Posterior lumbar interbody fusion; PRF, platelet-rich fibrin; PRP, platelet-rich plasma; RCT, randomized controlled trial; rhBMP2, recombinant human bone morphogenetic protein 2; S.M., split mouth study.

compared to ABG was calculated at p = 0.0004.[47] After 24 months, fusion was 97% (144/148) in the test and 94% (136/144) in the control group.[48] A six-year follow-up found significant non-inferiority (p < 0.0001) in fusion achieved with ABM/P-15 in 99% (103/104) compared to ABG 98% (109/111).[49] Maharaj et al[46] reported early successful cervical fusion in all three participants after nine months' follow-up in the same study. Successful fusion was defined as trabecular bone bridging between the involved motion segments and translation motion < 3 mm and angular motion < 5°, as seen on radiological examination.[47-49]

After 12,[47] 24,[48] and 72[49] months, occurrence of adverse events was similar in test and control groups as described in Table II. One i-FACTOR patient developed a bone haemangioma in the lumbar spine, another was diagnosed with renal cancer, and two ABG patients developed chronic lymphocytic leukaemia. However, there was no indication that these complications were related to the intervention. No allergic reactions to i-FACTOR were reported.

The composite success, defined as those patients who met all four co-primary endpoints (successful fusion, neurological success, improved functional outcomes, no reoperations or device-related serious adverse events), was significantly higher in ABM/P-15 treated patients compared to the ABG group at one year[47] (69% (99/144) vs 57% (82/144) (p = 0.04)) and two years[48] (70% (81/116) vs 56% (71/126) (p = 0.03)).

Lumbar spinal fusion rates and safety: A detailed description of the results can be found in Table II. Jacobsen et al[52] reported a significant difference in successful lumbar fusion after 12 months in intertransverse spaces treated with ABM/P-15 (50% (63/126)) and allograft (20% (23/114)) groups. In a five-year follow-up study, Andresen et al[54] found a 57% (16/28) successful fusion for ABM/P-15 compared to 30% (9/30) for allograft. Fusion was defined as a continuous osseous bridge extending over the intertransverse space observed by radiograph or CT scan. Moreover, back pain visual analogue scale (VAS) scores (22.5 vs 39.0, p = 0.013) and Oswestry Disability Index (18.5 vs 27.4, p = 0.029) were significantly lower in the ABM/P-15 group than in the allograft group at 60 months, respectively.[54]

Lauweryns and Raskin[51] found that at 24 months, there was no significant difference in achieved fusion between ABM/P-15 (96%) and ABG (93%). However, fusion at six and 12 months was significantly greater in ABM/P-15 (98% 6 months, 98% 12 months) than in ABG (59% 6 months, 82% 12 months),[51] indicating that ABM/P-15 fuses faster than ABG. Similarly, Sathe et al[53] found no significant difference in total achieved fusion when comparing ABM/P-15 (98%) with rhBMP-2 (93%) and DMB (98%) at 12 months; however, fusion was achieved significantly earlier using ABM/P-15 (mean 4.05 months (SD 2.01)) compared to the rhBMP-2 (mean 10 months (SD 4.28)) and DBM (mean 9.44 months (SD 3.49)) groups.[53] Moreover, in a prospective non-comparative study, Mobbs et al[50] showed high total fusion rates at 12 (78.2%) and 24 (92.9%) months. Importantly, no complications related to ABM/P-15 were reported.[50]

After five-year follow-up, Andresen et al[54] found no significant differences in safety performance or adverse events when comparing ABM/P-15 to allograft. Grade 1 cage subsidence was a complication which occurred in the ABM/P-15 (22%), rhBMP-2 (30%), and DBM (14%) groups.[53] In posterior lumbar interbody fusion (PLIF) surgeries, graft migration posteriorly to the cage occurred significantly more in the ABM/P-15 (48%) group compared to ABG (14%), but this had no clinical consequences.[51]

