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Review article

The effect of bioactive glasses on spinal fusion: A cross-disciplinary systematic review and *meta*-analysis of the preclinical and clinical data

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ABSTRACT

Pseudarthrosis following spinal fusion is correlated with poorer patient outcomes and consequently is an area of continued interest within spinal research. Recently, bioactive glasses have been proposed as a means of augmenting fusion rates. Here, we present the first systematic review and *meta*-analysis of the existing preclinical and clinical literature on the effect of bioactive glasses on spinal fusion. Using the MEDLINE, Embase, and Web of Science databases, we queried all publications in the English-language literature examining the effect of bioactive glasses on spinal fusion. The primary endpoint was fusion rate at last follow-up and the secondary endpoint for clinical studies was the rate of deep wound infection. Random-effects *meta*-analyses were performed independently for the preclinical and clinical data. Twelve preclinical studies (267 animals) and 12 clinical studies (396 patients) evaluating a total of twelve unique bioactive glass formulations were included. Across clinical studies, fusion was seen in 84% treated with bioactive glass. On sub-analysis, fusion rates were similar for standalone autograft (91.6%) and bioactive glass-local autograft mixtures (89.6%). Standalone bioactive glass substrates produced inferior fusion rates relative to autograft alone (33.6% vs. 98.8%; OR 0.01, $p < 0.02$). Rates of deep wound infection did not differ between the bioactive glass and autograft groups (3.1%). The preclinical data similarly showed comparable rates of fusion between autograft and bioactive glass-treated animals. The available data suggest that bioactive glass-autograft mixtures confer similar rates of spinal fusion relative to standalone autograft without altering the risk of deep wound infection.

1. Introduction

Annually, some 400,000 Americans undergo spinal fusion procedures for degenerative conditions characterized by neck pain, back pain, radiculopathy, and/or myelopathy [1]. These procedures account for the highest aggregate hospital cost of any inpatient procedure, estimated at $13 billion annually [2]. Previous studies have suggested that post-operative symptomatic improvement correlates with radiological fusion, defined by continuous bony union across the fusion site [3–5]. For this reason, great emphasis has been placed on identifying interventions and technologies to reduce rates of pseudarthrosis, or non-union [6–8]. Despite this, nonunion continues to occur in nontrivial portions of the surgical population, with rates reported to exceed 80% in some small series [9–13]. One ongoing field of investigation targeted at improving these outcomes revolves around the creation of novel bone graft substitute materials [14,15]. Of the products falling within this category, one set showing promise in preliminary studies is bioactive glasses [16,17].

Bioactive glasses date to the late 1960s and were born out of the U.S. Army's desire for a material capable of repairing musculoskeletal battlefield injuries incurred by servicemen serving in Vietnam [18]. Though the first biomaterial was chemically prepared by the close of the decade [12,19,20], it was not until 1985 that the first commercially viable system became available, with the FDA approval of 45S5 Bioglass® (University of Florida, Gainesville, FL). Since that time bioactive glasses have been used to repair bone and dental defects in >1.5 million patients [20,21].

At their core, bioactive glasses are comprised of a silicon dioxide (the principal component of glass) and calcium oxide base, with other oxide species and ion dopants [22]. The exact makeup of these species [22,23], along with the surface chemistry and

Abbreviations: OR, odds ratio; QUOROM, Quality of Reporting of *Meta*-analyses; 95% CI, 95% confidence interval.

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topography of the glass structure [24,25], define the bioactive glass's properties, including: 1) osteoinduction and osteoconduction [24,26,27], 2) angiogenesis [28,29], and 3) antimicrobial activity [30,31] (Table 1 and Fig. 1) [22,32]. Additionally, recent evidence suggests that bioactive glasses may also promote a pro-regenerative immune response [33].

Though bioactive glasses have been used clinically in spinal fusion surgery for over 30 years [34], they are a somewhat underappreciated technology among practicing surgeons, as the available literature is dispersed over numerous small preclinical and clinical trials. Our goal with the present work is therefore twofold. First, we seek to provide a systematic review of this available literature, and second, we aim to provide a *meta*-analysis of the reported fusion rates as a means of evaluating the degree to which bioactive glasses can mediate higher arthrodesis rates in patient undergoing spinal fusion.

2. Material & methods

2.1. Electronic literature search

Using a query designed to obtain all of the available in vivo data (preclinical and clinical) examining the effect of bioactive glasses on spinal fusion, we systematically reviewed the available English language literature indexed in the PubMed/MEDLINE, Embase, and Web of Science databases. As an example, our query for the PubMed database was as follows: (“bioactive” OR “glass” OR “bioglass” OR “wollastonite” OR “Vitoss” OR “Actifuse” OR “Fibergraft” OR “Unigraft” OR “NovaBone” OR “BioSphere” OR “GlassBone” OR “PerioGlas” OR “Cerabone” OR “Signafuse” OR “S53P4” OR “CSPB*” OR “CS10B” OR “P20B80” OR “P10B90” OR “P5B95” OR “45S5”) AND (“spinal fusion” OR “spine fusion*” OR “spinal arthrodes*” OR “cervical fusion*” OR “lumbar fusion*” OR “lumbosacral fusion*” OR “interbody fusion*” OR “posterolateral fusion*” OR “cervical arthrodes*” OR “lumbar arthrodes*” OR “lumbosacral arthrodes*” OR “interbody arthrodes*” OR “posterolateral arthrodes*”). This query was stylistically modified for use in the Embase and Web of Science databases. We also queried the bibliographies of the included studies for additional sources.

Included studies comprised peer-reviewed preclinical or clinical publications with full English-language text availability that evaluated the effect of one or more bioactive glasses on spinal fusion. Bioactive glass was defined as any biomaterial comprising silicon dioxide, calcium oxide, and one or more other oxide species and/or ion dopants [22]. Studies were excluded if they examined a surgical model other than spinal fusion, did not present original data, or did not provide data on arthrodesis. Eligible studies were screened against these criteria by two reviewers (E.C. and N.L.); a third reviewer (Z.P.) served as a referee, resolving any discrepancies between the first two reviewers. The quality of each included clinical study was assessed using Critical Appraisal Checklists obtained from the Joanna Briggs Institute at The University of Adelaide [35]. A similar appraisal was not performed for the preclinical studies, as all are classified as level of evidence V. In addition, the QUOROM (Quality of Reporting of *Meta*-analyses) checklist was used for this systematic review and *meta*-analysis [36].

2.2. Data extraction

Full texts of included studies were reviewed to extract details regarding bioactive glass composition, surgical technique, treatments employed in the experimental (i.e., bioactive glass) and control groups (if available), means of evaluating spinal fusion, and fusion rate at last follow-up. For the preclinical studies, we also recorded the surgical model and animal species employed, and for the clinical studies, we included details on the patient demographics and surgical approach. In both the preclinical and clinical studies, the primary outcome was fusion rate at last follow-up for each treatment group. For the clinical studies, we also recorded the rate of deep wound infection for all groups as a means of evaluating the relative antibacterial properties of bioactive glasses. Surgical site infections not described as superficial were defined as deep wound infections.

