Use of graft materials and biologics in spine deformity surgery: a state-of-the-art review

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Abstract

Purpose The aim of the current review is to summarize the current evidence on graft materials used in fusion procedures for spinal deformity corrections.

Methods PubMed, Embase, and Cochrane Library were searched for relevant published observational studies and clinical trials using osteobiologics and biomaterials in spinal deformity surgery.

Results The use of autograft in deformity correction surgeries has been reported in a limited number of studies, with the harvest sites including iliac crest, ribs, and local bone. Various allografts and biologics have been used in the treatment of spinal deformities including idiopathic and degenerative scoliosis, either as stand alone or in combination with autograft. Limited number of studies reported no differences in fusion rates or outcomes. Use of rh-BMP2 in anterior, posterior or front/back approaches showed higher fusion rates than other graft materials in patients with spinal deformities. Due to the limited number of quality studies included in the review, as well as alternative factors, such as costs, availability, and surgeon expertise/preference, no definitive conclusion or recommendations can be made as to the ideal graft choice in spinal deformity surgery.

Conclusions Most commonly used grafts included autograft, allograft and rh-BMP2, with new biologics and biomaterials constantly emerging in the market. Limited number of high-quality comparative studies and heterogeneity in study design prevented direct comparisons that can lead to meaningful recommendations. Further studies are needed to prove superiority of any single graft material and/or biologic that is also cost-effective and safe.

Keywords Thorcaci spine · Osteobiologics · Evidence · Deformity · Review · Outcomes

Introduction

There have been significant advancements in the field of spinal instrumentation and biologics to promote bony fusion in spinal deformity surgery [1, 2]. However, pseudarthrosis continues to be a problem and contributes to significant postoperative pain, implant failure, and increased risk of reoperation [3, 4]. Historical rate of pseudarthrosis quoted in the literature is 17% following adult deformity correction and 5–34% following fusion for degenerative conditions [4, 5]. Reasons for failure ranges from biomechanics and construct design, local biology, and patient-related comorbidities leading to poor bone quality and to compromised new bone formation [6].

Solid bony fusion requires an intricate interplay between three principles of bone graft material properties: osteogenesis, osteoinductivity, and osteoconductivity [7]. In principle, osteogenic stem cells must be stimulated to migrate to the site of fusion, while osteoinductive signals must support the cell population lineage, and a low-strain mechanical conductive environment must be maintained until fusion occurs [8]. Autograft and allograft may possess each of these properties to a varying degree and are placed within the surgical fusion bed to promote arthrodesis. Iliac crest bone graft (ICBG) has historically been used as the gold standard graft material, although risk of harvest-site morbidity and subsequent

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long-term functional impairment is significant [9]. In addition, the native levels of matrix factors in autografts may also vary greatly between individuals based on age, smoking status, and medical comorbidities. Consequently, there has been significant research interest and financial investment in designing novel graft materials and biologics that can reproduce high fusion rates without the risk of autologous bone harvest [10].

Ceramic-based substitutes including hydroxyapatite (HA) and tricalcium phosphate (TCP) have chemical similarities to bone and possess biocompatibility, osteoconductivity, and strong mechanical properties despite lacking osteogenic potential [7, 11]. Demineralized bone matrix (DBM) is a composite of collagen, noncollagenous proteins, and growth factures with increased osteoconductive and osteoinductive properties. It is also provided in many formulations, including a putty, which allows the DBM to be molded to the target lesion with greater ease of application [12–14]. Its ease of use has made it a popular option for surgeons and is commonly combined with local autograft for added osteogenic effect.

Bone-morphogenetic proteins (BMPs) represent a family of differentiation factors that promote bone formation and remodeling. In 2002, the Food and Drug Administration (FDA) approved rhBMP-2 with a collagen carrier as an iliac crest bone graft (ICBG) substitute for single level anterior lumbar interbody fusion (ALIF). Patients with rhBMP-2 had significantly better fusion rates (98% BMP vs. 76% ICBG), shorter length of surgery, decreased blood loss and shorter hospital stay [15]. Given its success in ALIFs, off-label use of rhBMP-2 has increased and is now used in approximately 25% of all fusion cases nationally including posterolateral fusions for deformity [15]. Complication rates following use of rhBMP-2 vary; however, for thoracic fusion cases, these are negligible if rhBMP-2 is used in appropriate amounts. Given the recent increase in the array of products and techniques used to enhance fusion rates, it is of paramount importance for surgeons and scientists to critically assess the efficacy, risks, and costs of these products compared to traditional autografts. As such, the aim of this review was to analyze the current literature regarding the use of biologics in thoracic/ thoracolumbar deformity surgeries.