Trauma

Patient characteristics: One paper reported on ABM/P-15 performance in traumatological procedures, specifically delayed union and nonunion fractures.[55] A total of 22 participants were treated in two different hospitals from June 2000 until October 2003. Two series of patients were treated. Series I included seven men and two women with an average age of 50 years. Series II included eight men and five women with an average age of 52 years. Series I consisted of three fractures in the femoral diaphysis, two in the humeral diaphysis, one in the tibial diaphysis, two in the distal tibial metaphysis, one in the proximal tibial metaphysis, and one in the radial diaphysis. Series II entailed four fractures in the femoral diaphysis, four in the humeral diaphysis, three in the tibial diaphysis, one in the distal femoral metaphysis, one in the proximal tibial diaphysis, and one in the distal tibial metaphysis. Average time since initial diagnosis was 14 months.[55]

Characteristics of interventions: All fractures were internally fixated with either screws-on plates, nail plates, or plaster after fracture site treatment with particulate ABM/P-15 BGS. No control group was used.[55]

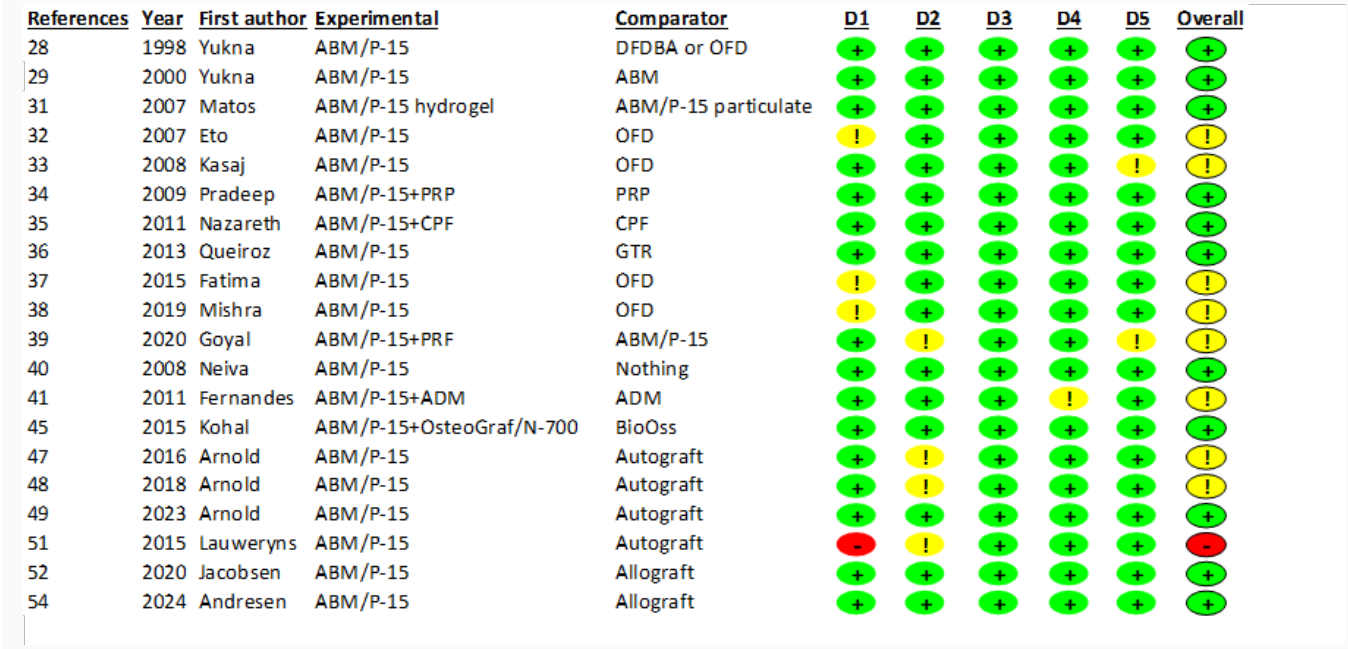
Fusion rates over time and safety: Consolidation was confirmed by radiograph, and both time elapsed until initial bone bridging and time until consolidation were documented. Full consolidation of patients treated for delayed or nonunion in long-bone fractures was achieved in 90% (20/22) of the participants. Bone bridging occurred after 1.7 months, on average, and full consolidation was observed at four months.[55] Histological assessment of the fracture callus in five of the patients confirmed the positive clinical and radiological results. Healing was classified as poor in one patient.[55]

