Review Article

Bone graft substitutes used in anterior lumbar interbody fusion: a contemporary systematic review of fusion rates and complications

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Background: Anterior lumbar interbody fusion (ALIF) uses a broad-footprint interbody cage designed to maximize fusion rates for treating degenerative disc disease. Bone graft substitutes are being increasingly utilized during ALIF to replace or supplement autologous iliac crest bone grafts. This approach aims to optimize fusion efficacy while minimizing associated postoperative complications. The objective of this systematic review was to examine recent studies on fusion rates and postoperative complications associated with bone graft substitutes used in ALIF.

Methods: We conducted a systematic review of the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, MEDLINE, and PubMed databases, to critically examine a decade of research (January 1, 2012, to July 6, 2023) on the effectiveness and safety of various bone graft substitutes in ALIF. This timeframe was chosen to build on a previous systematic review published in 2013. The PRISMA guidelines were used.

Results: In total, 27 articles met our stringent inclusion and exclusion criteria. A substantial portion of these studies (67%) focused on recombinant human bone morphogenetic protein-2 (rhBMP-2) and highlighted its efficacy for achieving high fusion rates. However, the literature presents a dichotomy regarding the association of rhBMP-2 with increased postoperative complications. Notably, the methodologies for evaluating spinal fusion varied across studies. Only one-third of studies employed computed tomography to assess interbody fusion at 12 months postoperatively, highlighting the urgent need to establish uniform fusion criteria to facilitate more accurate comparative analyses. Moreover, there was considerable variability in the criteria used for diagnosing and detecting postoperative complications, significantly influencing the reported incidence rates.

Conclusions: This review underscores the need for continued research into bone graft substitutes, particularly focusing on assessment of long-term complications. Future research endeavors should concentrate on developing comprehensive clinical guidelines to aid in the selection of the most suitable bone graft substitutes for use in ALIF, thereby enhancing patient outcomes and surgical efficacy.

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Keywords: Anterior lumbar interbody fusion (ALIF); bone graft substitutes; bone morphogenetic protein; complications; fusion rate

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Introduction

Background

Interbody fusion is used for spine stabilization during the management of common spine conditions causing back or radicular leg pain, such as degenerative disk disease and spondylolisthesis (1,2). Multiple factors affect the chosen surgical approach, with the anterior retroperitoneal approach for anterior lumbar interbody fusion (ALIF) permitting the use of a wide footprint cage filled with high volumes of bone graft (1,3). Bone grafts are biological materials used to provide a scaffold and promote bone growth for complete fusion (4). In an interbody fusion, the nucleus of the intervertebral disc is removed, and then a biocompatible implant, cage, or spacer that can be filled with bone graft is inserted into the disc space (4).

Autologous iliac crest bone grafts (ICBGs) have been traditionally used for ALIF, but they are associated with postoperative complications, including donor site morbidity (4). Therefore, several biological bone graft substitutes have been developed to replace or augment ICBGs. The effectiveness of bone graft substitutes is assessed by determining the fusion rate, which is the proportion of patients with successful solid fusion at a specified time. Unsuccessful fusion can lead to pseudoarthrosis, which may result in persistent pain, reduced mobility, and the need for further surgery (1).

Rationale and knowledge gap

In 2013, Mobbs *et al.* reported the results of their systematic review of bone graft substitutes used in ALIF and concluded that autologous ICBGs remained the gold standard (4). However, subsequent developments in bone graft substitutes during the past decade have prompted the need for further analysis and review. Furthermore, the landscape of bone graft substitutes in Australia has undergone substantial changes. Use of recombinant human bone morphogenetic protein 2 (rhBMP-2) in Medtronic's Infuse Bone Graft/LT-Cage Lumbar Tapered Fusion Device was approved by the United States (US) Food and Drug Administration in 2002 (5) and by the Australian Therapeutic Goods Administration in 2006 for single-level ALIFs from L4 to S1 in adults (6), as fusion rates were similar to those achieved with ICBGs (7-9). However, in March 2020, rhBMP-2 was removed from the commercial market in Australia following reports that rhBMP-2 was being used "off label" without the LT-

Highlight box

Key findings
- Nine studies assessed fusion by computed tomography (CT) at 12-months. Assessment of bone fusion by X-ray tends to show earlier fusion, but CT is more accurate at showing true interbody bridging bone; however, it has the obvious disadvantages of cost and radiation exposure. Fusion criteria were not standardized between studies.
- rhBMP-2 was used in 18/27 studies with 88.5–100% fusion rates. However, there is conflicting evidence about associated complications.
- Fusion rates reported for other bone substitutes [allografts (84.2–96%), synthetics (77.78–100%), peptide-based (93.6%)] are promising. However, the literature is limited and presents heterogeneous methodologies reinforcing the need for future research.

What is known and what is new?
- Iliac crest bone grafts are considered the gold standard graft type in anterior lumbar interbody fusion (ALIF) but have the disadvantage of post-operative complications and donor site morbidity.
- Over the past decade, novel bone graft substitutes have become available but require further safety and efficacy analysis and systematic review. This study systematically reviewed 27 studies exploring fusion and complication rates for various bone graft substitutes used in ALIF and expands on a systematic review from 2013.