Methods

To conduct this review, PubMed, Embase, and Cochrane Library were searched for relevant published observational studies and clinical trials using biologics and biomaterials in spine deformity surgery. To qualify for inclusion, studies had to focus on thoracic or thoracolumbar deformity patients who had deformity correction and spine fusion with a graft material. The included studies had to report on clinical or radiological outcomes, complications, or costs of the used graft material.

Search terms included "autograft", "allograft", "bone morphogenetic protein 2", "stem cells", "bone marrow aspirate", "demineralized bone matrix", "ceramics", "peptide", "synthetic bone graft", "bone substitute", OR "biosynthetic bone graft" AND "scoliosis" OR "spine deformity", AND "spine fusion", "scoliosis correction", "spinal deformity surgery". Studies were restricted to those published from 2000 to 2021 to reflect the current trends in practice. Only English articles with available full text were chosen. Identified articles were first screened by title and abstract, then full-text screening was conducted. Finally, the included studies were categorized based on the type of graft used, and each category was used for the relevant section of this review.

After title and abstract screening, the full texts of 110 articles were assessed. We found 57 articles that focused of biologics in spine deformity surgery and their outcomes, complications, or costs and were used for the main part of this review. The other 53 articles were used for the introduction and the introductory statement of each osteobiologics (Fig. 1).
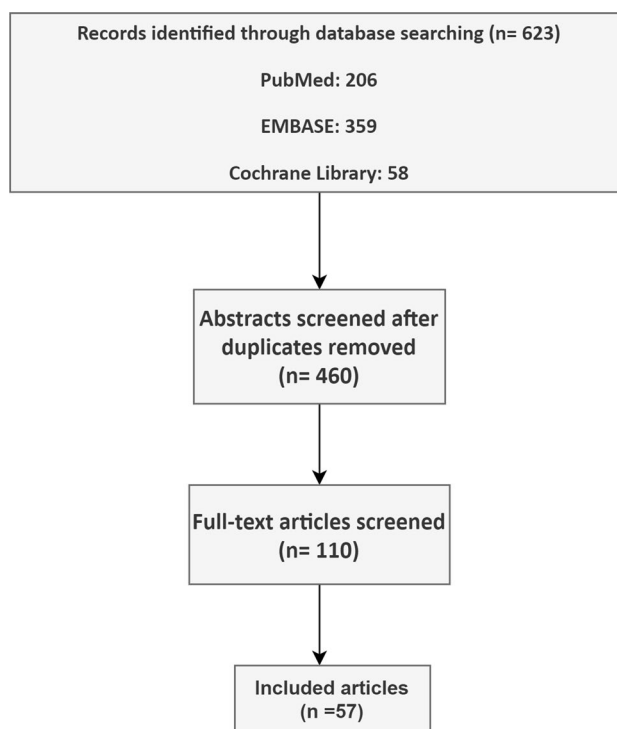


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┌─────────────────────────────────────────────┐
│ Records identified through database searching │
│                  (n= 623)                     │
│                                               │
│                PubMed: 206                    │
│                                               │
│                EMBASE: 359                    │
│                                               │
│             Cochrane Library: 58              │
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│      Abstracts screened after                 │
│      duplicates removed                       │
│          (n= 460)                             │
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│      Full-text articles screened              │
│              (n= 110)                         │
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│          Included articles                    │
│              (n =57)                          │
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Fig. 1 PRISM chart

Results

Iliac crest bone graft (ICBG) and local autografts

Autografts used in the correction of spinal deformities are harvested from the iliac crest, spinous process, transverse process, lamina, or facets (Tables 1, 2) [16–20]. Iliac crest bone graft (ICBG) is known as the gold standard for spinal fusion surgeries due to its osteogenic, osteoconductive, and osteoinductive properties [16, 21]. There are multiple methods suitable for the preparation of autogenous bone grafts for implantation, including forming struts or morselizing the bone. In comparing the use of rib strut grafts to morselized rib bone, Ouellet et al. concluded that there was no difference between the two in the maintenance of coronal or sagittal plane correction in scoliosis patients when using single solid rod instrumentation; however, there was a significant difference in pseudarthrosis rates between the two (Tables 1, 2) [22].