2.3. Statistical analysis

Separate *meta*-analyses were performed for the preclinical and clinical literature using R version 3.4.2 (The R Foundation for Statistical Computing, Vienna, Austria). Mean fusion rates were calculated in stepwise fashion using the Freeman-Tukey double arcsine transformation, an established method for normalizing proportions with variance stabilization [37], and an inverse-variance random-effects *meta*-analysis [38]. Sub-analyses of the preclinical and clinical fusion rates were additionally performed for each type of bioactive glass. When single proportions were encountered, 95% confidence intervals (95% CI) were estimated using exact binomial limits [39]. Additionally, for clinical studies, odds of achieving fusion with bioactive glasses were compared to autograft-alone in aggregate and in subgroups. Comparison of infection rates in the autograft (control) and bioactive glass groups was similarly performed. Where appropriate, an alpha of 0.05 was used as the definition of statistical significance.

3. Results

Our search identified 367 unique articles, of which 39 underwent full-text review and 24 studies were included in the final review (Fig. 2). Of the 15 excluded studies, the reasons for exclu-

Table 1
Summary of the primary biological effects of bioactive glasses in the repair or regeneration of bony defects.

Primary Biological Effect	Mechanism of Action & Supporting Evidence
Formation of bone [24,26,27]	Contact with body fluids initiates rapid glass surface dissolution and formation of a hydrated silicon-rich layer on the glass surface. Extracellular calcium and phosphate ions then precipitate onto the glass surface, forming a hydroxyl carbonate apatite layer. Extracellular proteins adsorb to this layer, attracting macrophages, mesenchymal stem cells, and osteoprogenitor cells, which proliferate and differentiate into bone matrix-producing osteoblasts. Normal bone remodeling then occurs.
Formation of vasculature [28,29]	Dissolution of glass ions stimulates: 1) production of angiogenic growth factors (e.g., VEGF, bFGF, eNOS, PDGF, EGF, IGF-1, HIF-1α); 2) endothelial cell homing, migration, and proliferation; and 3) endothelial tubule formation. The addition of ionic dopants into the glass (e.g., cobalt and magnesium) may enhance the angiogenic effect.
Antibacterial properties [30,31]	Leaching of glass ions increases the local osmotic pressure and pH, making the surrounding environment inhospitable to many microbes. Additionally, bioactive glasses have been shown to directly reduce microbial biofilm production. The addition of antimicrobial ionic dopants into the glass (e.g., silver and copper) may enhance the antibacterial effects.

Key: bFGF – basic fibroblast growth factor; EGF – epidermal growth factor; eNOS – endothelial nitric oxide synthase; HIF-1α – hypoxia-inducible factor 1α; IGF-1 – insulin-like growth factor 1; VEGF – vascular endothelial growth factor.

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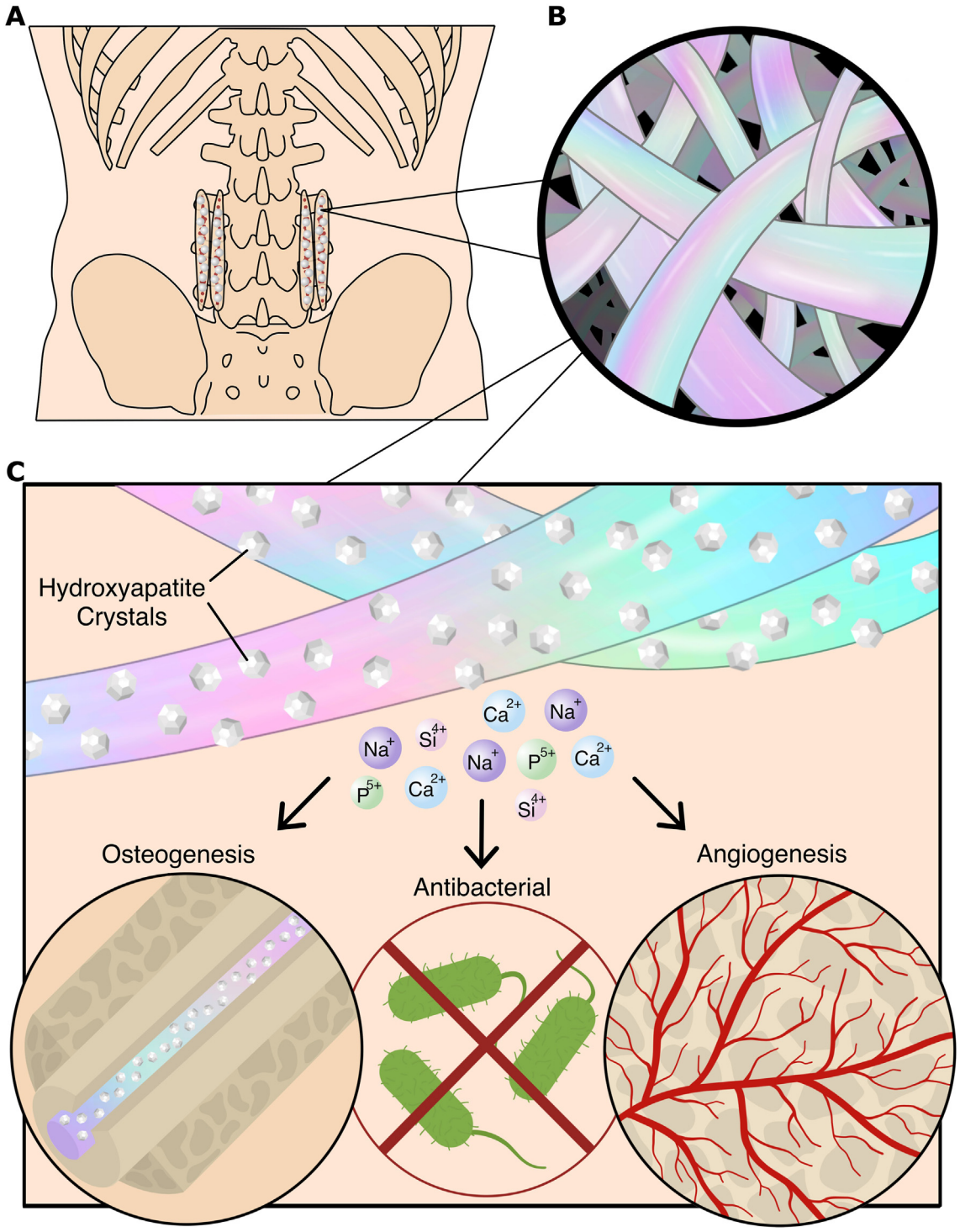

Fig. 1. Conceptual illustration of the effect of bioactive glasses on spinal fusion. **A**: Posterolateral L3-5 inter-transverse process spinal fusion using autologous bone graft mixed with bioactive glass particles. **B**: Magnified representation of bioactive glass fibers. **C**: Primary mechanisms of action of bioactive glasses on spinal fusion – including bone formation, antibacterial activity, and vascular formation – mediated by the release of ions from the bioactive glass into the surrounding environment as well as the surface chemistry and topography of the glass structure (see Table 1).

sion were: full English-language text unavailability (n = 9) and irrelevant endpoint (n = 6). The 24 included studies included 12 preclinical (267 animals) [40–51] and 12 clinical (396 patients) studies [16,17,34,52–60]. Based upon Critical Appraisal Checklists (Supplemental Material), all clinical studies were deemed to be of sufficient quality for inclusion in the *meta*-analysis. Descriptive summaries of the included preclinical and clinical studies are provided in Tables 2 and 3, respectively.

3.1. Effect of bioactive glasses on spinal fusion

3.1.1. Preclinical data

Species employed in the preclinical studies were rat (n = 1), rabbit (n = 10), and sheep (n = 1) (Table 2). All surgical models involved one- or two-level fusions of the lumbar spine, with 10 using posterior/posterolateral fusion and 2 using interbody fusion. A total of ten unique bioactive glasses were investigated (Table 2).

