Review Article

Utility of bioactive glasses as fusion substrates for cervical and lumbar fusion: a systematic review

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Background: There has been a continued search for synthetic graft materials to replace iliac crest bone graft and allograft in spinal fusion. Recently, there has been interest in bioactive glasses (BGs) as graft substitutes, but a confusing landscape of current literature creates difficulty in evaluating their clinical effectiveness. As such, we conducted an updated systematic review on BG use in cervical and lumbar spinal fusion.

Methods: A systematic review of the MEDLINE, Cochrane, Embase, and Web of Science databases was conducted on March 26th, 2024. Studies were included if they pertained to BGs and spine fusion. Risk of bias for included studies was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB 2). Only prospective clinical studies and randomized controlled trials were ultimately included. Data were analyzed narratively.

Results: Five studies with low bias, four with some concerns for bias, and three with high bias were included in the final review. Sample sizes ranged from 17–74 patients, and BG types included BGS-7, S53P4, 45S5, Chitra-HABg, and apatite- and wollastonite-containing glass-ceramic (AWGC). Procedures included posterolateral lumbar fusion (PLF), posterior lumbar interbody fusion (PLIF), anterior lumbar interbody fusion (ALIF), and anterior cervical discectomy and fusion (ACDF). When BGs were used as standalone grafts, fusion rates ranged 0–70.6% at >1-year follow-up. In one study of PLF, grafts composed of AWGC and autograft mixtures resulted in fusion rates between 81.8–83.3%. 45S5 showed comparable fusion to autograft at 1 year postoperatively in ALIF. When BGS-7 was used as a cage material, fusion rates varied from 75.0–95.0% at >1-year follow-up, compared to 65.4–100% for titanium, allograft, or polyether ether ketone (PEEK) cages.

Conclusions: When used as standalone fusion grafts in PLF, pure Chitra-HABg and S53P4 are ineffective compared to autograft. However, grafts made of 45S5 or mixtures of AWGC with autograft show fusion rates comparable to autograft alone. BGS-7 cages showed noninferior fusion rates to titanium, allograft, and PEEK cages. Additional prospective studies with quality methodologies are necessary to validate these results.

Keywords: Bioactive glass (BG); spinal fusion; lumbar fusion; cervical fusion

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Introduction

Spinal fusions are effective and established treatment options for various spine pathologies, and the number of patients undergoing these procedures has been steadily increasing over time (1-4). The historical gold standard fusion material has been autograft (AG) harvested from the iliac crest, although this process is associated with morbidity rates of 2.4–6.2% for complications like surgical site infection, hematoma formation, and residual pain (5). As such, costly cadaveric allografts, often in the form of demineralized bone matrix, are more frequently being utilized (6). In an effort to reduce the need for these materials, there has been an impetus to develop fully synthetic grafts that are efficient to produce and achieve comparable fusion rates.

Bioactive glasses (BGs) are a fully synthetic type of ceramic that have diverse applications as medical devices. Owing to their osteoconductive and osteoinductive properties, lack of donor site morbidity, and long-term cost-effectiveness, there is growing interest in exploring BGs as graft substitutes in spinal fusion (7-9). It is important to note that the term "bioactive glass" refers to a broad category of materials, each with unique chemical compositions. Although there are numerous clinical studies that have investigated the efficacy of BGs as fusion grafts, the current landscape of data is considerably disorganized due to variations in BG type, application of BGs, surgery type, and study design (10,11). Additionally, inconsistency in how adverse outcomes are reported between studies is also prevalent in the current literature. This heterogeneity in methodologies and results has made it difficult to extract meaningful conclusions applicable to surgical practice, as one study on BGs may report promising fusion rates as high as 100% (12), while another might show dismal rates as low as 0% (13).

In this study, we present an updated systematic review on the current landscape of clinical studies that investigate the use of BGs in cervical and lumbar spinal fusion, with a focus on fusion rates and adverse outcomes. Given the expected methodological heterogeneity between studies, we opt to conduct a systematic review without quantitative meta-analysis. The goal of this review is to provide context to the existing literature so future clinical research can focus on the most promising BG types and uses in spine surgery. We present this article in accordance with the PRISMA reporting checklist (available at https://jss.amegroups.com/article/view/10.21037/jss-25-110/rc).