What is the implication, and what should change now?
- The findings of this systematic review should guide subsequent long-term research.
- Future investigations of bone graft substitutes in ALIF should use optimal and uniform selection criteria for fusion and post-operative complications as guided by this review. This will aid in their safe use in clinical practice.

cage and because of concerns about the cost and potential complications associated with rhBMP-2 (10,11).

Objective

The objective of this systematic review was to examine recent studies on fusion rates and postoperative complications associated with bone graft substitutes used in ALIF. Although bone graft substitutes other than rhBMP-2 have been developed, there is currently no consensus on which bone graft is preferred for ALIF. The findings of this review can be used to identify gaps in research, including identifying which bone grafts require further evaluation, and to help guide the selection of bone grafts for ALIF in clinical practice. We present this article in accordance with the PRISMA reporting checklist (available at https://jss.amegroups.com/article/view/10.21037/jss-24-24/rc).

Table 1 Search terms

Search line	Search term(s)[†]
1	"anterior"
	AND
2	"lumbar"
	AND
3	"interbody fusion*" OR "inter-body fusion*"
	AND
4	"bone graft*" OR "bone substitute*" OR "synthetic bone" OR "allograft*" OR "Allografts"[Mesh] OR "autograft*" OR "Autografts"[Mesh] OR "bone matrix" OR "bone morphogenetic protein*" OR "Bone Morphogenetic Proteins"[Mesh]
	AND
5	"cost*" OR outcome* OR "fusion rate*" OR "effect*" OR "complication*" OR "subsidence" OR "morbidit*" OR "morbidity"[Mesh] OR "mortality" OR "mortality"[Mesh] OR "infection*"

[†], a combination of natural language keywords and Medical Subject Headings (MeSH) terms were used.

Methods

Search strategy

To identify relevant studies, we first developed search terms combining natural language and Medical Subject Headings, along with Boolean operators, as outlined in *Table 1*. These terms were utilized to query databases [Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, MEDLINE, and PubMed], focusing particularly on bone graft substitutes. The terms were grouped using 'OR' Boolean operators to widen the scope of our searches. Similarly, a broad range of key terms relating to postoperative outcomes from recent studies were grouped using 'OR' operators. 'AND' operators were then used to merge search terms related to ALIF, bone graft substitutes, and outcomes into a single comprehensive search. We restricted our searches to articles published between 1 January 2012 and 6 July 2023. This timeframe was chosen to build upon the systematic review by Mobbs *et al.* published in 2013 (4).

Study inclusion and exclusion criteria and selection process

We established appropriate inclusion and exclusion criteria to select studies focusing on the relevant population, types of interventions, and outcomes, as summarized in *Table 2*. The study selection process began with detecting and removing duplicates using Rayyan software. Following this, the abstract of each article was independently screened

Table 2 Study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Adults (age ≥18 years) who underwent an ALIF	• Nonhuman animal study
• ≥1 bone graft substitute used during ALIF	• *In vitro* study
• Original human research study	• Systematic review, meta-analysis, case report, editorial, or conference abstract
• English language	
• Published between 1 January 2012 and 6 July 2023	
• Available full-text version of the study	

ALIF, anterior lumbar interbody fusion.

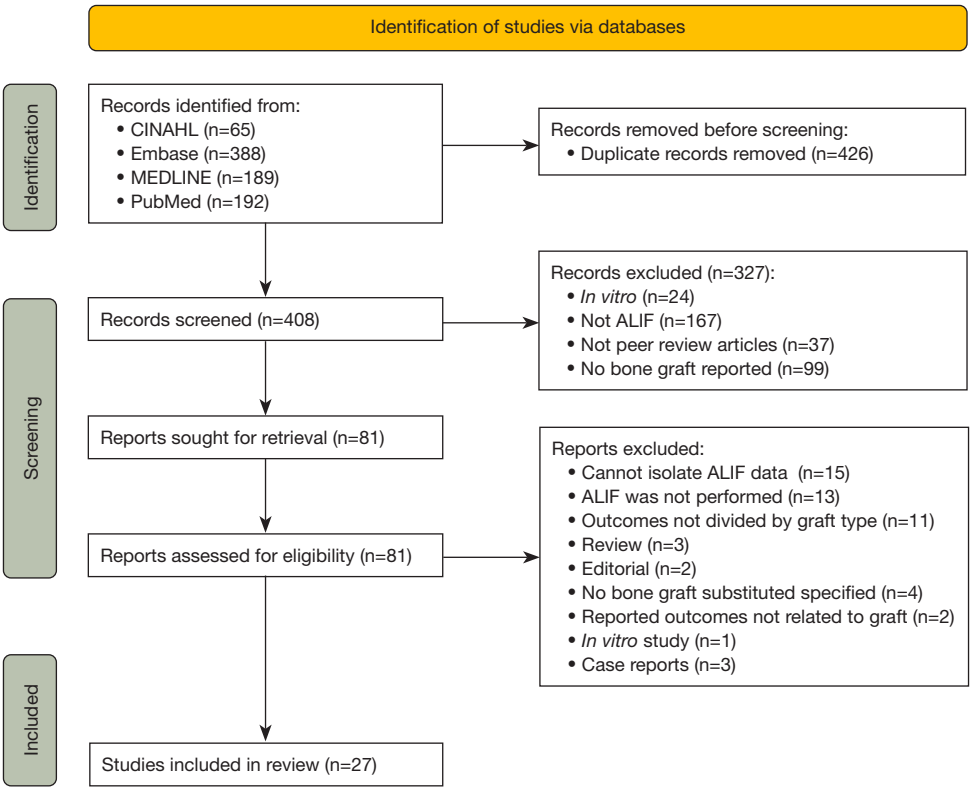

Figure 1 PRISMA diagram showing the process resulting in the 27 included studies. ALIF, anterior lumbar interbody fusion; CINAHL, Cumulative Index to Nursing and Allied Health Literature.