After a plate failure in one patient a new plate with new P-15 material was required, after which consolidation was achieved. The second patient without consolidation at 12 months was subsequently lost to follow-up.[55]

Methodological quality assessment

A total of 20 RCTs were assessed according to ROB2 guidelines (Figure 2):[24] 11 showed low risk of bias;[28,29,31,34-36,40,45,49,52,,54] eight had some concerns of bias;[32,33,37-39,41,47,,48] and one had a high risk of bias.[51] This was a consequence of randomization by birthdate, which is not considered true randomization. Other concerns arose from an insufficient description of the randomization process,[32,37,38] deviations from protocol,[39,47,48,51] selection bias of result,[33,39] or measurement outcome selection.[41]

Four controlled trials[42-44,53] and four non-comparative trials[30,46,50,55] were assessed according to MINORS (Table III).[25] Two studies scored as high quality[46,53] and six as moderate quality.[30,42-44,50,,55] Lower quality was caused by the lack of power calculations[30,42-44,46,50,53,,55] or an adequate control group,[44,53] failure to report comprehensive baseline measurements,[42-44] adequate statistical analysis,[42-44] blinding during endpoint assessment,[42,43,50] or failure to provide a protocol.[30,42,44,46,50,55]



References	Year	First author	Experimental	Comparator	D1	D2	D3	D4	D5	Overall
28	1998	Yukna	ABM/P-15	DFDBA or OFD	+	+	+	+	+	+
29	2000	Yukna	ABM/P-15	ABM	+	+	+	+	+	+
31	2007	Matos	ABM/P-15 hydrogel	ABM/P-15 particulate	+	+	+	+	+	+
32	2007	Eto	ABM/P-15	OFD	!	+	+	+	+	!
33	2008	Kasaj	ABM/P-15	OFD	+	+	+	+	!	!
34	2009	Pradeep	ABM/P-15+PRP	PRP	+	+	+	+	+	+
35	2011	Nazareth	ABM/P-15+CPF	CPF	+	+	+	+	+	+
36	2013	Queiroz	ABM/P-15	GTR	+	+	+	+	+	+
37	2015	Fatima	ABM/P-15	OFD	!	+	+	+	+	!
38	2019	Mishra	ABM/P-15	OFD	!	+	+	+	+	!
39	2020	Goyal	ABM/P-15+PRF	ABM/P-15	+	!	+	+	!	!
40	2008	Neiva	ABM/P-15	Nothing	+	+	+	+	+	+
41	2011	Fernandes	ABM/P-15+ADM	ADM	+	+	+	!	+	!
45	2015	Kohal	ABM/P-15+OsteoGraf/N-700	BioOss	+	+	+	+	+	+
47	2016	Arnold	ABM/P-15	Autograft	+	!	+	+	+	!
48	2018	Arnold	ABM/P-15	Autograft	+	!	+	+	+	!
49	2023	Arnold	ABM/P-15	Autograft	+	+	+	+	+	+
51	2015	Lauweryns	ABM/P-15	Autograft	-	!	+	+	+	-
52	2020	Jacobsen	ABM/P-15	Allograft	+	+	+	+	+	+
54	2024	Andresen	ABM/P-15	Allograft	+	+	+	+	+	+

Fig. 2

Bias assessment of included randomized controlled trials (RCTs) using the ROB2 guidelines and tool.[24] A total of 11 RCTs were assessed as low risk of bias, eight RCTs were assessed with some concerns for bias, and one RCT had a high risk for bias. +, low risk; !, some concerns; -, high risk; ABM, anorganic hydroxyapatite bone minerals; ADM: acellular dermal matrix; CPF, coronally positioned flap; D1, randomization process; D2, deviations from the intended interventions; D3, missing outcome data; D4, measurement of the outcome; D5, selection of the reported results; DFDBA: demineralized freeze-dried bone allograft; GTR: guided tissue regeneration; OFD, open flap debridement; PRF, platelet-rich fibrin; PRP, platelet-rich plasma.