Highlight box

Key findings

- Single prospective studies show that grafts composed of 45S5 or mixtures of apatite- and wollastonite-containing glass-ceramic (AWGC) with autograft result in fusion rates that are comparable to pure autograft. Multiple other studies show that BGS-7 cages are noninferior in terms of fusion rates and adverse event profiles when compared to titanium, allograft, and polyether ether ketone cages.

What is known and what is new?

- The current literature surrounding the use of bioactive glasses in spinal fusion contains studies that vary considerably in their designs. As such, it has been difficult to determine their clinical effectiveness.
- This updated systematic review incorporates more recent prospective clinical studies and randomized controlled trials to evaluate the effectiveness of bioactive glasses in spinal fusion. Using a select group of prospective studies, we assess fusion rates and adverse event profiles between patients who received bioactive glass products and those who received standard fusion grafts and cage materials.

What is the implication, and what should change now?

- Additional high-quality prospective studies are required to validate the clinical effectiveness of bioactive glasses as fusion grafts and cage materials, specifically BGS-7 cages, AWGC-autograft mixtures, and 45S5 grafts.

Methods

Electronic database search and screening

Inclusion criteria were defined using the PICOS (patients, intervention, comparison, outcomes, and study design) principles, as shown in *Table 1*. Our literature search was conducted using keywords designed to find all available clinical studies involving BGs and spinal fusion. The databases queried were MEDLINE, Cochrane, Embase, and Web of Science. The literature search was conducted on March 26th, 2024. Exclusion criteria included conference abstracts, comments, editorials, and preprints. For example, the query string used to search Cochrane was: (bioactiv* ADJ6 glass* OR CaO-SiO2-P2O5-B2O3 OR BGS-7 OR BGS7 OR bioglass* OR "45S5" OR "S53P4" OR BioSphere Putt* OR novomax) AND (spine OR spinal OR vertebrae OR vertebral OR intervertebral OR cervical OR lumbar OR lumbar interbody fusion OR lumbar inter-body fusion OR cervical decompress* OR cervical discectom* OR cervical diskectom* OR degenerative cervical disc OR cervical disc

Table 1 Inclusion criteria per PICOS principles

Principle	Inclusion criteria
Patients	Adult patients (age >18 years) undergoing spinal fusion surgery, including ACDF, ALIF, PLF, PLIF, TLIF, or XLIF, for degenerative or fracture etiologies
Intervention	Implantation of BGs as a direct fusion material, including as a standalone graft or in combination with a traditional fusion cage
Comparison	Implantation of traditional fusion grafts, including autograft bone or allograft bone, or use of traditional fusion cages, including PEEK and titanium
Outcomes	Rates of radiographic fusion and adverse outcomes, including hardware migration, cage subsidence, hardware failure, pseudoarthrosis, osteolysis, postoperative dysphagia, and reoperation
Study design	Prospective controlled studies, including RCTs

ACDF, anterior cervical discectomy and fusion; ALIF, anterior lumbar interbody fusion; BG, bioactive glass; PEEK, polyether ether ketone; PLF, posterolateral fusion; PLIF, posterior lumbar interbody fusion; RCT, randomized controlled trial; TLIF, transforaminal lumbar interbody fusion; XLIF, extreme lumbar interbody fusion.

degeneration OR intervertebral disc degeneration OR degenerative intervertebral disc OR thoracic vertebrae). This query string was stylistically translated for proper use in each database.

The published, peer-reviewed studies found by our initial search included all those written in English on the use of any type of BG, including the most common ones of BGS-7 (CaO-SiO2-P2O5-B2O3) and Bioglass® (45S5), in cervical, thoracic, or lumbar spinal fusion surgery. Duplicate studies were identified and removed using EndNote 20 (Clarivate, Philadelphia, PA, USA). The titles and abstracts of the remaining studies were then screened by two reviewers (K.G.L. and E.K.). Studies were excluded if they involved animal, cadaver, or *in vitro* experiments, had pediatric or dental populations, were retrospective in nature, or were review articles. A third reviewer (I.S.) provided arbitration in cases of disagreement. Studies that passed initial abstract screening were retrieved for full-text review, where they were further excluded if they did not report radiographic fusion rates or if they met the exclusion criteria from the first round of manual review. The studies that passed this full-text review were ultimately included in our systematic review.