according to the inclusion and exclusion criteria by two reviewers (Z.A.W. and D.T.B.), who were blinded to each other's assessments. Discrepancies between the reviewers were resolved through discussion. Full-text articles that met the inclusion/exclusion criteria were then retrieved, and the screening process was repeated. The reasons for excluding full-text articles are shown in *Figure 1*.

Data collection

Information about the study characteristics, methodology, and outcomes were independently extracted from each study included in this review by two reviewers (Z.A.W. and D.T.B.), with discrepancies being resolved through discussion. The study characteristics included the first author, year of publication, country where the study was conducted or nationality of the first author, and type of study. Information on the study populations was collected, including the size (number of patients and spinal levels) and proportion of males. Intervention details, such as the type and dose of bone graft substitutes, cage specifications, and spinal levels, were recorded. Information regarding study methodology was also collected, focusing on the imaging modality and fusion criteria, including whether these criteria were specified in the *Methods* section, whether fusion was considered a binary or categorical outcome, and how functional outcomes were assessed. Finally, data regarding the fusion rate and postoperative complications were extracted. This structured approach allowed us to obtain a comprehensive understanding of the methodologies and outcomes assessed in the literature on bone graft substitutes for spinal surgery.

Results

Study selection and characteristics

As shown in *Figure 1*, 834 articles were initially retrieved through our database searches (CINAHL, 65; Embase, 388; MEDLINE, 189; PubMed, 192). After removing duplicates, the abstracts of the remaining 408 papers were assessed, and 327 were removed based on the inclusion and exclusion

criteria. Of the 81 articles that underwent full-text review, 54 studies were excluded for these reasons: ALIF outcomes could not be determined (n=15), ALIF was not performed (n=13), outcomes were not separated by graft type (n=11), no bone graft substitute was specified (n=4), outcomes of interest (fusion rate and postoperative complications) were not assessed (n=2), and the article was not a full-text version of an original human research study (n=9: 3 reviews, 3 case reports, 2 editorials, and 1 *in vitro* study). Thus, 27 studies remained for inclusion in this review.

The characteristics of each of the 27 included studies are shown in *Table 3*. The studies were most frequently conducted in the US (n=13), followed by mainland Europe (n=7) and Australia (n=5). Only one study was performed in South Korea and one in the United Kingdom. As shown in *Table 4*, two-thirds of studies (18/27) involved the use of rhBMP-2 alone or combined with allograft or synthetic material.

Fusion rates

Table 4 shows the final fusion rates reported for each main type of graft material used for ALIF. rhBMP-2 was associated with the highest overall final fusion rates when assessed by computed tomography (CT). Synthetics were associated with the greatest range of fusion rates across different imaging modalities (9).

Of the included studies, only nine studies assessed fusion rates using CT at 12 months after surgery. As shown in *Table 5*, the highest fusion rates were seen with rhBMP-2 (71–100%), whereas less CT fusion data is available for allograft, synthetics, and peptide-based grafts (9,33).

Discussion

Fusion criteria

The fusion rates in ALIF differed between studies, at least partly because of a lack of standardized imaging methods, fusion criteria, and timing of assessment. The included studies assessed fusion radiologically by CT (n=11), X-ray (n=4), or both CT and X-ray (n=5), or the method was not specified (n=7). Most studies in Australia used CT, whereas most studies in the US used X-ray only. Fusion rates assessed by CT tend to be lower than those assessed by X-ray (33). For example, Lechner *et al.* (24) assessed fusion rates by both CT and X-ray and noted that fusion rates were lower with CT (77.78%) than with X-ray (85.48%) when using β-tricalcium phosphate (β-TCP) plus bone marrow aspirate as bone graft material (23). However, use of CT is accompanied by distinct disadvantages, especially higher radiation exposure and cost (23). Although most studies (n=16) specified their fusion criteria in the *Methods* section, these criteria often differed, leading to difficulties in comparing fusion rates between studies. Furthermore, studies assessed fusion at differing times after surgery, ranging from 6 months (19,33) to a mean of 47 months (13) for CT and from 6 to 24 months (14,33) for X-ray. However, fusion was often assessed at 12 months, allowing us to use this as a reasonable assessment time for comparisons. Importantly, Malham *et al.* reported that CT fusion rates using rhBMP-2 were 66% at 6 months, 96% at 12 months, and 100% at 24 months, suggesting that fusion does not differ substantially between 12 and 24 months postoperatively (3). Establishing standard fusion criteria would allow for more accurate comparisons between studies.