Discussion

This systematic review examined the clinical safety and efficacy of ABM/P-15 compared to other bone graft treatment options in multiple surgical procedures. The spinal comparator studies showed that ABM/P-15 achieves fusion rates similar or greater than their comparator groups. Similar results were reported by 13/16 maxillofacial studies. Due to the biomimetic mode of action of P-15, it is unsurprising that the available evidence indicates a strong propensity for ABM/P-15 to illicit bone regeneration in healing environments throughout the skeletal system.

Specifically, in the treatment of osseous periodontal defects, six RCTs reported significant increase in bone regeneration using ABM/P-15 compared to PRP,[34] FD with defect filling,[28,29,33,37,38] or DFDBA,[28] while two RCTs presented similar outcomes comparing ABM/P-15 to GTR[36] and particulate ABM/P-15.[31] This is in line with a review by Golubovsky et al,[8] describing lower osteoinductive potential and decreased fusion rates in allograft and DBM. Moreover, one RCT demonstrated benefit of a mixture of ABM/P-15 with PRF compared to ABM/P-15 alone.[39] However, two RCTs found no effect when ABM/P-15 was used to treat gingival recession[35] or furcation defects.[32] A positive effect of ABM/P-15 on bone regeneration was found in ridge preservation treatment as well, where it was compared to ADM[41] and no substance.[40] Similarly, a review and meta-analysis by Shaikh et al[21] reported a significant gain in CAL for intrabony defects and reduction in probing depth when comparing ABM/P-15 to open flab debridement. Comparable to our results, Shaikh et al[21] found no significant benefit of ABM/P-15 for furcation and gingival recession defects. Application of ABM/P-15 in sinus augmentation found equal performance compared to BioOss and ABG.[42] This is in line with clinical observations by Valentin et al,[22] who reported enhanced bone regeneration in sinus augmentation. Finally, ABM/P-15 performed significantly better than C-Graft and Puros[44] and equal to BioOss[45] when used for implant fixation.

In cervical spinal fusion, ABM/P-15 was found to have a similar rate of achieved fusion as ABG.[47-49] Additionally, the IDE study found significant superiority in success of the ABM/P-15 group over the ABG group at one[47] and two years.[48] In both instrumented and PLIF surgery, total achieved fusion was similar between ABM/P-15 when compared to rhBMP-2, DBM,[53] and ABG.[51] Time until fusion was significantly shorter in the ABM/P-15 group compared to rhBMP-2 and DBM.[53] When compared to ABG, ABM/P-15 achieved significantly more fusion at six and 12 months.[51] In non-instrumented lumbar interbody fusion surgery, ABM/P-15 achieved significantly more successful fusion than the allograft group at both 12[52] and 60 months.[54] This is in line with results observed by Park et al,[56] who found significantly more successful fusion with ABM/P-15 (87/91, 95.6%) compared to ABG (93/107, 86.9%) in PLIF. Unfortunately, this study only showed up in a Korean database, which was not included in the search. Furthermore, these results are similar to the conclusions of a recent systematic review on ABM/P-15 in lumbar spine surgery.[57]

Lastly, a case report[55] showed consolidation in nonunion, delayed, and malunion fractures after internal fixation and application of ABM/P-15 at the fracture site. A subgroup of tibia fractures reported consolidation times similar to studies investigating rhBMP2. Furthermore, a

Table III. Quality assessment outcomes of seven non-randomized studies using the Methodological Index for Non-Randomized Studies (MINORS) tool.[25]

Author	Year	1	2	3	4	5	6	7	8	9	10	11	12	Total
Comparative														
Sathe et al[53]	2022	2	2	2	2	2	2	2	0	1	0	2	2	19
Thompson et al[44]	2006	2	1	1	1	2	2	2	0	1	2	1	1	16
Scarano et al[43]	2006	2	2	2	2	0	2	2	0	2	2	0	0	16
Degidi et al[42]	2004	2	1	1	2	0	2	2	0	2	2	0	1	15
Non-comparative														
Maharaj et al[46]	2016	2	2	1	2	2	2	2	0	X	X	X	X	13
Mobbs et al[50]	2014	2	2	1	2	1	2	2	0	X	X	X	X	12
Gomar et al[55]	2007	2	2	1	1	2	1	2	0	X	X	X	X	11
Yukna et al[30]	2002	2	2	1	2	2	2	0	0	X	X	X	X	11