Assessment of quality and data extraction

Risk of bias for included studies was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB 2), which takes into account randomization processes, deviations from intended interventions, missing outcome data, how outcomes are measured, and authors' selection of reported results (14). In a similar manner to the literature screening process, each study and associated trial protocol (if available) was systematically evaluated for the above factors, with a final judgement being made of low, some concerns, or high risk of bias for each study.

For data collection, each included study was examined to extract descriptive characteristics as well as fusion rates and adverse events. The type of BG used, surgery type, inclusion criteria, study design, initial and follow-up sample size, and reasons for participant loss were recorded for each study. The percent of patients who achieved bony fusion and the percent of levels with successful fusion were recorded at the longest reported follow-up time. Adverse events to be collected included hardware migration, cage subsidence, hardware failure, pseudoarthrosis, osteolysis, postoperative dysphagia, reoperation, and any additional adverse outcome reported by the authors.

Results

Included studies after screening

From the initial database query, we identified 607 total studies, of which 209 were identified as duplicates and removed. Of the remaining 398 studies, 367 were excluded before full-text review. Among the 31 studies retrieved for full-text review, 19 were subsequently excluded, with 10 being retrospective in nature, five having dental or pediatric populations, two being cadaver studies, and another two being animal or *in vitro* studies. Ultimately, 12 studies were included in the final systematic review (*Figure 1*). Descriptive summaries of each of these studies along with

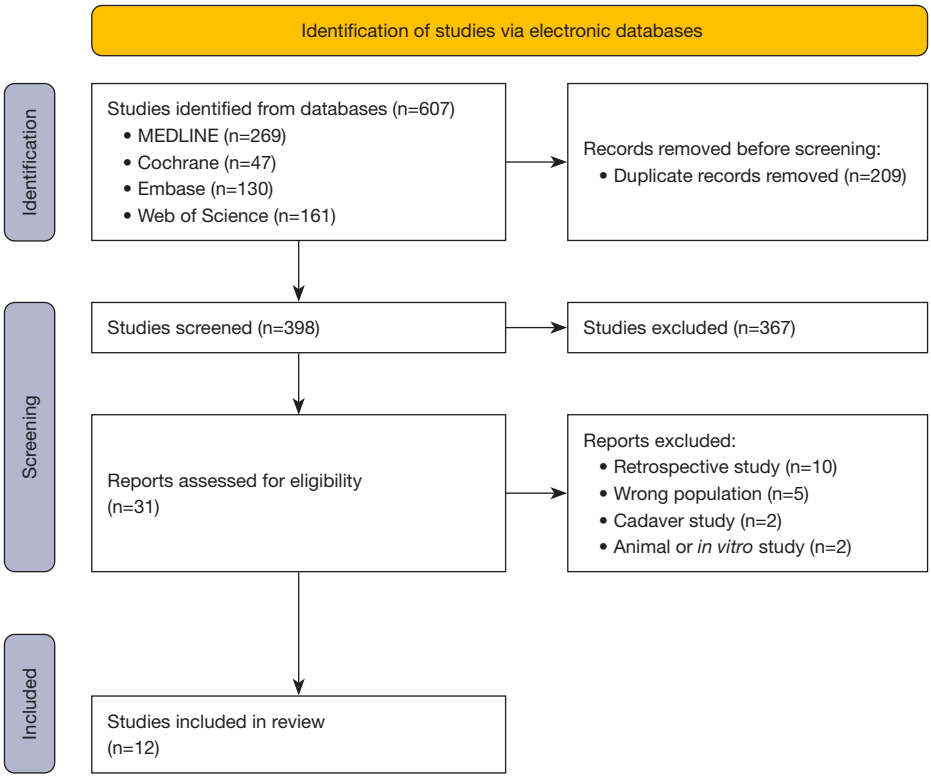

Figure 1 PRISMA flow diagram.

their reported fusion rates are presented in *Table 2*. Rates of reported adverse outcomes are presented in *Table 3*. Of the 12 studies, none reported any subgroup analyses or results stratified by patient characteristics.