Many authors have highlighted the inadequacies of X-rays for assessing spinal fusion postoperatively. While both X-rays and CT scans are commonly used for this purpose, the limitations of X-rays, including inferior soft tissue visualization, resolution, and accuracy of detecting early fusion, render CT scans more dependable in many ways. CT excels in offering an intricate evaluation of mineralized bone structures and accurately identifying hardware-related complications, such as pseudarthrosis and infection. Despite their widespread use because of easy accessibility and cost-effectiveness, X-rays do not provide the comprehensive view essential for assessing spinal fusion progression and hardware complications. In our review, many authors firmly recommended using 'focused' CT (involving only the operative level/s to reduce radiation exposure) for more accurate, up-to-date fusion assessment, superseding the outdated and less precise X-ray methods.

Urologic complications of rhBMP

Recent studies have focused on the possible association between rhBMP-2 and urologic complications, but their results are conflicting. Comer *et al.* (15) found that rhBMP-2 was associated with a higher incidence of retrograde ejaculation (RE), but Lubelski *et al.* (27) detected no association between rhBMP-2 and urologic complications, including RE, erectile dysfunction, and persistent retention. Lammi *et al.* (23) and Malham *et al.* (3)

Table 3 Studies on bone graft substitutes used for anterior lumbar interbody fusion published in 2012–2023 (n=27)

Author	Country	Type of study	No. of patients (% male)	No. of ALIF levels	Bone graft and cage	Spinal levels	Fusion rate (% of levels)	Imaging	Fusion criteria	Functional outcomes	Complications (patients)
Alimi *et al.* (12)	USA	Retrospective	2 (total n=234) (47%)	2	SiCaP in cage	Not specified	At a mean of 14.2±4.3 months: 100%	CT	Not specified; binary	ODI, VAS pain score (but could not be isolated to ALIF)	Not specified
Aurouer *et al.* (13)	France	Retrospective	37 (41%)	42	$SCCO_2$-processed bone allograft in PEEK cage	L2–S1	At a mean of 47 months: 90.5%	CT	Bridwell grade; categorical	ODI, VAS lumbar pain score, VAS radicular pain score, Odom's criteria	No complications
Behrbalk *et al.* (14)	Germany	Retrospective	25 (28%)	32	rhBMP-2 in PEEK cage	L3–S1	At a mean of 6 months: 90.6%	X-ray or CT	Specified; binary	N/A	Implant subsidence: 5 (15.6%; union in 2 patients by 6 months; nonunion with revision surgery in 3 patients)
Comer *et al.* (15)	USA	Retrospective	472 (100%)	642	rhBMP-2 (n=239); without rhBMP-2 (n=233)	L4–S1	N/A	N/A	N/A	N/A	RE: 15 (6.3%) with rhBMP-2; 2 (1.2%) without rhBMP-2 (P=0.0012)
Flouzat-Lachaniette *et al.* (16)	Germany	Retrospective	51 (28%)	62	rhBMP-2 in PEEK cage; ICBG in PEEK cage		At 12 months: 71% for rhBMP-2, 88.7% for ICBG (P=0.001)	CT	Specified; categorical	N/A	Pseudarthrosis: 3 (4.8%)
Hindoyan *et al.* (17)	USA	Retrospective	41,865 (38%)	Not specified	rhBMP-2 (n=14,384); without rhBMP-2 (n=27,481)	Not specified	N/A	N/A	N/A	N/A	RE: <11 Urinary retention: 4.4% with rhBMP-2; 5.1% without rhBMP-2 Reoperation: 0.9% with rhBMP-2; 1% without rhBMP-2 Radiculopathy: 4.4% with rhBMP-2; 4.3% without rhBMP-2 Heterotopic ossification: <11
Im *et al.* (18)	South Korea	Prospective	18 (5.6%)	18	rhBMP-2 with ß-tricalcium phosphate	L5/S1	At 6 months: 68.4% At 12 months: 100%	CT	Specified; categorical	At 12 months: ODI, VAS back pain score, VAS leg pain score	No associated complications
Kasis *et al.* (19)	UK	Retrospective	100 (37%)	108	Allograft femoral head with ICBG	L3–S1	At 5–6 months: 94%	X-ray and CT	Williams criteria; binary	ODI, VAS back pain score, VAS leg pain score, EQ-5D score	Temporary donor-site pain: 1 (1%) Symptomatic nonunion: 1 (1%)
Kayanja and Orr (20)	USA	Retrospective	60 (55%)	81	Allograft femoral ring with rhBMP-2	L3–S1	At 12 months: 74% At 29 months: 96%	CT	Specified; binary	VAS pain score	Discordant levels: 9 with rhBMP-2 dose of 4.2 mg/level
Khalid *et al.* (21)	USA	Retrospective	22,380	22,380	rhBMP-2 (n=8,971); without rhBMP-2 (n=13,139)	Not specified	N/A	N/A	N/A	N/A	Pseudoarthrosis: 1.9% with rhBMP-2; 1.4% without rhBMP-2 (OR 1.44, 95% CI: 1.16–1.76) Revision surgery: 3.7% with BMP, 3.5% without BMP (OR 1.06, 95% CI: 0.91–1.22)
Kolcun *et al.* (22)	USA	Retrospective	41 (29%)	61	rhBMP-2	L2–S1	At 12 months: 88.5%	X-ray and CT	Not specified; binary	N/A	Mean disc height subsidence: 1.8±1.7 mm (P<0.001).
Lammli *et al.* (23)	USA	Retrospective	118	Not specified	rhBMP-2 with or without cage	L4–S1	At 2 years: 93%	X-ray	Mean optical density; binary	At 12 months: ODI, VAS pain score	RE: 0 Pseudarthrosis and revision surgery: 1
Lechner *et al.* (24)	Austria	Prospective	50 (62%)	71	β-tricalcium phosphate with bone marrow aspirate	L2–S1	At 12 months: 77.78% on CT, 85.48% on x-ray	X-ray and CT	Specified; categorical	At 12 months: ODI, VAS back pain score, VAS leg pain score	Pseudarthrosis: 1 (2%) Paresis at L5: 1 (2%) Migration of cage: 1 (2%)
Lee and Kim (25)	USA	Retrospective	41 (39%)	66	Cellular allogenic bone graft (n=20) in PEEK cage; rhBMP-2 (n=21) in PEEK cage	L3–S1	At 12 months: 91% in both groups (P=0.89)	X-ray or CT	Specified; binary	ODI, VAS pain score	PEEK implant subsidence: 0 Postoperative radiculitis: 2 with map3 allograft; 8 with rhBMP-2