1: Clearly stated aim, 2: inclusion of consecutive patients, 3: prospective data collection, 4: endpoints appropriate to the aim of the study, 5: unbiased assessment of the study endpoint, 6: follow-up period appropriate to the aim of the study, 7: loss to follow-up less than 5%, 8: prospective calculation of the study size, 9: an adequate control group, 10: contemporary groups, 11: baseline equivalence of groups, 12: adequate statistical analyses. Score 0: not reported, 1: inadequately reported, 2: adequately reported. Comparative studies can score high (19 to 24), moderate (13 to 18), or low (0 to 12). Non-comparative studies can score high (13 to 16), moderate (9 to 12), or low (0 to 8).

retrospective study by O'Brien et al[58] found three-times greater odds of partial/full union in periacetabular osteotomy surgery for dysplasia of the hip when using i-FACTOR compared to DBM. However, the study population partially consisted of 15- to 17-year-olds and could thus not be included in the analysis.

It is important to note that bone graft biomaterials aim to promote new bone formation and often exhibit radiodensity similarities to native bone, especially for calcium phosphate compositions. Continuity of bridging bone is currently the most reliable radiological criterion used to assess fusion status. The radiological appearance of bone graft materials can vary, but it is important to discern postoperative changes in bone graft structure to follow ongoing remodelling and progression to fusion.[59] In the immediate postoperative phase, chipped/prepared autograft may resemble osseous fragments on radiographs, with a radiodensity similar to that of native bone. In contrast, ceramic biomaterials often present as a radiodense amorphous material, with clearly defined boundaries. Remodelling via creeping substitution results in loss of defined boundaries, with incorporation into adjacent tissue and internal morphological changes as new bone is formed. These characteristic radiological changes are described in established fusion evaluation criteria, and the acquisition of serial images within studies can be useful in evaluating progression of fusion and remodelling.[60] ABM/P-15 has been demonstrated to show discernible radiological differences indicative of graft remodelling and early fusion in a high-resolution preclinical study.[60]

Evaluation of radiological consolidation and fusion may be compounded by anatomical location and artefact from surgical hardware, and is influenced by the imaging modality used to determine the presence of bridging bone.[61] Given the inconsistent application of imaging and fusion criteria, it is often difficult to compare the performance of different biomaterials between studies, and care should be taken to evaluate the scientific rigour of fusion evaluation. More high-level randomized controlled studies, which include the measured use of biomaterials in both treatment and control arms, along with standardized methods for radiological assessment preferably utilizing high-resolution CT, are warranted.

With regards to safety, no allergic reaction or intolerability to ABM/P-15 were reported in any of the assessed studies. Three maxillofacial studies reported procedure-related complications.[29,42,45] Importantly, a three-year follow-up study did not report any long-term safety concerns.[30] In cervical fusion, adverse events were common in both ABM/P-15 and ABG treatment. Interestingly, development of new radiculopathy was significantly more common in the ABG group than in the ABM/P-15 group at both 12[47] and 24 months.[48] However, a six-year follow-up study no longer showed a significant difference in adverse events.[49]

A recent five-year follow-up study found no significant difference between safety performance of ABM/P-15 compared to allograft in non-instrumented lumbar fusion surgery.[54] Moreover, in instrumented lumbar interbody fusion, cage subsidence was a common complication in ABM/P-15, rhBMP-2, and DBM groups, but was rarely associated with clinical symptoms.[53] Notably, class 1 cage subsidence is an expected complication in lumbar fusion surgery.[62] Additionally, in PLIF surgery, bone graft migration was reported more often in the ABM/P-15 group (48%) than in the ABG group (14%).[51] These findings were primarily radiological for both groups,[51] and migration of ABM/P-15 is significantly lower when compared to reported migration of similar BGS such as rhBMP-2 (75%).[63] Migration was not reported in other studies included in this review. Serious complications such as ectopic bone formation, osteolysis, and retrograde ejaculation associated with rhBMP-2 use in the spine were not reported with ABM/P-15.[64] In treatment of long-bone fractures, two fractures were classified as poor consolidation.[55] Unfortunately, what poor consolidation entails was not further explained.