Effect of BGS-7 in posterior lumbar interbody fusion (PLIF)

Seven studies assessed the use of BGS-7 in spinal fusion, with three looking at PLIF (15-17) and four at anterior cervical discectomy and fusion (ACDF) (12,18-20). Of the three PLIF studies, Kwon *et al.* [2023] had patients receive either an AG-filled BGS-7 spacer or an AG-filled polyether ether ketone (PEEK) cage (15). This study's 28% loss at follow-up raises some concern for bias, although there was a relatively equal number of patients lost from each group. The authors found that fusion rates were similar at 1 year postoperatively (77.8% BGS-7 *vs.* 81.0% PEEK, P=0.807), with two instances of hardware migration and one hardware failure in the BGS-7 group. However, average cage subsidence was significantly lower in the BGS-7 group (0.77 *vs.* 2.53 mm, P=0.001), and there was no difference in osteolysis by level between groups (25.0% BGS-7 *vs.* 21.4% PEEK, P=0.496).

The two other studies by Lee *et al.* are part of one longer trial comparing AG-filled BGS-7 spacers with AG-filled titanium spacers, with one reporting on 1-year follow-up data (17) and the other on 4-year follow-up results (16). These two studies' patient blinding, randomization, complete follow-up, and multiple independent assessors of imaging lead to them having a low risk of bias. These studies found that fusion rates were similar both at 1 year (89.7% BGS-7 *vs.* 91.4% titanium, P>0.99) and at 4 years (90.6% BGS-7 *vs.* 93.3% titanium, P>0.99). In addition, the average cage subsidence (1.10 mm BGS-7 *vs.* 0.94 mm titanium, reported as non-significant by the authors) and osteolysis by level (7.7% BGS-7 *vs.* 5.9% titanium, reported as non-significant by the authors) were comparable at 1 year. Adverse event profiles at 4 years were not reported by the authors.