Table 3 (*continued*)

Table 3 (*continued*)

Author	Country	Type of study	No. of patients (% male)	No. of ALIF levels	Bone graft and cage	Spinal levels	Fusion rate (% of levels)	Imaging	Fusion criteria	Functional outcomes	Complications (patients)
Lindley *et al.* (26)	USA	Retrospective	54 (total n=95) (100%)	Not specified	rhBMP-2 (n=54)	At least L5/S1	N/A	N/A	N/A	N/A	RE: 4 (7.4%; resolved in 1 patient)
Lubelski *et al.* (27)	USA	Retrospective	110 (100%)	Not specified	rhBMP-2 (n=59); without rhBMP-2 (n=51)	L4–S1	N/A	N/A	N/A	N/A	Persistent urinary retention: 15% with rhBMP-2; 21% without rhBMP-2 (P=0.7) Erectile dysfunction: 24% with rhBMP-2; 21% without rhBMP-2 (P=1.0) Pain/difficulty ejaculating: 12% with rhBMP-2; 13% without rhBMP-2 (P=0.5) RE: 12% with rhBMP-2; 17% without rhBMP-2 (P=0.7)
Malham *et al.* (28)	Australia	Prospective	86 (total n=131) (51%)	91	rhBMP-2 in PEEK cage	L4–S1	At 6 months: 72.1% At 9 months: 94.2% At 12 months: 96.5%	CT	Specified; binary	ODI, VAS back pain score, VAS leg pain score, SF-36 PCS and MCS	RE: 1 (1.5%)
Malham *et al.* (29)	Australia	Retrospective	84 ALIF (total n=527) (47%)	94	rhBMP-2 (77%); rhBMP-7	Not specified	At 12 months: 94.7%	CT	Specified; binary	N/A	No significantly increased risk of cancer
Malham *et al.* (3)	Australia	Retrospective	50 ALIF (total n=90) (46%)	50	rhBMP-2 in PEEK cage	L4–S1	At 6 months: 66% At 12 months: 96% At 24 months: 100%	CT	Specified; binary	At 24 months: ODI, VAS back pain score, VAS leg pain score, SF-36 PCS and MCS	Radiculopathy: 3 RE: 0 Dysesthesia: 3
Mobbs *et al.* (30)	Australia	Prospective	110 (44%)	142	iFACTOR† in PEEK cage	L2–S1	≥15 months: 93.6%	CT	Specified; binary (2 radiologists)	At a mean of 24 months: ODI, VAS pain score, Odom's criteria, SF-12	RE.: 4 (resolved within 4 months in 2 patients)
Mobbs *et al.* (31)	Australia	Prospective	15 (60%)	20	Allograft with rhBMP-2 in titanium/PEEK cage	Not specified	At a mean of 15 months: 95%	CT	Specified; binary	ODI, VAS pain score, Odom's criteria, PSI	Graft subsidence ≥2 mm: 3 RE: 0 Temporary erectile issues (for 3 months): 1
Moura *et al.* (32)	Portugal	Prospective	64 (75%)	152	rhBMP-2 with bone matrix	L3–S1	At 12 months: 100%	X-ray	Specified; binary	ODI, VAS pain score	No associated complications
Norotte and Barrios (33)	France	Prospective	65 (55.4%)	65	Hydroxyapatite in cages	L5/S1	At 12 months: 95.4%	X-ray	Specified; binary	At 24 months: ODI, VAS pain score	Bladder dysfunction: 6 (9.2%)
Singh *et al.* (34)	USA	Retrospective	Not specified (total n=101,953)	Not specified	BMP (56.7%)	Not specified	N/A	N/A	N/A	N/A	Mortality (per 1,000): 0.0 in 2002; 0.7 in 2011
Szadkowski *et al.* (35)	France	Retrospective	40 (35%)	58	Bioactive glass in cage; ICBG in cage	L4–S1	At 12 months: 97% for bioactive glass; 97% for autograft At 15±5 months: no difference (P=0.416)	CT	Bridwell grade; categorical	At 24 months: ODI, VAS back pain score, VAS leg pain score, SF-12	Reoperation at L4/L5 (Bridwell grade III): 2
Tepper *et al.* (36)	USA	Prospective	41 (100%)	Not specified	rhBMP-2 with femoral ring allograft (n=21); ICBG (n=20)	L4–S1	N/A	N/A	N/A	N/A	RE diagnosed by questionnaire: 15 (resolved in 2 patients) RE diagnosed by laboratory analysis: 2 (9.5%) with rhBMP-2 (resolved in 1 patient); 2 (10%) with ICBG (resolved in 1 patient)
Wan *et al.* (37)	USA	Retrospective	48	83	Allograft femoral ring (n=30)	L4–S1	At 12 months: 79% At final follow-up (>1 year): 84.2%	X-ray	Bridwell-Lenke grade; categorical	Prolo functional scores	No complications