Fusion rates

Franzin et al. reported fusion rates of 95.4% and 100% for ICBG and local autograft, respectively, in posterior spinal fusion with pedicle screw instrumentation [17]. There were no statistically significant differences in fusion or pseudarthrosis rate, loss of correction over time, or quality of life in adolescent idiopathic scoliosis (AIS) patients who received ICBG vs. local autograft.

Iwai et al. showed radiographic evidence of complete fusion in all 10 AIS patients in their study using a fibular strut autograft (FSAG) with a rib strut graft in the space between the cut fragment and the remaining vertebral bodies, resembling a "hot dog" [25]. There was no evidence of postoperative erosion after a mean follow-up time of 9 years and 9 months. Likewise, Farshad et al. showed a 100% fusion rate across 20 patients with local autograft from the rib in anterior short fusion with pedicle screws [21]. Milinkovic et al. showed a 98% fusion rate across 188 patients with local autograft in posterior spinal fusion with dual-rod fixation [19]. Similarly, Presenti et al. showed a success rate of 97.7% with local autograft from the spinous processes in posterior spinal fusion with sublaminar bands in 44 patients [20].

Outcomes

Kager et al. have concluded that ICGB should remain the gold standard for anterior or posterior instrumented fusion as there is minimal risk for postoperative harvest site pain, especially in adolescents [24]. They reported that 10% of patients experienced postoperative pain (NRS pain score of 3/10) at the harvest site. For those with a 1-year follow-up the pain dropped to 9% of patients with NRS scores of 1–2/10. None of these patients took pain medication, nor reported any reduction in activity. Postoperative pain caused by ICBG harvest can be effectively treated as well. Samartzis et al. conducted a pilot study on the effect of levobupivacaine infusion at the ICBG site compared to a control group receiving saline [23]. They found a twofold decrease in pain at the ICBG site in the experimental group, as well as a fourfold overall physical pain decrease in a group of Southern Chinese participants.

Complications

The use of autografts eliminates the risk of viral, bacterial, or prion disease transmission or the risk of immune response, which can occur when using allograft or bone substitutes [17, 19, 20]. However, ICBG is associated with postoperative donor site pain, numbness, and fracture, as well as infection, hematoma formation, arterial injury, nerve injury, increased blood loss, and increased operative time [16, 19, 20, 23]. It also requires a separate incision in the skin, unlike alternative graft options [20].

Pseudarthrosis occurs when solid intervertebral fusion fails to take place and can cause persistent back pain, which may indicate revision surgery [20]. Franzin et al. reported 4.6% pseudarthrosis (1/41) in a study comparing thoracic spine arthrodesis of AIS patients with pedicle screws with or without ICBG [17]. There was no significant difference in pseudarthrosis between the local autograft and ICBG groups. Milinkovic et al. saw 2% (4/188) pseudarthrosis with mild back pain in a retrospective case study of AIS patients who underwent posterior fusion [19]. The pseudarthrosis rate was 30% (15/50) for a retrospective study by Ouellet et al. comparing strut autografts and morselized autografts and was significantly different between graft types ($p = 0.029$) [22]. Pseudarthrosis occurred in 2 of 18 (11.1%) patients who were given strut grafts and 13 of 32 (40.6%) who were given morselized grafts. Three of these patients required revision surgery, two for pain and one for implant failure and loss of correction. Pesenti et al. saw a rate of 2.3% (1/44) for the local autograft group and 4.5% (2/44) for the control group with no graft with no significant difference between the groups [20]. One of the two patients in the control group had a rod breakage that caused loss of correction and significant back pain, resulting in reoperation. Iwai et al. reported 10% (1/10) pseudarthrosis using a "hot dog" application of rib strut grafts during anterior fusion of AIS patients. This patient required reoperation [25].

Additional complications reported include delayed deep infection in 2% (4/188) that was resolved after implant removal in all cases (Milinkovic et al.) [19], 8%

Table 1 Summary of studies using autograft for the correction of thoracic spine deformities