Use of BGS-7 in ACDF

For the four studies that assessed the use of BGS-7 in

Table 2 Descriptive summaries of each included study

Author, year, risk of bias	BG type, procedure type	Inclusion criteria	Study design	Reasons for patient loss	Sample size at follow-up	Assessment of fusion outcome	Fusion rate by patient	Fusion rate by level
Acharya *et al.*, 2008 (13), high	Chitra-HABg, PLF	24 consecutive patients, who underwent instrumented posterolateral fusion for various reasons	Each patient received BG on one side and AG on the other side of the intertransverse region as fusion material	1 died from unrelated causes, 1 was LTFU	22	X-ray at 1 year	0% BG side; 72.7% AG side	–
Kwon *et al.*, 2023 (15), some concerns	BGS-7, PLIF	54 patients aged 30–80 years who required who required 1- or 2-level PLIF between L1 and S1 among those who required an extensive laminectomy or facetectomy to correct severe disc extrusion, severe spinal stenosis, or spondylolisthesis	28 patients received a PEEK cage, 26 patients received a BGS-7 spacer, all filled with autograft	2 underwent implant removal due to surgical site infection, 7 in BG group and 6 in PEEK group were LTFU	39	CT at 1 year	77.8% BG group; 81.0% PEEK group	–
Lee *et al.*, 2020 (16), low	BGS-7, PLIF	62 patients aged 30–80 years who required 1-level PLIF between L1 and S1 among those who required an extensive laminectomy or facetectomy to correct severe disc extrusion, severe spinal stenosis, or grade I or II spondylolisthesis	32 patients received a BGS-7 spacer, 30 patients received a titanium cage, all filled with AG	–	62	CT and X-ray at 4 years	90.6% BG group on CT; 87.5% BG group on X-ray; 93.3% titanium group on CT; 100% titanium group on X-ray	–
Lee *et al.*, 2016 (17), low	BGS-7, PLIF	74 patients aged 30–80 years who required 1-level PLIF between L1 and S1 among those who required an extensive laminectomy or facetectomy to correct severe disc extrusion, severe spinal stenosis, or grade I or II spondylolisthesis	39 patients received a BGS-7 spacer, 35 patients received a titanium cage, all filled with AG	–	74	CT at 1 year	89.7% BG group; 91.2% titanium group	–
Liu *et al.*, 2025 (18), low	BGS-7, ACDF	40 patients aged 18–75 years who demonstrated clinical symptoms of cervical radiculopathy or myelopathy stemming from subaxial cervical degenerative disc disease due to soft disc herniation or spondylosis, who had radiological validation of cervical disc degeneration on MRI or CT, and who failed nonsurgical management for at least 3–6 months	18 patients received an allograft cage, 22 patients received a BGS-7 spacer	–	40	CT at 1 year	75.0% BG group; 87.8% allograft group	–
Park *et al.*, 2023 (19), low	BGS-7, ACDF	72 patients aged 20–80 years who were expected to undergo 1- or 2-level ACDF for degenerative cervical spine diseases	39 received a PEEK cage, 33 received a BGS-7 spacer	–	72	CT at 1 year	81.8% BG group; 74.4% PEEK group	–
Ryu *et al.*, 2023 (12), high	BGS-7, ACDF	44 consecutive ACDF surgeries in patients who had degenerative cervical disease from the C3/4 to C6/7 levels, including cervical disc herniation and foraminal stenosis	26 received an allograft cage, 18 received a BGS-7 spacer	–	44	CT at 7.5 years	77.8% BG group; 65.4% allograft group	–
Kwon *et al.*, 2024 (20), some concerns	BGS-7, ACDF	40 consecutive patients aged 19–75 years with symptoms of radiating pain and/or myelopathy requiring single-level ACDF between C3–7	19 received a PEEK cage filled with AG, 20 received a BGS-7 spacer	1 was LTFU	39	CT at 1 year	95.0% BG group; 94.7% PEEK group	–
Frantzén *et al.*, 2011 (21), some concerns	S53P4, PLF	20 patients with lower back pain between March 1996 and August 1997	Each patient received BG on one side and AG on the other side of the fusion bed as fusion material	2 died from unrelated causes, 1 was LTFU	17	CT at 11 years	70.6% BG side; 100% AG side	80% BG side; 100% AG side
Rantakokko *et al.*, 2012 (22), high	S53P4, PLF	16 patients aged 31–58 years with an unstable lumbar burst fracture classified according to Denis's classification	Each patient received BG on one side and AG on the other side of the fusion bed as fusion material	3 died from unrelated causes, 3 declined to participate	10	CT at 10 years	50% BG side; 100% AG side	71.4% BG side; 100% AG side
Kasai *et al.*, 2003 (23), some concerns	AWGC, PLF	35 patients who were diagnosed with lumbar spinal canal stenosis	12 patients received 2:1 AG:BG, 12 patients received 1:1 AG:BG, 11 patients received 1:2 AG:BG as fusion material at both intertransverse regions	–	35	X-ray at 2 years	83.3% 2:1 AG:BG group; 83.3% 1:1 AG:BG group; 81.8% 1:2 AG:BG group	–
Szadkowski *et al.*, 2022 (24), low	45S5, ALIF	40 consecutive patients who underwent 1- or 2-level ALIF at L5–S1 or L4–S1	Each patient received half bioactive glass, half AG within a chambered ALIF cage	2 required reoperations	38	CT at 1 year	–	52% BG side; 40% AG side

ACDF, anterior cervical discectomy and fusion; AG, autograft; ALIF, anterior lumbar interbody fusion; AWGC, apatite- and wollastonite-containing glass-ceramic; BG, bioactive glass; CT, computed tomography; LTFU, lost to follow up; MRI, magnetic resonance imaging; PEEK, polyether ether ketone; PLF, posterolateral fusion; PLIF, posterior lumbar interbody fusion.

Table 3 Adverse events reported in each included study

Author, year, BG type, procedure type	Hardware migration	Average cage subsidence (by level)	Hardware failure	Pseudoarthrosis	Osteolysis (by level)	Dysphagia	Reoperation	Other
Acharya *et al.*, 2008 (13), Chitra-HABg, PLF								
Frantzén *et al.*, 2011 (21), S53P4, PLF	2		5					3 instances of hardware loosening
Kasai *et al.*, 2003 (23), AWGC, PLF								
Kwon *et al.*, 2023 (15), BGS-7, PLIF	2 in BG group	0.77 mm in BG group; 2.53 mm in PEEK group	1 in BG group		25.0% in BG group; 21.4% in PEEK group		1 in PEEK group	1 unspecified "severe adverse event" in BG group
Lee *et al.*, 2020 (16), BGS-7, PLIF								
Lee *et al.*, 2016 (17), BGS-7, PLIF		0.94 mm in BG group; 1.10 mm in titanium group			7.7% in BG group; 5.9% in titanium group			
Liu *et al.*, 2025 (18), BGS-7, ACDF				1 in allograft group		1 in allograft group		1 instance of transient hoarseness in allograft group
Park *et al.*, 2023 (19), BGS-7, ACDF								
Rantakokko *et al.*, 2012 (22), S53P4, PLF								
Ryu *et al.*, 2023 (12), BGS-7, ACDF	1 in BG group	1.33 mm in BG group; 2.27 mm in allograft group	6 in allograft group					
Szadkowski *et al.*, 2022 (24), 45S5, ALIF								1 hematoma, 1 new radiculopathy
Kwon *et al.*, 2024 (20), BGS-7, ACDF				1 in BG group; 1 in PEEK group				