†, iFACTOR is a synthetic bone matrix with P-15 osteogenic cell binding peptide. ALIF, anterior lumbar interbody fusion; CT, computed tomography; ODI, Oswestry Disability Index; VAS, visual analog scale; PEEK, polyetheretherketone; rhBMP, recombinant human bone morphogenetic protein; N/A, not available; RE, retrograde ejaculation; ICBG, iliac crest bone graft; EQ-5D, European Quality of Life-5 Dimensions; OR, odds ratio; CI, confidence interval; BMP, bone morphogenetic protein; SF-36, 36-Item Short Form Health Survey; PCS, physical component summary; MCS, physical component summary; SF-12, 12-Item Short Form Health Survey; PSI, patient satisfaction index.

Table 4 Range of study sample sizes and final fusion rates reported for the main types of bone graft substitutes

Bone graft substitute	Number of studies	No. of patients per study	Final fusion rate	Complications assessed
rhBMP	18	1–14,384	88.5–100%	Pseudoarthrosis, graft subsidence, discordant levels, urologic complications, cancer
Allograft	6	37–100	84.2–96%	Pain, nonunion, graft subsidence, discordant levels
Synthetics	5	2–65	77.78–100%	Pseudoarthrosis, paresis, urologic complications
Peptide-based grafts	1	110	93.6%	Reoperation, urologic complications

rhBMP, recombinant human bone morphogenetic protein.

Table 5 Fusion rates of bone graft substitutes assessed by computed tomography at 12 months postoperatively

Author	No. of patients (% male)	No. of ALIF levels	Bone graft and cage	Fusion rate at 12 months	Functional outcomes	Complications (patients)
Im *et al.* (18)	18 (5.6%)	18	rhBMP-2, β-tricalcium phosphate	100%	At 12 months: ODI, VAS back pain score, VAS leg pain score	No associated complications
Szadkowski *et al.* (35)	40 (35%)	58	Bioactive glass in cage	97%	At 24 months: ODI, VAS back pain score, VAS leg pain score, SF-12	Reoperation at L4/L5 (Bridwell grade III): 2
Malham *et al.* (28)	86 (total n=131) (51%)	91	rhBMP-2 in PEEK cage	96.5%	ODI, VAS back pain score, VAS leg pain score, SF-36 PCS and MCS	RE: 1 (1.5%)
Malham *et al.* (3)	50 ALIF (total n=90) (46%)	50	rhBMP-2 in PEEK cage	96%	At 24 months: ODI, VAS back pain score, VAS leg pain score, SF-36 PCS and MCS	Radiculopathy: 3 RE: 0 Dysesthesia: 3
Malham *et al.* (29)	84 ALIF (total n=527) (47%)	94	rhBMP-2 (77%); rhBMP-7 (23%)	94.7%	N/A	No significant increased risk of cancer
Kolcun *et al.* (22)	41 (29%)	61	rhBMP-2	88.5%	N/A	Mean disc height subsidence: 1.8±1.7 mm (P<0.001)
Lechner *et al.* (24)	50 (62%)	71	β-tricalcium phosphate with bone marrow aspirate	77.78%	At 12 months: ODI, VAS back pain score, VAS leg pain score	Pseudarthrosis: 1 (2%) Paresis at L5: 1 (2%) Migration of cage: 1 (2%)
Kayanja and Orr (20)	60 (55%)	81	rhBMP-2 with femoral ring allograft	74%	VAS pain score	Discordant levels: 9 with rhBMP-2, 4.2 mg/level
Flouzat-Lachaniette *et al.* (16)	51 (28%)	62	rhBMP-2 in PEEK cage	71%	N/A	Pseudarthrosis: 3 (4.8%)

ALIF, anterior lumbar interbody fusion; rhBMP, recombinant human bone morphogenetic protein; ODI, Oswestry Disability Index; VAS, visual analog scale; SF-12, 12-Item Short Form Health Survey; PEEK, polyetheretherketone; SF-36, 36-Item Short Form Health Survey; PCS, physical component summary; MCS, Mental Component Summary; RE, retrograde ejaculation; N/A, not available.

likewise reported no urologic complications with rhBMP-2 use. Although RE is a potential complication of ALIF itself because of mechanical and inflammatory damage, rhBMP-2 has been associated with inflammatory adverse effects, which may contribute to an increased risk of RE (15). However, most studies assessing urologic complications were retrospective and contained no comparison group. Only Tepper *et al.* (36) evaluated urologic complications diagnosed via laboratory analysis of semen and urine. They found that RE was overreported in questionnaires, as 15 patients reported RE in these questionnaires, whereas only four had true RE based on laboratory analysis. This suggests that the method of assessing RE can significantly affect the reported incidence. The authors also found no significant difference in RE incidence between patients who received rhBMP-2 plus femoral ring allografts (FRA) (9.5%) versus ICBG (10%). In both groups, RE resolved spontaneously, indicating that RE may be a short-term complication, as suggested in other studies (26).