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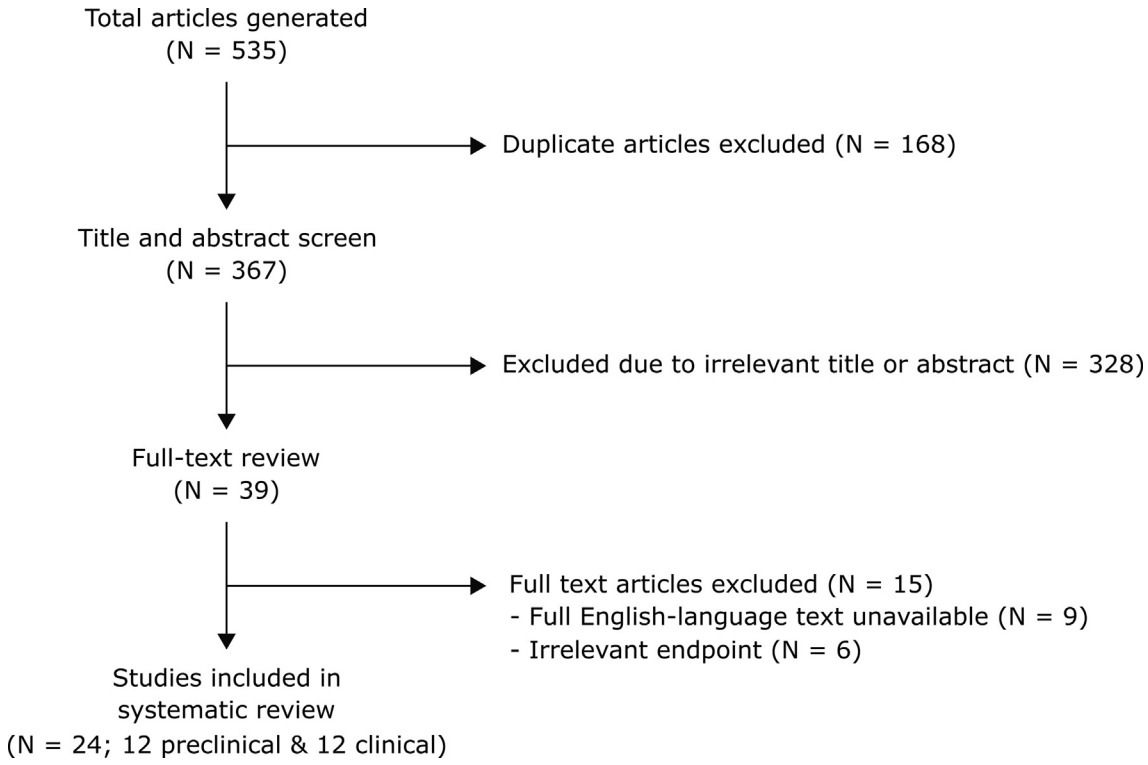

Fig. 2. Diagram of the consolidated standards of reporting trials for article selection.

Eleven of the twelve preclinical studies reported fusion rates for animals treated with bioactive glass, with a mean fusion rate of 58% (95% CI 38–76%; I^2 = 84.2%; range 0–100%, Fig. 3). Six of the studies compared bioactive glass-containing bone grafts to autograft [41,43,44,47,49,51]. Among these six, mean fusion rate for animals treated with bioactive glass was 46.9% (95% CI 17.1–78.0%; I^2 = 91.1%) compared to 72.3% (95% CI 46.7–91.8%; I^2 = 71.1%) for animals treated with autograft alone. This difference was not statistically significant (OR 0.41 [95% CI 0.08–2.05], p > 0.05).

3.1.2. Clinical data

Of the 12 clinical studies, one included pediatric patients only, nine included adult patients only, and two reported results from a mixed pediatric-adult cohort. Surgeries comprised a combination of single- and multi-level procedures following posterior, posterolateral and/or interbody techniques (Table 3). With the exception of Barrey et al., who evaluated cervical and lumbar fusion procedures [54], all studies investigated bioactive glasses in thoracolumbar spine surgeries. A total of five unique bioactive glasses were investigated (Table 3).

Across all studies, the mean fusion rate for patients treated with bioactive glass bone grafts was 84% (95% CI 68–95%; I^2 = 90.6%; range 4–100%; Fig. 3). Within the seven studies directly comparing bioactive glass to autograft [16,17,52,53,55,58,60], mean fusion rate was 75.3% for patients treated with bioactive glasses (95% CI 45.9–95.6%; I^2 = 94%) and 94.2% for patients treated with autograft-alone (95% CI 89.4–97.7%; I^2 = 20.9%). As with the animal literature, these differences were not statistically significant (OR 0.29 [95% CI 0.05–1.79], p > 0.05).

3.2. Effect by type of bioactive glass

Sub-analyses using random-effects modeling were performed for each of the 12 unique bioactive glasses, with mean fusion rates provided in Table 4. Interestingly, preclinical and clinical data were found only for three types of bioactive glass: S53P4, AW-GC, and 45S5. Among the preclinical studies, the fusion rate ranged from 0% (95% CI 0–28.5%) for P10B90 to 90.9% (95% CI 58.7–99.8%) for CSPB3. In the clinical studies, the fusion rate ranged from 4.5% (95% CI 0–22.8%) for Chitra-HABg to 94.6% (95% CI 86.2–99.2%) for AW-GC. Successful fusion was seen in 93.9% (95% CI 88.1–97.9%) of cases for the archetypal 45S5 formulation.

3.3. Subgroup meta-analysis of the clinical data

The included literature reported use of bioactive glasses both as a standalone substrate and as part of a bone graft-bioactive glass composites. Consequently, we preformed sub-analyses of fusion rate by bioactive glass usage and fusion technique for the seven clinical studies that directly compared bioactive glass-containing bone grafts to autograft by type of usage (Table 5). Across all studies, successful fusion was achieved in 89.6% of cases (95% CI 76.6–97.7%) when bioactive glass was mixed with local autograft, compared to 91.6% of patients (95% CI 86.0–95.9%) fused with autograft alone. This difference was not statistically significant (OR 1.11 [95% CI 0.38–3.26]; p > 0.05). By comparison, when bioactive glass was used as a standalone substrate, inferior fusion rates were seen relative to autograft alone (33.6% vs. 98.8%; OR 0.01 [95% CI 0.01–0.24]; p < 0.02).

With regard to the secondary endpoint, deep wound infection rates were reported in eight of the 12 clinical studies [16,17,53–56,59,60]. Deep wound infections were seen in 3.1% of patients treated with bioactive glass (95% CI 1.1–5.9%; I^2 = 0%). Five of these 8 studies reported infection rates for both bioactive glass and autograft groups [16,17,53,55,60]; wound infections were seen in 3.1% of patients treated with bioactive glass (95% CI 0.7–7.3%; I^2 = 0%) and 3.1% (0.6–7.4%; I^2 = 0%) of those treated with autograft alone. This difference was not statistically significant (OR: 0.81 [95% CI 0.15–4.40]; p > 0.05).

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Table 2
Descriptive summaries of the identified preclinical studies (n = 12).