ACDF, anterior cervical discectomy and fusion; ALIF, anterior lumbar interbody fusion; AWGC, apatite- and wollastonite-containing glass-ceramic; BG, bioactive glass; PEEK, polyether ether ketone; PLF, posterolateral fusion; PLIF, posterior lumbar interbody fusion.

ACDF, two compared BGS-7 spacers with allograft cages (12,18), while two compared BGS-7 spacers with PEEK cages (19,20). One allograft-control study by Liu *et al.* that included comprehensive randomization and blinding strategies (low risk of bias) highlighted a non-significantly higher fusion rate in the allograft group (87.8% *vs.* 75.0%, reported as non-significant by the authors) compared to the BGS-7 group (18). Regarding adverse outcomes, there was one instance of pseudoarthrosis in the allograft group. The other allograft-control study by Ryu *et al.* was prospective in nature but examined a consecutive series of patients without randomization or blinding, which leads to a high risk of bias (12). This study reported a 100% fusion rate for the BGS-7 spacer group at an average of 7.5 years postoperatively compared to 88.5% for the allograft group (P=0.258). For adverse outcomes, in the allograft group, there were six hardware failures compared to none in the BGS-7 group, although the difference was not significant (P=0.708). However, allografts showed significantly higher subsidence compared to BGS-7 (2.27 *vs.* 1.33 mm, P=0.009) at 7.5 years postoperatively.

For the studies with PEEK cages as controls, the one by Park *et al.* was deemed to have low risk of bias due to its detailed blinding and randomization procedures and large sample size with complete patient follow-up (19), while the other by Kwon *et al.* [2024] was determined to have some concerns for bias due to a lack of true randomization (20). Park *et al.* (19) found a higher but non-significantly different fusion rate in the BGS-7 spacer group at 1 year postoperatively [81.8% *vs.* 74.4%, risk difference =7.4% (95% CI: −11.5% to 26.5%)] and reported no adverse outcomes. Kwon *et al.* (20) also found similar fusion rates (95.0% BGS-7 *vs.* 74.7% PEEK, P=0.970) and only reported one case of pseudoarthrosis in each group (P=0.970).

Use of S53P4 in posterolateral lumbar fusion (PLF)

Two studies investigated the use of S53P4 in PLF. Regarding bias, Frantzén *et al.*'s study has some concerns for bias as radiographic assessors were unblinded (21), while Rantakokko *et al.*'s study has a high risk of bias due to scant details about how fusion was determined radiographically (22). Additionally, both have small sample sizes of less than 20 with some patient dropout. Nevertheless, these studies are unique in that each patient received half S53P4 and half AG as standalone graft material, allowing patients to serve as their own controls. Frantzén *et al.* found that at 11 years postoperatively, only 80% of levels on the S53P4 side had achieved fusion compared to 100% of levels on the AG side (no P value reported) (21). For adverse events, the authors reported two instances of hardware migration, five hardware failures, and three instances of hardware loosening. The other study by Rantakokko *et al.* found a 71.4% fusion rate on the S53P4 side compared to 100% on the AG side at 10 years (no P value reported), and the authors did not report any adverse events (22). Due to the nature of having individuals serve as their own controls, comparing adverse events between groups is not possible in these studies.

Use of apatite- and wollastonite-containing glass-ceramic (AWGC) in PLF

One study by Kasai *et al.* investigated the use of AWGC in PLF (23). This study had no patient dropout when compared to the other PLF studies, but there are still some concerns for bias due to the lack of patient or investigator blinding. In this study, patients were divided into three groups and received either 1:2, 1:1, or 2:1 mixture ratio of AWGC to AG as standalone fusion grafts. At evaluation 2 years postoperatively, no group had achieved 100% fusion on X-ray, and according to the authors, each group had statistically similar fusion rates with no adverse events.