In a number of studies, patients were not specifically asked about postoperative urologic complications. However, in two studies by Malham *et al.* (3,28), an independent physician assessed specific complications and found that only one patient (1.5%) developed RE. Furthermore, most studies focusing on urologic complications did not report fusion rates, preventing more comprehensive comparisons between bone graft substitutes. The differing complication rates between studies were likely affected by variances in postoperative protocols between surgeons and hospitals. Further studies are required to specifically evaluate the potential association between rhBMP-2 and urologic complications.

Nonurologic complications of rhBMP-2

The studies included in this review assessed several nonurologic complications potentially associated with rhBMP-2 use, including pseudoarthrosis, subsidence, radiculopathy, and dysesthesia. The study with the largest sample size showed that the incidence of complications (including reoperation and radiculopathy) within 12 months after surgery was not significantly different between patients receiving rhBMP-2 and those not receiving rhBMP-2 (17). Heterotrophic ossification was also detected in a small number of patients, indicating that further studies should also assess this potential complication (17). However, Khalid *et al.* (21) recently reported that the rate of pseudoarthrosis was higher in patients treated with rhBMP-2 than in those without rhBMP-2 (21). Although subsidence was reported in some studies, it can be affected by the type of cage (38). Behrbalk *et al.* (14) found that 15.6% of patients treated with rhBMP-2 in PEEK cages had implant subsidence, and Kolcun *et al.* (22) reported that the mean disc height subsidence was 1.8 mm when rhBMP-2 was used in an OptiMesh device. However, Lee and Kim (25) detected no implant subsidence in patients receiving rhBMP-2. Therefore, future studies should account for the type of cage when evaluating the association between bone graft substitutes and implant subsidence.

Higher incidences of neurologic complications were found in patients who received rhBMP-2. In one study, postoperative radiculitis occurred in eight patients (38%) receiving rhBMP-2 and only two patients (10%) treated with map3 cellular allogenic bone grafts (25). Malham *et al*. (3) reported that among 50 patients receiving rhBMP-2 for ALIF, three (6%) developed radiculopathy and three (6%) experienced dysesthesia. Only one study, Malham *et al.* (28) assessed cancer and found no increased risk of cancer in patients who received rhBMP-2 or rhBMP-7 for lumbar interbody fusion, including ALIF, with a minimum 1.8-year follow-up. Further studies should assess the incidences of cancers specifically following ALIF. Only one study (34) reported in-hospital mortality after ALIF with rhBMP-2 but did not specify whether the deaths were related to rhBMP-2. Overall, the methods for detecting and diagnosing complications differed between studies, which likely affected the reported incidences and highlighted the need for further studies to compare rates of complications between bone graft substitutes based on the same methodology.

Optimal rhBMP-2 dose

Studies have used a range of rhBMP-2 doses to achieve high fusion rates with ALIF while minimizing complications. The dose of 6 mg/level rhBMP-2 was associated with a fusion rate of 90.6% at 6 months and no subsidence (14). However, when rhBMP-2 and ICBG were used in different chambers of a cage in the same individuals, the 12-month fusion rate was 71% with 6 mg of rhBMP-2 and 88.7% with ICBG, and three patients (4.8%) experienced pseudoarthrosis (30). In a study of rhBMP use during ALIF by Malham *et al.* (28), patients received mean doses of 10.2 mg (range, 2.5–48.0 mg) for rhBMP-2 and 3.3 mg (range, 1.7–6.6 mg) for rhBMP-7 in ALIFs, but only the overall fusion rate was reported (94.7%), so the effectiveness of each dose could not be determined. Future studies are

required to determine the optimal dose of rhBMP-2.

New combinations of rhBMP-2 with other bone graft substitutes have been developed. A 100% fusion rate and no associated complications were recently reported in 18 patients receiving *Escherichia coli*-derived rhBMP-2 plus β-TCP (18). These promising results justify conducting further studies with larger sample sizes and longer follow-ups to assess long-term complications of this treatment strategy (18). rhBMP-2 with bone matrix was also reported to have a 100% rate of fusion on X-ray at 12 months (32), but the fusion rate was not assessed by CT, preventing accurate comparisons with other bone graft substitutes. rhBMP-2 plus supercritical carbon dioxide ($SCCO_2$)-processed allograft for ALIF resulted in a fusion rate of 95%, with only one patient (6.7%) experiencing temporary erectile issues and three patients (20%) developing graft subsidence (30). However, rhBMP-2 with FRA resulted in discordant levels in nine patients with double-level ALIFs, which was only detected in this study. As fusion rates associated with combining rhBMP-2 plus other bone graft substitutes are promising, future studies should be performed to compare fusion rates and assess for long-term complications. However, since rhBMP-2 is currently off the market in Australia, further studies of the material from this country will be limited to retrospective studies, and other bone graft substitutes will need to be considered.