References	Study design	Patient age	# Patients	Procedure type	# Levels	Graft material
Choo [16]	Prospective case study	Adolescent	40	Instrumented posterior spinal fusion	333 thoracic and 81 lumbar	Local autograft ($n = 40$)
Farshad [21]	Retrospective case study	Adolescent	20	Anterior short scoliosis correction with screws	Average of 3 per patient	Rib autograft ($n = 10$)
Franzin [17]	Retrospective case study	Adolescent	41	Posterior spinal fusion with pedicle screw instrumentation	N/A	Local autograft ($n = 19$) or ICBG ($n = 22$)
Iwai [25]	Retrospective case study	Age range 6—46 years; average age 21.6 years	10	Posterior spinal fusion with instrumentation and Anterior Spinal Fusion With FSAG[a]: "Hot Dog" Anterior Strut Grafting Procedure	N/A	Rib strut autograft ($n = 10$)
Kager [24]	Prospective case study	Adolescent	71	Anterior or posterior spinal fusion with instrumentation	N/A	ICBG ($n = 71$)
Kobayashi [18]	Retrospective case study	Adolescent	83	Posterior spinal fusion with pedicle screw instrumentation	Average of 10.0 per patient	Local autograft ($n = 83$)
Milinkovic [19]	Retrospective case study	Adolescent	188	Posterior spinal fusion with dual-rod fixation	N/A	Local autograft ($n = 188$) with or without ICBG
Ouellet [22]	Retrospective radiographic study	Adolescent	50	Anterior spinal fusion with solid-rod TSRH[b] instrumentation	N/A	Rib strut autograft ($n = 18$) or morselized rib autograft ($n = 32$)
Pesenti [20]	Prospective and retrospective case study	Adolescent	88	Posterior spinal fusion with sublaminar bands	Average of 11.9 per patient in control group and 12.5 in autograft group	Control group without graft ($n = 44$, prospective), articular or spinous processes autograft ($n = 44$, retrospective)
Samartzis [23]	Parallel, double-blinded randomized controlled trial	Adolescent	12	Posterior spinal fusion with instrumentation	Average of 12.3 per patient	ICBG ($n = 12$)

[a]*FSAG* Fibular strut autograft

[b]*TSRH* Texas Scottish Rite Hospital

Table 2 Summary of fusion rates, complications, and cost

References	Fusion rates/clinical outcomes	Complications	Cost
Farshad [21]	With autograft (74% curve improvement, 88% Cobb angle improvement) vs. without autograft (60% curve improvement, 53% Cobb angle improvement)	Not reported	Not reported
Franzin [17]	No significant differences	Pseudoarthrosis rates: local autograft (0%) vs. ICBG (4.6%); $p = 0.537$	Not reported
Iwai [25]	100% fusion, Mean curve correction rate 34.6%	Pseudoarthrosis requiring revision surgery (10%), Cerebral spinal fluid leak (20%), Megableeding of more than 4000 mL during the operation (20%)	Not reported
Kager [24]	Not reported	Spine pain 10%	Not reported
Kobayashi [18]	Mean curve correction rate 75.3%	Not reported	Cost of scoliosis surgery $15,130
Milinkovic [19]	Mean thoracic curve was 47.6 ± 12.53 pre-operatively and 18.6 ± 10.2 at last follow-up; Mean lumbar curve was 43.2 ± 15.3 pre-operatively and 14.6 ± 7.2 at last follow-up (students T test $p > 0.005$)	Pseudarthrosis (2%), Caudad hook dislodged during the follow-up period (2%), delayed deep infection (2%)	Not reported
Ouellet [22]	Scoliosis averaged 53.5° (range 37–82°) pre-operatively, mean curve correction to 15° (range − 3 to 35°) immediately after surgery, and 21°(range − 3 to 46°) at last follow-up	Pseudarthrosis rates: rib strut (4%) vs. morselized (26%); $p = 0.029$ Implant failure (10%) Revision surgery (6%)	Not reported
Pesenti [20]	No significant differences	Pseudarthrosis rates: autograft (2.3%) vs. no graft (4.5%); $p = 0.56$	Not reported
Samartzis [23]	Not reported	Wound dehiscence (8%)	Not reported

(1/12) wound dehiscence (Samartzis et al.) [23], 20% (2/10) cerebral spinal fluid leakage, and 20% (2/10) extensive blood loss of more than 4000 mL during the operation (Iwai et al.) [25].

Cost

Autografts, including ICBG, are less costly than allografts or bone substitutes, because the graft comes from the patient themselves. Presenti et al. stated that bone substitutes account for 6% of the total cost of fusion surgery when employed [20]. However, one must consider that increased operative time for harvest also adds expense [24]. Kobayashi et al. analyzed the costs of autografting in Japan, which increased from $734 to $1,862 per person during the span of 2008 to 2017 [18]. The overall cost of scoliosis correction surgery has gone up in the same time period by about 1.6 times (from $9515 to $15,130), despite the slight national decrease in costs over time. Decreased costs include hospital fees per day and the substantial decrease in reimbursement prices for surgical instruments, which are a result of cost control policies by the Japanese government.