Strengths and limitations

This study has several strengths. It is the first systematic overview of ABM/P-15 behaviour in a broad variety of bone regenerative procedures. An extensive search was performed in multiple databases to ensure that all eligible studies were obtained. ABM/P-15 was evaluated in participants from 12 different countries in four continents, aiding generalizability of the study findings. Additionally, long-term follow-up studies were included for all groups, allowing for long-term safety assessment. Another strength is the moderate-to-high level of methodological quality of the included studies.

However, a limitation is the heterogeneity in measurement outcomes, procedures, and study design, resulting

in reduced generalizability. This was further complicated by variation in methods and definitions used to assess fusion. Sample size of maxillofacial studies was limited, and cervical fusion population originates almost exclusively from a single IDE exemption study.[47-49] Additionally, the IDE exemption studies by Arnold et al[47–49] and the study by Mobbs et al[50] included patients with diabetes. Thus, it is possible that the fusion rates reported are an underestimation. While most studies used a (randomized) control group, some studies did not compare ABM/P-15 to a control.[43,46,55] Subsequently, the results of those studies could not be statistically verified. Of note, most studies were, partially, funded by the industry producing ABM/P-15, which may result in publication bias. Therefore, it might be possible that previous conducted studies with unfavourable results were not published.

Eight out of the 20 included RCTs had some concerns for bias, with most concerns being caused by deviations from the protocol or unclear randomization and blinding. One RCT had high concerns for bias resulting from randomization by birthdate, which is defined as non-random by the ROB2 tool.[51] In cohort studies and comparative studies, the main causes for concern were a lack of access to a protocol, unclear assessment of end points, and a lack of prospective power calculations. Due to the nature of these studies, we expect that these concerns were of minor influence on the results.

Implications

Finally, studies that investigated ABM/P-15 in systemic bone disease, such as osteoporosis, were excluded. Thus, no remarks can be made about how ABM/P-15 performs in suboptimal bone tissue. Future research should be focused on ABM/P-15 performance in suboptimal environments. Likewise, RCTs with a large study population are needed before conclusions can be drawn on the effectiveness of ABM/P-15 in sinus augmentation and implant fixation. Similarly, to assess the efficacy and safety of ABM/P-15 in a traumatological setting, a RCT is necessary.

Overall, ABM/P-15 demonstrated a clear ability to support and promote bone regeneration regardless of the anatomical locations. Additionally, fusion was similar for ABM/P-15 compared to rhBMP-2, DBM, and ABG in both lumbar and cervical fusion surgery. Importantly, no serious complications concerning the use of ABM/P-15 were reported. While no definitive conclusions can be drawn on the behaviour of ABM/P-15 in traumatological procedures due to a lack of studies, fusion was achieved in most patients.

Conclusion

The evidence reported in this review suggests that ABM/P-15 is effective and safe to use in multiple surgical contexts as a BGS for bone regenerative indications. ABM/P-15 was shown to be an effective and safe BGS in maxillofacial defects and spinal fusion. More research into the role of ABM/P-15 in oral implant fixation, sinus augmentation, and trauma surgery is needed. ABM/P-15 was equally as effective as ABG, and was associated with similar complications in ACDF procedures. Furthermore, fusion was achieved earlier with ABM/P-15 compared to rhBMP-2, DBM, and allograft in spinal lumbar fusion procedures. The evidence reported in this review suggests that ABM/P-15 is effective and safe to use in multiple surgical contexts as a BGS for bone regenerative indications.

Supplementary material

The PRISMA checklist and search string used.

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Data sharing

The data that support the findings for this study are available to other researchers from the corresponding author upon reasonable request.

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