Allografts

A variety of allografts continue to be developed. Recently, Kasis *et al.* (19) developed the Northumbria technique combining femoral head allograft with ICBG and reported a 94% CT fusion rate after 5–6 months (19). Only one patient (1%) developed temporary donor-site pain, a known complication of autografts (4). However, further studies by other surgeons are required to assess the technique's reproducibility, and this combined technique involved the use of autografts. The map3 cellular allogenic bone graft had a 91% fusion rate, with no statistical difference in fusion rates compared to rhBMP-2 (25). Furthermore, the rate of radiculitis was lower with this allograft (n=2; 10%) than with rhBMP-2 (n=8; 38%) (27). $SCCO_2$-processed bone allografts were associated with a fusion rate of 90.5% at 47 months on CT and no reported complications, but the fusion rate at 12 months was not available, preventing comparisons to other materials (13). FRA had the lowest fusion rate (79%) on X-ray at 12 months, with no complications detected, but CT assessment of fusion rates was not performed (34). FRA used in combination with rhBMP-2 showed a 74% CT fusion rate at 12 months (20). Overall, $SCCO_2$-processed bone allografts appear promising, but further studies are required to compare fusion rates with other bone grafts and assess for a range of complications.

Calcium phosphate compounds

Ceramics are synthetic grafts containing calcium phosphate combined with hydroxyapatite or silicate. β-TCP with bone marrow aspirate had a fusion rate of 85.48% on X-ray and 77.78% on CT at 12 months (24). Silicate-substituted calcium phosphate [SiCaP (Actifuse)] has been used, but we identified its use in only two patients undergoing ALIF (36). Although fusion was successful in both patients, a larger sample size is required. However, a meta-analysis comparing SiCaP with rhBMP-2 for posterolateral fusion found no difference in fusion rates between the two materials (9). However, no studies used the same type of calcium phosphate compound, so it was not possible to determine the components potentially contributing to improved fusion and complication rates. Overall, these studies regarding calcium phosphate compounds have had small sample sizes and no comparison groups, but their results were promising and warrant future larger studies, including randomized controlled trials.

Bioactive glass contains biodegradable granules that are osteoconductive, not osteoinductive. In 2022, Szadkowski *et al.* (35) reported fusion rates of 89–100% with bioactive glass, which were not significantly different from the rates achieved with autografts. Notably, the fusion rates in this study were assessed within the same patients, as one chamber of the cage contained bioactive glass and the other chamber contained ICBG. Although this methodology is useful for comparing fusion rates between bone graft substitutes, it leads to difficulties in determining which type of graft is responsible for complications. Bioactive glass also has unique properties, including antibacterial and anti-inflammatory properties, that may improve overall outcomes of ALIF (39,40). Therefore, further research is required to evaluate the effectiveness and safety of bioactive glass grafts for ALIF.

Peptide-based grafts

iFACTOR is the only peptide-based graft currently available. It is a bone graft substitute matrix containing P-15 osteogenic cell binding peptide combined with an

organic bone matrix material suspended in a hydrogel carrier. Overall, iFACTOR appears to be a promising substitute, producing high fusion rates with minimal complications. However, only one study has been published using iFACTOR for ALIF. In this prospective study of 110 patients, the fusion rate assessed by CT was 94% at 2 years (31). Of note, this study was partially funded by Cerapedics, the company that manufactures iFACTOR. Overall, investigations of bone graft substitutes are industry led, with studies often funded by manufacturers. Early studies on rhBMP-2 in ALIF were widely supported financially by industry, and later independent studies reported more complications associated with this agent (41). Future independently funded studies are encouraged to reduce potential bias.

Review limitations

One limitation of this review was that outcomes for specific bone graft substitutes were often difficult to extract from studies because of combined outcomes from different bone graft substitutes or types of lumbar interbody fusions. Previous studies and meta-analyses (42) identified factors that could affect differing fusion and complication rates between approaches. This highlights the need for randomized controlled trials (RCTs) with larger sample sizes to achieve sufficient statistical power to detect significant differences in outcomes between different bone graft substitutes for ALIF.

Another limitation was that the methods used to measure functional outcomes after ALIF were patient-reported outcome measurements. Although some studies reported Oswestry Disability Index and visual analog scale scores for back or leg pain, many factors unrelated to bone graft material affect these scores. Future studies should control for factors affecting functional outcomes other than type of bone graft substitute.

A third limitation was that we did not search the grey literature, so very recently developed bone graft substitutes may not have been included. However, early studies are likely to be funded by companies that developed these substitutes, leading to a substantial risk of bias. Independently funded RCTs are required to more accurately compare fusion rates and assess complications.

Conclusions

This systematic review examined 27 studies published over the past decade regarding various bone graft substitutes used for ALIF and focused on their rates of fusion and postoperative complications. The majority of studies evaluated rhBMP-2 and reported robust fusion rates. Nonetheless, the association between rhBMP-2 and increased risk of postoperative complications remains a contentious subject, with divergent findings reported. Of note, the methodologies for quantifying spinal fusion were heterogeneous, with only one-third of studies using CT to assess spinal fusion at 12 months postoperatively, thereby underscoring the need for a uniform set of fusion criteria to enable more accurate comparative analyses. The criteria for diagnosing and identifying postoperative complications also varied significantly across studies, influencing the reported complication rates. Consequently, there is a need for further research into bone graft alternatives, particularly to ascertain and evaluate potential long-term dangers through extended postoperative surveillance. The findings from this narrative review can be used to guide future research to determine how bone graft substitutes used in ALIFs should be selected in clinical practice. Future scholarly efforts should endeavor to formulate clinical protocols delineating the optimal selection criteria for bone graft substitutes in the setting of ALIF surgery.

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Footnote

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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