Allograft

Allograft is another commonly used biological material that has shown success in thoracic deformity procedures (Tables 3, 4). While autologous ICBG is typically considered the gold standard graft material in spine surgery, allograft has the benefit of avoiding donor site morbidity. In addition, particularly in the frail and/or pediatric population, harvesting a sufficient amount of ICBG for grafting can be challenging, and thus use of allograft can mitigate this issue [26]. Studies have shown that allograft can achieve high rates of fusion and minimal loss of curve, both alone and in combination with autograft [27–29], with minimal or no complications [26]. In addition, comparative studies have demonstrated that allograft produces clinical outcomes equal to [29–31] or better [27, 28] than autograft, providing evidence for its efficacy as a suitable alternative graft material.

Fusion/correction rates

A study by Johari et al. used irradiated femoral head and tibial slice allograft in pediatric patients with various forms of scoliosis, and 100% of patients showed union at the grafting site. No patients demonstrated evidence of infection,

Table 3 Summary of studies using allograft for the correction of thoracic spine deformities

References	Study design	Patient age	# Patients	Procedure type	# Levels	Graft material
Betz [35]	Randomized control trial	Adolescent	76	Posterior spinal fusion	N/A	Allograft ($n = 37$)
Bozzio [41]	Retrospective cohort	Adolescent	42	Spinal fusion	4–12	Allograft (n not reported)
Buttermann [39]	Retrospective cohort	Adult	105	Spinal fusion	4–6	Allograft ($n = 68$) vs. autograft ($n = 37$)
Izatt [29]	Retrospective cohort	Adolescent	43	Thoracoscopic anterior spinal fusion	N/A	Allograft ($n = 29$) vs. autograft ($n = 14$)
Johari [26]	Case series	Adolescent	30	Various spinal deformity procedures	N/A	Allograft ($n = 30$) vs. allograft + rib autograft (used among subset of allograft pts, n not reported)
Jones [27]	Retrospective cohort	Adolescent	55	Spinal fusion	N/A	Freeze-dried cancellous allograft ($n = 55$)
Knapp [36]	Retrospective cohort	Adolescent	111	Spinal fusion	N/A	Allograft ($n = 111$)
Lowe [31]	Non-randomized control trial	Adolescent	41	Anterior spinal fusion	3–8	Cortical allograft dowel (n not reported) vs. autograft ($n = 20$)
Price [37]	Retrospective cohort	Adolescent	88	Posterior spinal fusion	7–14	Autologous ICBG ($n = 17$) vs freeze-dried corticocancellous allograft ($n = 28$) vs composite graft of autologous bone-marrow and DBM ($n = 43$)
Sinagra [34]	Retrospective cohort	Adolescent	78	Posterior spinal fusion with instrumentation	N/A	Allograft ($n = 30$) vs. allograft + local autograft ($n = 48$)
Smith [40]	Prospective case series	Adult	287	Various spinal deformity procedures	8–17	Allograft, iliac crest autograft, locally harvested autograft, DBM, and/or BMP-2 (n not reported)
Theologis [30]	Retrospective cohort	Adolescent	461	Posterior spinal fusion	4–16	Iliac crest autograft ($n = 152$) vs. allograft ($n = 110$) vs. bone substitute** ($n = 110$)
Wang [38]	Retrospective cohort	Adolescent	123	Posterior spinal fusion	N/A	Local autograft, iliac crest allograft, allograft, and/or biological bone material (n not reported)
Watkins [28]	Retrospective cohort	Adolescent	34	Anterior instrumented spinal fusion	N/A	Structural graft (such as femoral ring allograft or Syncage Moss Miami cage) ($n = 16$) vs. morselized rib autograft ($n = 18$)
Weinzapfel [33]	Retrospective cohort	Adolescent	40	Anterior thorascopic spinal fusion	10.5–18.0	Allograft ($n = 12$) vs. Grafton™ DBM Flex*** ($n = 28$)

DBM demineralized bone matrix

**Bone substitutes included DBM (DePuy Synthes), tricalcium phosphate (Depuy Synthes), coralline hydroxyapatite (Medtronic), and Cellect (DePuy Synthes—Selective Cell Retention technology with a combination of bone-marrow aspirate with matrix)

***A commercially sold flexible DBM

pseudarthrosis, fracture, or any other complication (Table 4) [26]. Another study in children under 18 with idiopathic scoliosis demonstrated a radiographic fusion rate of 92.7%, with the mean number of fused levels being 12.4 [27].