Author, Year, (LOE)*	Animal (n); Surgical Model	Study Groups (n)†	Definition of Fusion Outcome	Fusion Rate (n fused/n total)
Lindfors et al., 2000 (V)	Rabbit (n = 8); one or two one-level thoracic posterior (spinous process and facet joint) fusion with either (a) bioactive glass, (b) bioactive glass/iliac crest autograft mixture (70/30 by volume), or (c) iliac crest autograft	A. S53P4 bioactive glass (630–800 μm) (n = 4) B. S53P4 bioactive glass (630–800 μm)/ iliac crest autograft mixture (70/30 by volume) (n = 4) C. Iliac crest autograft (n = 4)	N/A	Fusion rate was not reported; however, by 12 weeks, no significant difference in bone formation between the three groups was observable.
Lindfors et al., 2002 (V)	Rabbit (n = 12); two one-level thoracolumbar posterior (spinous process and facet joint) fusion with either (a) bioactive glass, (b) bioactive glass/iliac crest autograft mixture (70/30 by volume), or (c) iliac crest autograft	A. S53P4 bioactive glass (630–800 μm) (n = 4) B. S53P4 (630–800 μm)/iliac crest autograft mixture (70/30 by volume) (n = 4) C. Iliac crest autograft (n = 4)	Computed tomographic (CT) evidence of bony union, defined as a continuous fusion mass consolidated to both vertebrae at 12 weeks post-operatively	A. 75% (3/4) B. 75% (3/4) C. 50% (2/4)
Lee et al., 2005 (V)	Rabbit (n = 41); L5–6 posterolateral inter-transverse process fusion with (a) porous bioactive glass, prepared via the polymer sponge method, or (b) iliac crest autograft	A. CSPB2 bioactive glass (n = 11) B. CSPB3 bioactive glass (n = 11) C. AW-GC bioactive glass (Cerabone®) (n = 10) D. Iliac crest autograft (n = 9)	Fusion via manual palpation at 12 weeks post-operatively	A. 81.1% (9/11) B. 90.9% (10/11) C. 80% (8/10) D. 100% (9/9)
Takahata et al., 2005 (V)	Sheep (n = 4); L2-L3 and L4-L5 anterior lumbar interbody fusion using either a smooth or porous surface AW-GC bioactive glass ceramic interbody device and a one-rod anterior spinal instrumentation system (Kaneda-Smooth Rod)	A. Smooth surface AW-GC bioactive glass ceramic interbody device (n = 4) B. Porous surface AW-GC bioactive glass ceramic interbody device (n = 4)	Radiographic evidence of fusion, defined as continuous bridging bone formation between the vertebral bodies, at 52 weeks post-operatively	A. 100% (4/4) B. 100% (4/4)
Lee et al., 2006 (V)	Rabbit (n = 24); L5–6 posterolateral inter-transverse process fusion with (a) bioactive glass, (b) hydroxyapatite, or (c) tricalcium phosphate	A. CS10B bioactive glass (3–4 μm) (n = 8) B. Hydroxyapatite (n = 8) C. Tricalcium phosphate (n = 8)	Absence of motion by manual palpation at 12 weeks post-operatively	A. 62.5% (5/8) B. 75% (6/8) C. 37.5% (3/8)
Lee et al., 2014 (V)	Rabbit (n = 43); L5–6 posterolateral inter-transverse process fusion with bioactive glass or iliac crest autograft	A. P20B80 bioactive glass (n = 17) B. P10B90 bioactive glass (n = 11) C. P5B95 bioactive glass (n = 7) D. Iliac crest autograft (n = 8)	Immobility to twisting, bending, and folding motions by manual palpation at 12 weeks post-operatively	A. 29.4% (5/17) B. 0% (0/11) C. 14.3% (1/7) D. 100% (8/8)
Smucker et al., 2015 (V)	Rabbit (n = 45); L5–6 posterolateral inter-transverse process fusion with (a) Vitoss BA, (b) Actifuse ABX, (c) SiCaP-30, or (d) iliac crest autograft	A. Vitoss BA (beta-tricalcium phosphate, bovine Type I collagen, and 45S5 bioactive glass [20% by weight; 32–150 μm]) (n = 11) B. Actifuse ABX (porous silicon-substituted hydroxyapatite [portion of the phosphate groups, PO4, are replaced with silicate, SiO4]; 0.8 wt% Si) (n = 12) C. SiCaP-30 (porous silicon-substituted hydroxyapatite [portion of the phosphate groups, PO4, are replaced with silicate, SiO4]; 0.8 wt% Si) (n = 11) D. Iliac crest autograft (n = 11)	Absence of motion via manual palpation at 12 weeks post-operatively	A. 0% (0/11) B. 33% (4/12) C. 82% (9/11) D. 45% (5/11)
Fredericks et al., 2016 (V)	Rabbit (n = 20); L5–6 posterolateral inter-transverse process fusion with (a) Signafuse Bioactive Bone Graft Putty or (b) Actifuse ABX	A. Signafuse Bioactive Bone Graft Putty (biphasic calcium phosphate [60% hydroxyapatite and 40% beta-tricalcium phosphate; 1–2 mm granules] and 45S5 bioactive glass [212–420 μm] suspended in a resorbable alkylene oxide polymer matrix) (n = 10) B. Actifuse ABX (porous silicon-substituted hydroxyapatite [portion of the phosphate groups, PO4, are replaced with silicate, SiO4]; 0.8 wt% Si) (n = 10)	Absence of motion via manual palpation at 12 weeks post-operatively	A. 50% (5/10) B. 50% (5/10)

(*continued on next page*)

Table 2 (*continued*)

Author, Year, (LOE)*	Animal (n); Surgical Model	Study Groups (n)†	Definition of Fusion Outcome	Fusion Rate (n fused/n total)
Shiels et al., 2017 (V)	Rabbit (n = 6); L5–6 posterolateral inter-transverse process fusion with an injected polymer (ester urethane)/composite bone graft comprising rhBMP-2 and (a) bioactive glass or (b) Mastergraft Mini Granules	A. Polyester urethane composite bone graft comprising rhBMP-2 and 45S5 bioactive glass (n = 3)	Absence of motion via manual palpation at 8 weeks post-operatively	A. 100% (3/3)
		B. Polyester urethane composite bone graft comprising rhBMP-2 and Mastergraft Mini Granules (85% beta-tricalcium phosphate and 15% hydroxyapatite) (n = 3)		B. 100% (3/3)
Pugely et al., 2017 (V)	Rabbit (n = 26); L5–6 posterolateral inter-transverse process fusion with either (a) iliac crest autograft, bone marrow aspirate, and Bi-Ostetic; (b) iliac crest autograft, bone marrow aspirate, and Formagraft; or (c) iliac crest autograft alone	A. Bi-Ostetic (bovine Type I collagen, biphasic calcium phosphate [60% hydroxyapatite and 40% beta-tricalcium phosphate], and 45S5 bioactive glass granules) mixed with iliac crest autograft and bone marrow aspirate (n = 9)	Absence of motion via manual palpation at 12 weeks post-operatively	A. 56% (5/9)
		B. Formagraft (bovine Type I collagen and biphasic calcium phosphate [60% hydroxyapatite and 40% beta-tricalcium phosphate]) mixed with iliac crest autograft and bone marrow aspirate (n = 9)		B. 56% (5/9)
		C. Iliac crest autograft alone (n = 8)		C. 50% (4/8)
Khoshakhlagh et al., 2017 (V)	Rat (n = 8); L4–L5 posterolateral inter-transverse process fusion with an injected bioactive glass (BG)/chitosan composite bone graft	Composite bone graft comprising chitosan and BG bioactive glass — A. 50% BG bioactive glass, by weight (n = 4)	Absence of motion via manual palpation at 8 weeks post-operatively	A. 75% (3/4)
		B. 70% BG bioactive glass, by weight (n = 4)		B. 100% (4/4)
Ke et al., 2018 (V)	Rabbit (n = 30); L5–L6 interbody fusion with a 3-D printed bioceramic cage or iliac crest autograft	3-D printed cage comprising akermanite ($Ca_2MgSi_2O_7$) and 45S5 bioactive glass — A. 0% 45S5 bioactive glass (n = 6)	Absence of motion via manual palpation at 12 weeks post-operatively	A. 0% (0/6)
		B. 15% 45S5 bioactive glass (n = 6)		B. 67% (4/6)
		C. 30% 45S5 bioactive glass (n = 6)		C. 67% (4/6)
		D. 3-D printed beta-tricalcium phosphate cage (n = 6)		D. 17% (1/6)
		E. Iliac crest autograft (n = 6)		E. 67% (4/6)

*Levels of evidence (LOE) classified according to guidelines of the North American Spine Society.