Use of Chitra-HABg in PLF

A single study by Acharya *et al.* looked at using Chitra-HABg as a standalone fusion graft in PLF. The risk of bias is of some concern in part due to the determination of fusion by a single, unblinded individual (13). This study also utilized each patient as their own control by placing either Chitra-HABg or AG on each side as a standalone graft. Notably, at 1-year follow-up, none of the patients had achieved solid bony fusion on the Chitra-HABg side, while 72.7% had fusion on the AG side (P<0.001). In fact, the authors reported that 77.3% of patients had experienced complete bone resorption on the Chitra-HABg side. The authors did not explicitly report any other adverse events, but again, the single-person control design would make it difficult to determine whether the BG alone contributed to any adverse outcomes.

Use of 45S5 in anterior lumbar interbody fusion (ALIF)

One study by Szadkowski *et al.* investigated the use of 45S5 (Glassbone®) as graft material in ALIF (24). Its

single-blinded design and use of a validated classification system for radiographic fusion result in this study having a low risk of bias. Notably, 60% of patients in this cohort received additional posterior instrumented fixation due to either having spondylolisthesis or requiring posterior decompression. As for the study design, the authors used a special cage that had two compartments separated by a midline beam, which allowed them to fill one side with 45S5 and the other with AG. At 1 year postoperatively, there was 52% fusion by total number of levels on the 45S5 side compared to 40% on the AG side (P=0.416). For adverse events, they reported one unspecified postoperative hematoma and one instance of new radiculopathy.

Discussion

Due to the known comorbidities associated with harvesting iliac crest bone graft (25-27) and the costs associated with producing cadaveric allograft (6,28), there has been a desire to find fully synthetic fusion graft materials that are easy to manufacture, cost-effective, and improve clinical outcomes. As BGs are both osteoconductive and osteoinductive, they have recently become a popular target in research on suitable graft replacements, although large design variations between studies have made it difficult to evaluate the utility of BG in spine surgery (10,11). Here, we presented an updated systematic review that included the most recent prospective clinical studies, looking at the impact of BG use on fusion rates and adverse outcomes.

We found that many of the available prospective studies on this topic have a high risk of bias due to methodological concerns, with only five out of 12 included studies being deemed to have low risk of bias. Common issues were a lack of stringent inclusion criteria, improper blinding or randomization, and small sample sizes that magnified the risk of results being biased by patient dropout. As a result, despite some studies having impressive follow-up times of 10 years or longer (21,22), their results must be interpreted with caution due to their less rigorous methodology. Additionally, due to the invasive nature of this type of research and the long follow-up times required to assess results, it is reasonable to expect a low volume of available studies with small individual sample sizes. However, given the large investment on both the part of the researcher and the patient in these studies, it is imperative that future studies are designed with rigorous methodologies that will allow us to confidently appreciate their results.

Notably, all included studies reported various patient-reported outcome (PRO) measures, although we decided not to focus on them in this review. This decision was based on the fact that a multitude of factors other than the degree of bony fusion contribute to PRO scores, such as severity of preoperative spine pathology, patient expectations (29), rates of follow-up (30), and patient satisfaction (31-33). As such, in the setting of finding a suitable fusion graft replacement, PROs seem to be less helpful in assessing graft efficacy. Additionally, we compiled the PRO data from the included studies and noted no significant differences in PROs between BG and control groups within studies (results not shown). Nonetheless, even if PROs in patients receiving BGs are noninferior to outcomes in those receiving standard grafts, switching to a material with inferior fusion capabilities would likely lead to an increased risk of long-term complications, such as hardware loosening and pseudoarthrosis.

The most recent systematic review by Cottrill *et al.* from 2020 included 12 clinical studies, with only five being prospective studies (10). In their meta-analysis, they found a mean fusion rate of 84% across all types of BGs. Although our updated systematic review contains more high-quality studies—with seven being from 2020 and later—we believed that a meta-analysis of fusion rates was unwarranted due to the large variation of BG types and methods of application (e.g., as a standalone fusion graft or as a cage material). As such, in this case, we deemed it best to present each study within its own context. Another recent systematic review on synthetic bone grafts by Salamanna *et al.* was only able to find a single prospective study on the use of BG in spinal fusion, which they believed was unsuitable for assessment due to its methodological limitations (11). Along these lines, although we were able to gather more prospective studies for our review, it does not change the fact that the limitations of individual studies should keep us cautious when trying to interpret grouped results.