A study on thoracoscopic anterior scoliosis correction in pediatric patients (mean age 14.9 years) did not report a significant difference ($p = 0.96$) in Sucato fusion scores involving T5–L1 between allograft (fusion score = 2.22) vs. autograft groups (fusion score = 2.15) [29]. Similarly, Theologis et al. reported nearly equivocal fusion rates among allograft vs. autograft vs. bone substitute patients

Table 4 Summary of fusion rates, complications, and cost

References	Fusion rates/clinical outcomes	Complications	Cost
Betz [35]	Not reported	Pseudoarthrosis rate: 2.7% (1/37)	Not reported
Bozzio [41]	Not reported	Not reported	$1495 of bone graft/patient
Buttermann [39]	Not reported	Posterior mixture of allograft and autograft (27%) Anterior strut allograft with posterior mixture of morselized allograft and autograft (25%) Anterior autograft (0%) Posterior allograft (0%)	Not reported
Izatt [29]	Allograft vs. autograft: $p = 0.96$	Not reported	Not reported
Johari [26]	Allograft: 100%	Not reported	Not reported
Jones [27]	Allograft: 92.7%	Not reported	Not reported
Knapp [36]	Not reported	Pseudoarthrosis rate: 2.7% (3/111)	$415–$830/patient
Lowe [31]	Autograft vs. autograft + allograft: $p > 0.05$	None	Not reported
Price [37]	Not reported	Pseudoarthrosis rates: allograft (4%) vs. autograft (6.25%) Allograft failure rate: 28% Autograft failure rate: 12.5%	Not reported
Sinagra [34]	10 g vs. 15 g allograft: $p = 0.3258$	PJK: allograft vs. autograft + allograft; $p = 0.6910$	$4650 AUD (~ $3505 USD)/30–50 g of irradiated allograft
Smith [40]	Not reported	No significant differences ($p > 0.05$)	Not reported
Theologis [30]	ICBG vs. allograft vs. bone substitute: $p = 0.87$	No significant differences ($p = 0.30$)	Not reported
Wang [38]	Not reported	PJK: allogenic bone v. autograft: 0.04 OR	Not reported
Watkins [28]	Cobb angle correction %: autograft (75%) vs. autograft w/allograft (67%); $p = 0.023$ Sagittal alignment kyphosis: autograft (14 degrees) vs. Autograft w/allograft (3 degrees); $p = 0.035$	Not reported	Not reported
Weinzapfel [33]	No significant differences ($p = 0.088$)	None	Not reported

PJK proximal junctional kyphosis

in treatment of adolescent idiopathic scoliosis (mean age 14.7) [30]. All three groups had a mean of 11.3–11.4 levels of fusion. A study by Weinzapfel et al. on thoracoscopic release for idiopathic scoliosis in teens compared anterior vertebral levels fused and curve correction between an allograft cohort vs. patients treated with a flexible demineralized bone matrix sheet (Grafton Flex DBM) [33]. At most recent follow-up, 60/73 (82%) levels in the allograft group and 100/109 (92%) levels in the DBM group were fused; this difference was not statistically significant ($p = 0.088$). Sinagra et al. investigated whether the volume of allograft per level fused or the addition of autograft to the volume of allograft impacted fusion rates in T1–T11 in idiopathic adolescent scoliosis (average age of patients was 16 years) [34]. Groups were given either 10 g or 15 g of allograft per level fused. They reported that neither the increased amount of allograft used nor the addition of autograft significantly improved rates of fusion ($p = 0.3258$). The average number of levels fused was 11 in all groups.

Complications

Efforts have been made to elucidate which biologic is responsible for the least postoperative morbidity or complications. A study by Betz et al. demonstrated that use of solely allograft for augmentation in the treatment of idiopathic scoliosis (mean age 14.5) resulted in pseudarthrosis in 1 of 37 (2.7%, Table 4) [35]. Another study again reported a pseudarthrosis rate of 3/111 in patients aged 12–14 for correction of idiopathic adolescent scoliosis (2.7%, Table 4) [36]. Pseudarthrosis rates have been also found to be lower in allograft patients (1/25; 4%) in comparison with autograft (1/16; 6.25%) [37].

In regards to risk of postoperative proximal junctional kyphosis in association with pseudarthrosis, one study found that the use of allogenic bone in adolescents (average age 15) has been reported to put patients at significantly lower odds (OR = 0.04) of developing proximal junctional kyphosis in comparison with patients receiving autograft bone ($p = 0.001$) [38]. However, another study in adolescents demonstrated no difference in risk of developing proximal

junctional kyphosis in an allograft group compared with an allograft plus autograft supplement group ($p = 0.6910$) [34].