†Chemical formulation (weight %) of investigated bioactive glasses in preclinical studies:

1. S53P4: 53% SiO_2, 23% Na_2O, 20% CaO, 4% P_2O_5
2. CSPB2: 44.07% CaO, 40.28% SiO_2, 8.1% P_2O_5, 5.0% B_2O_3
3. CSPB3: 43.76% CaO, 43.41% SiO_2, 4.05% P_2O_5, 7.5% B_2O_3
4. AW-GC (apatite- and wollastonite-containing glass ceramic): 44.9% CaO, 34.2% SiO_2, 16.3% P_2O_5, 4.6% MgO, 0.5% CaF_2
5. CS10B: 45.7% CaO, 45.7% SiO_2, 8.6% B_2O_3
6. P20B80: 45.54% CaO, 43.40% SiO_2, 3.26% P_2O_5, 8.00% B_2O_3, 0.92% MgO, 0.10% CaF_2
7. P10B90: 43.57% CaO, 45.30% SiO_2, 1.62% P_2O_5, 9.00% B_2O_3, 0.46% MgO, 0.05% CaF_2
8. P5B95: 43.51% CaO, 45.92% SiO_2, 0.81% P_2O_5, 9.50% B_2O_3, 0.23% MgO, 0.025% CaF_2
9. BG: 64% SiO_2, 31% CaO, 5% P_2O_5
10. 45S5: 45% SiO_2, 24.5% Na_2O, 24.5% CaO, 6% P_2O_5

Table 3
Descriptive summaries of the identified clinical studies (n = 12).

Author, Year, Study Design, (LOE)*	Inclusion Criteria	Surgical Model	Study Groups† (no. of pts)	Definition of Fusion Outcome	Fusion Rate (n fused/ n total)	Deep Wound Infection Rate (pts)‡
Kaneda et al., 1992, retrospective case series (IV)	Adult patients with neurological deficit due to delayed post-traumatic vertebral body collapse after osteoporotic compression fractures of the thoracolumbar spine undergoing anterior decompression and reconstruction with Kaneda instrumentation, autologous rib strut graft, and bioactive glass	Anterior decompression and reconstruction with Kaneda instrumentation, autologous rib strut graft, and AW-GC bioactive glass vertebral prosthesis	All patients received AW-GC bioactive glass vertebral prosthesis and autologous rib strut graft (n = 20)	Radiographic evidence of fusion with osseointegration and consolidation of the AW-GC vertebral prosthesis at 24 months post-operatively	95% (19/ 20)	N/A
Ido et al., 2000, retrospective case series (IV)	Adult patients with degenerative or traumatic indications undergoing instrumented single- or multi-level posterolateral lumbar fusion, with or without posterior lumbar interbody fusion, using porous sticks of apatite- and wollastonite-containing glass ceramic (AW-GC) mixed with autologous bone graft.	Instrumented posterolateral lumbar fusion, with or without posterior lumbar interbody fusion, using porous sticks of AW-GC bioactive glass mixed with autologous bone graft.	All patients received AW-GC bioactive glass (porous stick type) mixed with local autologous bone graft (n = 6)	Plain-film radiographic evidence of "subtotal" or "total" fusion, with a change in the configuration and/or density of > 2/3 of the implanted AW-GC bioactive glass, at 24 months post-operatively.	100% (6/6)	N/A
Hashimoto et al., 2002, retrospective case series (IV)	Pediatric and adult patients with back and/or leg pain undergoing one-level posterior lumbar interbody fusion using spinal instrumentation and the Brantigan I/F cage filled with a mixture of local autograft and AW-GC bioactive glass	One-level posterior lumbar interbody fusion using spinal instrumentation (e.g., Steffee Variable Screw Placement pedicle screw system) and the Brantigan I/F cage filled with a mixture of local autograft and AW-GC bioactive glass	All patients received a Brantigan I/F cage filled with a mixture of local autograft and AW-GC bioactive glass granules (n = 25)	Radiographic evidence of fusion, defined as continuous bridging bone across the disc space, at a minimum of 24 months post-operatively	100% (25/ 25)	0% (0/25)
Kasai et al., 2003, prospective, matched, randomized (II)	Adult patients with lumbar spinal canal stenosis undergoing two-level, non-instrumented posterolateral lumbar fusion with one of three ratios of bioactive glass and local autograft	Two-level, non-instrumented posterolateral lumbar fusion	Mixture of bone graft in different ratios (local autograft to AW-GC bioactive glass) A. 2:1 (n = 12)	Radiographic evidence of fusion at 2 years post-operatively	A. 83.3% (10/ 12)	A. 0% (0/12)
			B. 1:1 (n = 12)		B. 83.3% (10/ 12)	B. 0% (0/12)
			C. 1:2 (n = 11)		C. 81.8% (9/11)	C. 0% (0/11)
Ilharreborde et al., 2008, retrospective comparative cohort (III)	Pediatric patients with progressive thoracic adolescent idiopathic scoliosis undergoing posterior spinal fusion with (a) autograft mixed with bioactive glass or (b) autograft alone	Multi-level posterior spinal fusion using segmental fixation with hybrid instrumentation (pedicle screws at lumbar levels and hooks at thoracic levels) and either (a) autograft mixed with bioactive glass or (b) autograft alone	A. 45S5 bioactive glass (Bioglass; Novabone) mixed with local autograft (n = 48)	Radiographic evidence of fusion ("mechanical failure" defined as pseudarthrosis), at a 2-year minimum follow-up	A. 98% (47/ 48)	A. 2% (1/48)
			B. Local and iliac crest autograft (n = 40)		B. 92.5% (37/ 40)	5% (2/40)
Acharya et al., 2008, prospective, matched, controlled (II)	Adult patients undergoing single- or multi-level instrumented posterolateral lumbar fusion for spondylolisthesis or degenerative indications with Chitra-HABg bioactive glass and bone marrow aspirate (left side of fusion bed) and local autologous bone (right side of fusion bed)	Single- or multi-level instrumented posterolateral lumbar fusion with Chitra-HABg bioactive glass and bone marrow aspirate (left side of fusion bed) and local autologous bone (right side of fusion bed)	A. Chitra-HABg bioactive glass (80% hydroxyapatite and 20% bioactive glass [composition unknown]) plus bone marrow aspirate on the left side of the fusion bed (n = 22)	Radiographic evidence of fusion at 12-months follow-up; independent assessment of left and right sides of fusion beds	A. 5% (1/22)	N/A
			B. Locally harvested autograft (lamina and spinous process) on the right side of the fusion bed (n = 22; same patients as above)		B. 100% (22/ 22)	
Ameri et al., 2009, retrospective	Pediatric and adult patients with adolescent idiopathic scoliosis undergoing posterior fusion using local autograft and either (a) 45S5 bioactive	Posterior fusion (Cotrel and Dubousset technique) using local autograft and either (a) 45S5 bioactive glass or (b) iliac crest autograft	A. Local autograft and 45S5 bioactive glass (NovaBone); size 90–710 μm (n = 20)	Radiographic evidence of fusion, defined as a solid fusion mass without evidence of halo around the implants, at a minimum of	A. 90% (18/ 20)	5% (1/20)