It is crucial to note that within these studies, BG is used in two majorly different ways: as a bone graft substitute and as a cage material. Studies that compare BGs to AG show that using certain types of BG as standalone graft materials can vary from moderately to severely ineffective for fusion (13,21). However, one included study where AWGC was mixed with AG reported 2-year fusion rates between 81.8–83.3% (23). Comparatively, previously reported fusion rates for AG grafts in PLF at two years postoperatively range between 69% and 88% (34,35), and certain retrospective studies have reported 100% fusion at 2 years with AWGC-AG mixtures (36,37). The failure of some standalone BGs, including AWGC, may to some extent lie in their low

mechanical strengths when used alone (38). Additionally, given that osteoconductivity partly requires new bone growth through the porous spaces between BG granules, supplying existing AG in those spaces may enhance a graft's ability to solidify into a stable construct (39). Thus, more prospective studies on mixtures of BG and AG, especially AWGC-AG mixtures, as standalone fusion grafts are warranted.

In terms of comparing BGS-7 cages to PEEK, titanium, or allograft cages, all seven included studies showed similar performances between BGS-7 and other cage types in fusion rates. Notably, two studies reported significantly lower amounts of BGS-7 cage subsidence compared to PEEK and allograft cages (12,15). Given BGS-7's high mechanical strength and high elastic modulus (40), these reportedly lower subsidence rates may indicate a role for its use in artificial disc design, especially in helping anchor discs to end plates in total disc arthroplasty without the use of stems or screws (41). Additional potential roles for BGs are in spinal column reconstruction after resection due to tumor, infection, or osteoporotic fractures, with some small case series demonstrating seemingly successful use in these areas (42-44). Nevertheless, only three of the BGS-7 studies included in our review were deemed as having low bias. As such, further high-quality investigations into the use of BGS-7 cages are needed to validate the noninferiority results from these studies.

Limitations

Despite our best efforts, this systematic review has several limitations. Requiring studies to be in English, possible reviewer bias, and incomplete searching within a limited number of databases may have caused potentially helpful studies to be missed. However, screening four separate large databases in a systematic method helped minimize the number of studies that could have been overlooked. Another limitation is that within each study, there was a lack of technical details surrounding how BG was used during surgery. How the BG was applied during PLF or how it was used to fill an ALIF cage could very well affect how effectively it promotes fusion, as increased BG contact with well-decorticated bone likely leads to improved bony fusion. Perhaps the major limitation in this study is the heterogeneity of the studies included in this review, which makes it difficult to compare specific BG types within a single surgical category. In addition to the methodological limitations within individual studies, some assessed fusion using computed tomography (CT) while others used X-ray, follow-up times varied between one and 11 years, some used mixtures of BGs with AG while others used pure BGs, and some used BG cages while others used standalone BG grafts, among other differences. Although practical hurdles, such as potentially still needing AG to mix with BGs, may exist, the largest barrier to real world implementation of BGs in spine surgery is undoubtedly the significant variation in the existing clinical literature, leading to difficulty applying their results to clinical practice. Nonetheless, this diversity should help us appreciate the utility of BGs in various contexts and keep us motivated in continuing focused research into their applications in spine surgery.

Conclusions

In this study, we conducted an updated systematic review looking at prospective clinical studies on the use of BGs in spinal fusion. We found that despite multiple new studies being published since the last systematic review on this topic, there is still severe methodological heterogeneity regarding BG type, method of BG use, surgery type, and study design. Studies using standalone Chitra-HABg and S53P4 grafts showed clear inferiority to AG, while mixtures of AWGC with AG could lead to promising fusion grafts. BGS-7 cages may allow for high rates of fusion; however, they must continue to be tested against allograft, PEEK, and titanium cages. The number of adverse events associated with BG products was not significant enough to warrant independent concern over its use in spine surgery, and BGS-7 cages may actually reduce long-term subsidence. As we continue to search for cost-effective, easy to produce, and clinically effective graft substitutes in spine fusion, BGs can provide a wide range of possibilities in their various types and applications.

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Footnote

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