Lowe et al. that used a cortical allograft dowel to supplement autograft in T9–L4 resulted in no neurologic injuries, infections or reoperations [31]. A study comparing various autograft/allograft combinations in levels T10–L4 showed that use of posterior allograft had significantly fewer major medical complications (0%) in comparison with the posterior mixture of allograft and autograft (27%) ($p = 0.01$) and anterior strut allograft with posterior mixture of morselized allograft and autograft (25%) ($p = 0.04$) groups. However, the anterior autograft group had significantly lower complications (0%) in comparison with the mixed autograft/allograft groups (posterior mixture of morselized allograft and autograft: 25%, the posterior mixture of allograft and autograft: 27%) ($p < 0.05$) [39]. Nonetheless, this study ultimately determined that complication rates overall were not statistically significant based on type of bone graft used, but rather on surgical approach, with combined anteroposterior approaches carrying a greater likelihood of complication than isolated posterior or anterior approaches. Another study that reported that in posterior spinal fusions for idiopathic adolescent scoliosis, the allograft group had more than double the failure rate (28% vs. 12.5%) than the autograft group, which was defined by a loss of correction. The authors noted their use of strict criteria for failure, however, and postulated that if failure had instead been defined by need for repeat spinal instrumentation as a result of pseudarthrosis, the failure rate would have been higher in the autograft group (6.25%) than in the allograft group (4.0%) [37].

Cost

Cost can be a potentially limiting factor to the use of allograft. One study performed in a nonprofit community hospital reported an average cost of $1495 worth of bone graft per patient who underwent correction for AIS, which reportedly comprised 3.3% of the total hospital cost [41]. Another study conducted in a single tertiary center in Western Australia reported a cost of $4,650 AUD (~ $3505 USD) per 30–50 g of irradiated allograft. This study used 10–15 g of allograft per patient [34]. However, a multicenter retrospective study reported a much lower per-patient allograft cost range of $415–$830 (Table 4) [36].

Bone morphogenetic protein-2 (BMP-2)

The Food and Drug Administration (FDA) approved the use of recombinant human BMP-2 (rhBMP-2) for single-level anterior lumbar interbody fusion (ALIF) in 2002 as an alternative to iliac crest bone graft (ICBG) [42]. Since then, rhBMP-2 use has expanded as an off-label application

to include several spinal procedures, including deformity (Tables 5, 6) [43].

In spine deformity correction surgery, it is challenging to provide a sufficient amount of autologous bone to satisfy the required long fusion, making the need to use a bone graft substitute, such as rhBMP-2, of paramount importance. The use of rhBMP-2 eliminates the morbidity related to harvesting bone autografts from the iliac crest, or ribs [44]. Ruofeng et al. reported steadily increasing use of rhBMP-2 for posterior long segment fusion from 2005 to 2011, with the exception of a dramatic drop in 2010 [45].

Fusion rates

Luhman et al. used rhBMP-2 to achieve anterior or posterior fusion in 70 patients with adult spine deformity (ASD). With a minimum follow-up of 1 year, the reported fusion rates were 93% in the posterior and 96% in the anterior group, and 100% in posterior compassionate-use patients [44].

Mulconrey et al. reported fusion rates of 91%, 97%, and 100% for anterior (10 mg/level), posterior (20 mg/level), and high-dose (40 mg/level) posterior compassionate-use fusions, respectively [46].

Maeda et al. reported a higher rate of solid fusion in the BMP group (22/23 patients; 95.7%) than the ICBG group (23/32 patients; 71.9%) [47]. Similarly, Kim et al. reported a higher fusion rate with BMP compared to ICBG, 93.5% vs. 71.9%, respectively [48].

Outcomes

Maeda et al. reported that the BMP group had a slightly better but statistically non-significant correction rate than the ICBG group (50.6% vs. 42.5%) [47]. Kim et al. reported that the BMP group had higher Scoliosis Research Society scores within pain, function, self-image, and domains [48]. Puvanesarajah et al. reported that elderly patients with ≥ 8 fused levels were significantly less likely to require revision surgery when BMP was used [49]. Safaee et al. reported an 11% absolute risk reduction of revision for pseudarthrosis when BMP was used [50].