(*continued on next page*)

Table 3 (*continued*)

Author, Year, Study Design, (LOE)*	Inclusion Criteria	Surgical Model	Study Groups† (no. of pts)	Definition of Fusion Outcome	Fusion Rate (n fused/ n total)	Deep Wound Infection Rate (pts)‡
comparative cohort (IV)	glass or (b) iliac crest autograft		B. Local autograft and iliac crest autograft (n = 20)	24 months post-operatively	B. 85% (17/ 20)	0% (0/20)
Kanayama et al., 2010, retrospective case series (IV)	Adult patients with single- or multi-level osteoporotic vertebral collapse and neurological deficits undergoing anterior spinal reconstruction (Kaneda instrumentation), with or without posterior reinforcement, and anterior column support using either (a) AW-GC bioactive glass ceramic and rib strut graft, (b) cylindrical titanium cage and rib strut graft, or (c) iliac crest autograft and rib strut graft	Anterior spinal reconstruction using Kaneda anterior instrumentation for osteoporotic vertebral collapse, with or without posterior reinforcement, and anterior column support using either (a) AW-GC bioactive glass ceramic and rib strut graft, (b) cylindrical titanium cage and rib strut graft, or (c) iliac crest autograft and rib strut graft	A. Anterior column support using AW-GC bioactive glass ceramic spacer and rib strut graft (n = 18) B. Anterior column support using cylindrical titanium cage and rib strut graft (n = 12) C. Anterior column support using iliac crest autograft and rib strut graft (n = 1)	Radiographic evidence of fusion, defined as solid bone formation, at a mean of 57 months post-operatively (minimum follow-up not reported)	A. 100% (18/ 18) B. 100% (12/ 12) C. 100% (1/1)	N/A
Frantzén et al., 2011, prospective, matched, controlled (II)	Adult patients with degenerative lumbar spondylolisthesis undergoing instrumented posterolateral lumbar fusion with bioactive glass (left side of fusion bed) and autograft (right side of fusion bed)	Instrumented posterolateral lumbar fusion using bioactive glass (left side of fusion bed) and autograft (right side of fusion bed)	A. S53P4 bioactive glass (left side of fusion bed) (n = 17) B. Locally harvested autograft (lamina) and iliac crest autograft (right side of fusion bed) (n = 17; same patients as above)	Computed tomographic evidence of solid fusion at 11-years follow-up; independent assessment of left and right sides of fusion beds	A. 70.6% (12/ 17) B. 100% (17/ 17)	A. 0% (0/17) B. 0% (0/17)
Rantakokko et al., 2012, prospective, matched, controlled (II)	Adult patients with unstable thoracolumbar burst fractures undergoing instrumented posterolateral fusion with local autograft mixed with bioactive glass (left side of fusion bed) and autograft alone (right side of fusion bed)	Instrumented posterolateral lumbar fusion using local autograft mixed with bioactive glass (left side of fusion bed) and autograft alone (right side of fusion bed)	A. S53P4 bioactive glass mixed with local autograft (left side of fusion bed) (n = 10) B. Local and iliac crest autograft (right side of fusion bed) (n = 10; same patients as above)	Computed tomographic evidence of solid fusion at 10-years follow-up; independent assessment of left and right sides of fusion beds	A. 50% (5/10) B. 100% (10/ 10)	A. 0% (0/10) B. 0% (0/ 10)
Lee et al., 2016, prospective, randomized, multi-center case control study (II)	Adult patients with lumbar spinal stenosis, spondylolisthesis, or disc herniation undergoing one-level posterior lumbar interbody fusion with local autograft and either (a) bioactive glass ceramic spacer or (b) titanium cage	Posterior lumbar interbody fusion with pedicle screws and rod using local autograft bone and either (a) bioactive glass ceramic spacer or (b) titanium cage	A. BGS-7 bioactive glass ceramic interbody spacer (NovoMax) and local autograft (n = 39) B. Local autograft and titanium interbody cage filled with local autograft (n = 34)	Computed tomographic evidence of fusion at 12 months post-operatively	A. 89.7% (35/ 39) B. 91.2% (31/ 34)	A. 0% (0/10) B. 0% (0/10)
Barrey et al., 2019, retrospective case series (IV)	Adult patients with spinal degeneration, traumatic injury, and/or deformity undergoing instrumented cervical or lumbar posterior spinal fusion with bioactive glass and local autograft	Instrumented cervical or lumbar posterior spinal fusion with bioactive glass and local autograft	All patients received 45S5 bioactive glass (GlassBone) mixed with local autograft (1:1 vol ratio) (n = 29)	Computed tomographic evidence of fusion at a minimum of 12 months post-operatively	93% (27/ 29)	10% (3/29)

*Levels of evidence (LOE) classified according to guidelines of the North American Spine Society.

†Chemical formulation (weight %) of investigated bioactive glasses in clinical studies:

1. AW-GC (apatite- and wollastonite-containing glass ceramic): 44.9% CaO, 34.2% SiO_2, 16.3% P_2O_5, 4.6% MgO, 0.5% CaF_2
2. 45S5: 45% SiO_2, 24.5% Na_2O, 24.5% CaO, 6% P_2O_5
3. Chitra-HABg: composition unknown
4. S53P4: 53% SiO_2, 23% Na_2O, 20% CaO, 4% P_2O_5
5. BGS-7: 41.79% CaO, 35.82% SiO_2, 13.93% P_2O5, 5.97% MgO, 1.99% CaF_2, 0.5% B_2O_3

‡ Surgical site infections not described as superficial were defined as deep wound infections; if the infection rate was not indicated, N/A was recorded.

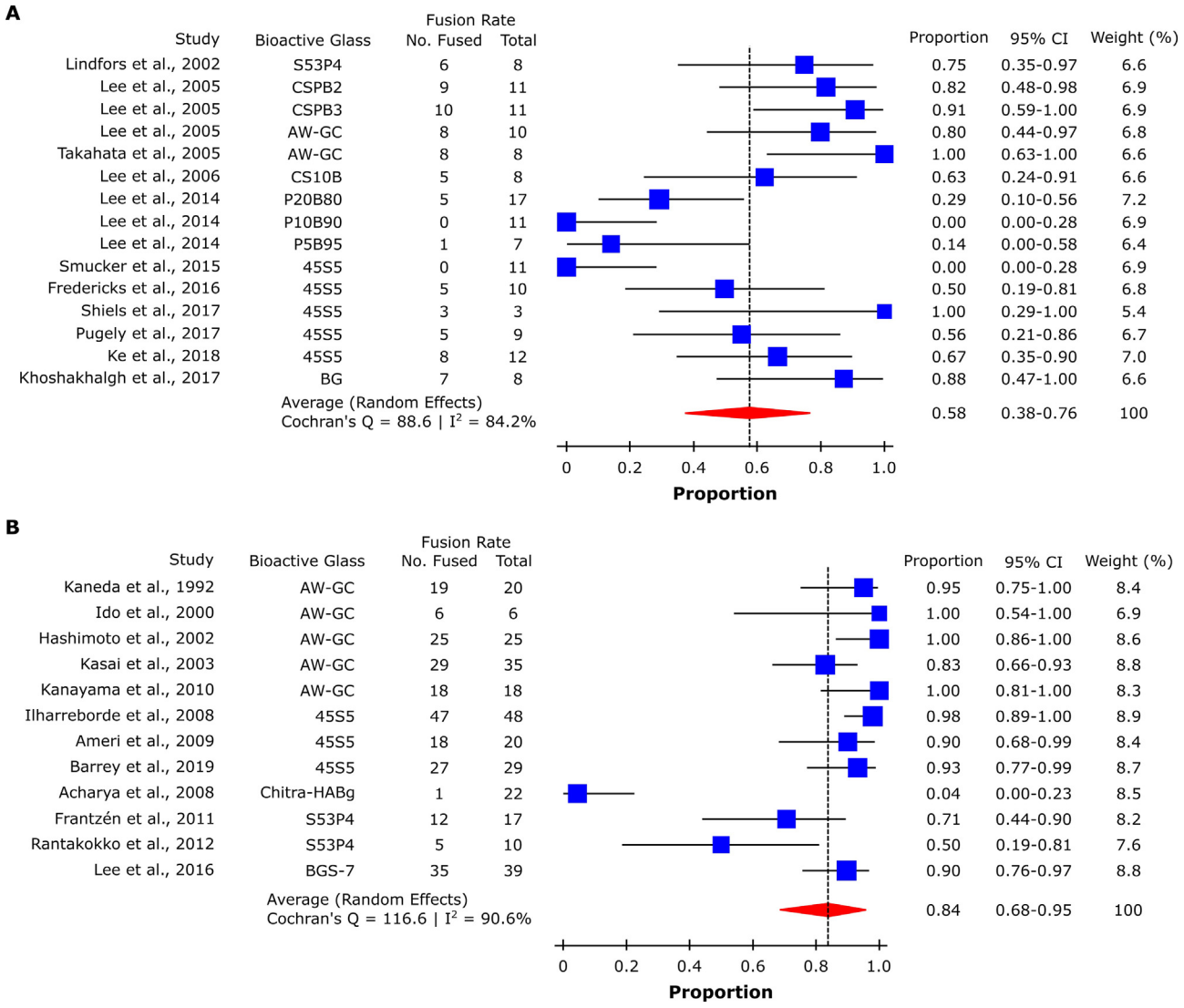

Fig. 3. Forest plots demonstrating random-effects *meta*-analyses of the fusion rates from the available **A**) pre-clinical studies (58% [95% CI 38–76%]) and **B**) clinical studies (84% [95% CI 68–95%]) evaluating the effect of bioactive glasses on spinal fusion.

4. Discussion

Some 400,000 Americans undergo spinal fusion procedures annually with cumulative costs estimated at $13 billion [1,2]. While most patients experience symptomatic improvement, 20–30% experience nonunion [61,62], which has been correlated with poorer clinical outcomes [3–5]. For this reason, there is great interest in developing surgical techniques and biomaterials capable of improving fusion rates. Here we examine one such biomaterial class – bioactive glasses – and provide the systematic review of the preclinical and clinical literature. Our analysis included 12 preclinical and 12 clinical studies evaluating 12 unique bioactive glass formulations. Mean fusion rate was 58% for the preclinical studies and 84% for the clinical studies, with high variability noted across the bioactive glass types. Analysis of those clinical studies directly comparing bioactive glass constructs with standalone autograft showed no significant difference in fusion rate. This finding remained identical on sub-analysis comparing autograft to bioactive glass-bone graft composite (91.6% vs 89.6%; $p > 0.05$); however, comparison of autograft with standalone bioactive glass showed significantly lower fusion rates in the group treated with bioactive glass alone (33.6% vs. 98.8%; OR 0.01 [95% CI 0.01–0.24]; $p < 0.02$). We saw no significant difference in deep wound infection rates between autograft and bioactive glass-treated patients (3.1% vs 3.1%; $p > 0.05$).

It is widely agreed upon that long-term stability of fusion constructs is contingent upon achieving bony fusion across the fused segments. Numerous options exist for reconstruction, including local autograft, cadaveric allograft, and bone graft substitutes. Local autograft is a preferred substrate for fusion as it eliminates the theoretical risk of rejection, has lower complication rates than iliac crest graft, and provides superior fusion outcomes relative to cadaveric allograft [63–66]. However, local autograft is often limited and may be insufficient to cover the length of the entire construct. Consequently, there has been great investment in the development of bone graft substitute materials, such as calcium phosphate-based materials and bioactive glasses. These materials carry with them the potential to extend native bone graft and may have greater usable shelf lives relative to cadaveric allograft.

It is in this role that the present data support the use of bioactive glasses. Though we find that fusion rates are inferior in constructs employing bioactive glass as a monotherapy relative to those employing native bone, constructs utilizing amalgams of bioactive glass and autograft result in similar rates of arthrodesis.

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Table 4
Mean fusion rates of bone grafts comprising bioactive glasses in preclinical and clinical studies determined by random-effects *meta*-analysis.

Type of Bioactive Glass	Authors & Year	Fusion Rate (no. fused/total)*	
		Preclinical	**Clinical**
S53P4	Lindfors et al., 2002	6/8	–
	Frantzén et al., 2011	–	12/17
	Rantakokko et al., 2012	–	5/10
	Overall (95% CI); I^2	**75% (34.9–96.8%)**	**62.1% (43.1–79.3%); 8.6%**
CSPB2	Lee et al., 2005	9/11	–
	Overall (95% CI); I^2	**81.8% (48.2–97.8%)**	**–**
CSPB3	Lee et al., 2005	10/11	–
	Overall (95% CI); I^2	**90.9% (58.7–99.8%)**	**–**
AW-GC	Lee et al., 2005	8/10	–
	Takahata et al., 2005	8/8	–
	Kaneda et al., 1992	–	19/20
	Ido et al., 2000	–	6/6
	Hashimoto et al., 2002	–	25/25
	Kasai et al., 2003	–	29/35
	Kanayama et al., 2010	–	18/18
	Overall (95% CI); I^2	**88.9% (62.6–99.9%); 52.2%**	**94.6% (86.2–99.2%); 55.5%**
CS10B	Lee et al., 2006	5/8	–
	Overall (95% CI); I^2	**62.5% (24.5–91.5%)**	**–**
P20B80	Lee et al., 2014	5/17	–
	Overall (95% CI); I^2	**29.4% (10.3–60.0%)**	**–**
P10B90	Lee et al., 2014	0/11	–
	Overall (95% CI); I^2	**0% (0–28.5%)**	**–**
P5B95	Lee et al., 2014	1/7	–
	Overall (95% CI); I^2	**14.3% (3.6–57.9%)**	**–**
45S5	Smucker et al., 2015	0/11	–
	Fredericks et al., 2016	5/10	–
	Shiels et al., 2017	3/3	–
	Pugely et al., 2017	5/9	–
	Ke et al., 2018	8/12	–
	Ilharreborde et al., 2008	–	47/48
	Ameri et al., 2009	–	18/20
	Barrey et al., 2019	–	27/29
	Overall (95% CI); I^2	**49.6% (17.4–82.0%); 83.8%**	**93.9% (88.1–97.9%); 9.15%**
BG	Khoshakhlagh et al., 2017	7/8	–
	Overall (95% CI); I^2	**87.5% (47.4–99.7%)**	**–**
Chitra-HABg	Acharya et al., 2008	–	1/22
	Overall (95% CI); I^2	–	**4.5% (0–22.8%)**
BGS-7	Lee et al., 2016	–	35/39
	Overall (95% CI); I^2	–	**89.7% (75.8–97.1%)**
All (95% CI); I^2		**57.6% (38.0–76.0%); 84.2%**	**84.0% (68.2–95.1%); 90.6%**

*For single proportions, 95% confidence intervals (95% CI) were determined via exact binomial limits.

Consequently, the evidence suggests that in cases where there is insufficient autograft to cover the complete construct, a composite of bioactive glass and native autograft may result in arthrodesis outcomes comparable to a construct fused solely with autograft. This role is further supported by consideration of the composition of bioactive glasses, which are completely devoid of the growth factors and osteoprogenitor cells that give rise to the osteoinductive properties of host bone.

In this osteoconductive role, however, we do note significant variability in the efficacy of the available bioactive glasses. As all bioactive glasses employ a core of silicon dioxide and calcium oxide, the observed variation in osteoconductive abilities likely stems from the unique properties of the glass, which are dictated by the other constituent ion dopants and surface topography. Given the relative novelty of bioactive glasses in the commercial setting, though, the exact topography and combination of dopants that produce the greatest osteoconductivity remain unknown. Investigations into this topic continue. It is possible that a better capture of the means by which these properties are created will result in novel bioactive glass formulations capable of being employed without intermixed autograft [22,67].

As with any new technology, evaluating the utility of bioactive glasses for spinal fusion is predicated upon demonstrating that they are at least equivalent to currently available alternatives, which in this case comprise other commercially available bone graft substitute materials (e.g., calcium phosphate-based, calcium sulfate-based, and demineralized bone matrices). Unfortunately, it is near-impossible for us to evaluate this endpoint at present given the absence of prior comparisons of fusion rates in constructs employing bioactive glasses or other graft substitutes. However, initial impressions can be gleaned by comparing the fusion rates seen in the present study to those documented in prior reports of fusion rates for constructs employing other commercially available bone graft substitutes. To this end, a 2014 systematic review reported a mean fusion rate in lumbar spine arthrodesis of 92.5% for beta-tricalcium phosphate (345 total patients across 7 studies), 86.7% for calcium sulfate (353 total patients across 6 studies), and 83.6% for biphasic beta-tricalcium phosphate/hydroxyapatite (152 patients across 4 studies) [68]. Similarly, a 2018 systematic review reported a mean fusion rate in lumbar spine arthrodesis across four studies of 81.2% for local autograft combined with demineralized bone matrix [15]. In both cases, the reported fusion rates are similar to the rate we saw for constructs incorporating bioactive glass (84%). Consequently, our initial impression is that the bioactive glass constructs are at the very least non-inferior to constructs employing other, commercially available graft substitutes. Future studies are needed to evaluate the cost-effectiveness of bone graft substitute materials in spinal fusion.

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Table 5
Results from random-effects *meta*-analyses of mean fusion rates and odds ratios from the available clinical data in aggregate and in subgroups.*

Variable	Authors & Year	Type of Bioactive Glass	Fusion Rate (no. fused/total)		Cochran's Q	OR (95% CI); p-value
			Bioactive Glass	Autograft		
All studies	Ilharreborde et al., 2008	45S5	47/48	37/40	17.46	0.29 (0.05–1.79); p > 0.05
	Acharya et al., 2008	Chitra-HABg	1/22	22/22		
	Ameri et al., 2009	45S5	18/20	17/20		
	Kanayama et al., 2010	AW-GC	18/18	13/13		
	Frantzén et al., 2011	S53P4	12/17	17/17		
	Rantakokko et al., 2012	S53P4	5/10	10/10		
	Lee et al., 2016	BGS-7	35/39	31/34		
	Overall (95% CI)		75.3% (45.9–95.6%)	94.2% (89.4–97.7%)		
Bioactive glass mixed with local autograft†	Ilharreborde et al., 2008	45S5	47/48	37/40	4.51	1.11 (0.38–3.26); p > 0.05
	Ameri et al., 2009	45S5	18/20	17/20		
	Kanayama et al., 2010	AW-GC	18/18	13/13		
	Rantakokko et al., 2012	S53P4	5/10	10/10		
	Lee et al., 2016	BGS-7	35/39	31/34		
	Overall (95% CI)		89.6% (76.6–97.7%)	91.6% (86.0–95.9%)		
Bioactive glass used without local autograft as a stand-alone graft substitute	Acharya et al., 2008	Chitra-HABg	1/22	22/22	1.68	**0.01 (0.01–0.24); p < 0.02**‡
	Frantzén et al., 2011	S53P4	12/17	17/17		
	Overall (95% CI)		33.6% (1.0–94.5%)	98.8% (93.1–99.8%)		
Posterior or posterolateral fusion	Ilharreborde et al., 2008	45S5	47/48	37/40	17.19	0.13 (0.01–2.06); p > 0.05
	Acharya et al., 2008	Chitra-HABg	1/22	22/22		
	Ameri et al., 2009	45S5	18/20	17/20		
	Frantzén et al., 2011	S53P4	12/17	17/17		
	Rantakokko et al., 2012	S53P4	5/10	10/10		
	Overall (95% CI)		64.6% (23.5–95.6%)	94.7% (88.2–98.7%)		
Interbody fusion	Kanayama et al., 2010	AW-GC	18/18	13/13	0.03	0.89 (0.21–3.87); p > 0.05
	Lee et al., 2016	BGS-7	35/39	31/34		
	Overall (95% CI)		94.1% (80.0–99.9%)	93.5% (82.6–99.3%)		

*Only studies reporting the fusion rates for both the experimental (i.e., bioactive glass) and control (i.e., autograft) groups were included in the *meta*-analysis of the odds ratios.
† Local autograft defined as autologous spinous process, lamina, and/or rib bone graft.
‡ Statistically significant ($p < 0.05$).

4.1. Study limitations

There are several limitations to this study. First, our clinical data *meta*-analyses rely upon heterogeneous data culled from a combination of prospective and retrospective studies of varying quality. Consequently, the present results are at best as good as the lowest quality study that was included, making the present study level IV evidence. It is therefore unknown whether the present results can be generalized to all spine patients. The limited available data similarly prevented us from analyzing bioactive glasses by particle size, architecture, or ion dopants, which could inform future materials-based research directions. Additionally, the included studies employed different methods for assessing bony fusion, which imparts heterogeneity to the results and limits our ability to compare the efficacy of bioactive glasses to other commercially available bone graft substitutes. We attempt to address this heterogeneity by describing the method and definition of fusion assessment for each included study and by using a random-effects versus fixed-effects model during our analysis. Given these limitations, though, it is apparent that additional, high-quality research is needed to more fully evaluate the efficacy – and cost-effectiveness – of bioactive glasses on spinal fusion.

5. Conclusions

Here we report the first systematic review and *meta*-analysis of the effect of bioactive glasses on spinal fusion across the preclinical and clinical literature. We found that when mixed with local autograft, bioactive glasses yield similar rates of spinal fusion compared to autograft alone, suggesting that bioactive glasses offer significant clinical value when used as an autograft extender. However, when used in isolation, bioactive glasses yield inferior fusion rates relative to autograft alone. Similar findings were observed in the animal literature, suggesting that these models are translatable

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to human populations. Additionally, as a secondary endpoint, we found that the use of bioactive glasses had no impact on the rate of deep wound infection relative to using autograft in isolation. Further high-quality research is needed to analyze the cost-effectiveness of bioactive glasses for spinal fusion.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2020.04.035.

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