Complications

Bess et al. evaluated the acute perioperative complications with or without rhBMP-2 use, with a mean follow-up of 34 months [43]. The rhBMP-2 group had a longer operative time, greater number of osteotomies per patient. Overall, rhBMP-2 patients had a significantly greater number of complications per patient (1.4 vs. 0.6). However, multivariate analysis found no significant correlation between rhBMP-2 use and neurological, wound, or superficial and deep infection complications.

Table 5 Summary of studies using recombinant human Bone Morphogenetic Protein 2 (rhBMP-2) or synthetics for the correction of thoracic spine deformities

References	Study design	Patient age	# Patients	Procedure type	# Levels	Graft material
rh-BMP2						
Luhmann [44]	Prospective study	Adult	70	Anterior and posterior fusions	Group 1 = 2.3 Group 2 = 2.9 Group 3 = 6.5	rhBMP-2 Group 1: anterior [10.8 mg/level] (*n* = 46) Group 2: posterior [13.7 mg/level] (*n* = 41) Group 3: posterior compassionate use [28.6 mg/level] (*n* = 8)
Mulconrey [46]	Prospective study	Adult	98	Anterior and posterior fusions	3.15	rhBMP-2 Group 1 [10 mg/level] (*n* = 47) Group 2 [20 mg/level] (*n* = 43) Group 3 [40 mg/level] (*n* = 8)
Maeda [47]	Prospective comparative study	Adult	55	Anterior and posterior fusions	BMP group: anterior = 3.6, posterior = 11.3 ICBG group: anterior = 6.5, posterior = 11.3	rhBMP-2 [10.0 mg/level (posteriorly), 11.7 mg/level (anteriorly)] (*n* = 23) vs. ICBG (*n* = 32)
Kim [48]	Prospective comparative study	Adult	63	Anterior and posterior fusion	BMP: 2.6 ICBG: 6.5	rhBMP-2 (*n* = 31) [11.1 mg/level (posteriorly), 30.9 mg/level (anteriorly)] vs. ICBG (*n* = 32)
Bess [43]	Prospective multi-center study	Adult	279	Anterior or posterior fusion	12	rhBMP-2 [2.5 mg/level (posterior fusion), 5 mg/level (interbody fusion)] (*n* = 172) vs. ICBG, local bone, and allograft (*n* = 107)
Puvanesarajah [49]	Retrospective comparative study	Elderly	9837	Posterolateral fusion	–	≥ 8 Levels: rhBMP-2 (*n* = 1143) vs. No-rhBMP-2 (*n* = 1111) 3–7 Levels: rhBMP-2 (*n* = 2813) vs. No-rhBMP-2 (*n* = 4770)
Safaee [50]	Retrospective study	Adult	151	Anterior and posterior fusion	10	rhBMP-2 (*n* = 98) vs. No-rhBMP-2 (*n* = 53)
Jain [51]	Economic modeling of data from a multicenter prospective registry	Adult	367	Posterior/posterolateral fusion and/or interbody fusion	≥ 5 levels	rhBMP-2 [2.5 mg/level] (*n* = 267) vs. No-rhBMP-2 (*n* = 100)
Synthetics						
Ameri [53]	Retrospective comparative study	Adolescent	40	Posterior spinal fusion	Bioactive glass = 10.2 ICBG = 9.5	Bioactive glass (*n* = 20) vs. ICBG (*n* = 20)
Harshavardhana [55]	Prospective study	Adolescent	35	Posterior spinal fusion	9.4	SiCaP mixed with locally harvested bone

Table 5 (continued)

References	Study design	Patient age	# Patients	Procedure type	# Levels	Graft material
Mashoof [56]	Prospective study	Adolescent	27	Posterior spinal fusion	–	Coralline hydroxyapatite ceramic mixed with ICBG (70/30 ratio)
Muschik [57]	Prospective comparative study	Adolescent	28	Posterolateral fusion	12	β-TCP + autograft ($n = 9$) vs. Allograft + autograft ($n = 19$)
Ploumis	Prospective study	Adult	28	Posterolateral instrumented fusion	Hydroxyapatite collagen sponge/bone-marrow aspirate = 2.3 ± 0.7 Allograft = 2.1 ± 0.7	Hydroxyapatite collagen sponge/bone-marrow aspirate ($n = 12$) vs. Allograft ($n = 16$)
Delécrin [58]	Prospective randomized study	Age range 13–25	58	Posterior spinal fusion	-	Calcium phosphate ceramic and local graft ($n = 28$) vs. ICBG and local graft ($n = 30$)
Ilharreborde [59]	Prospective comparative study	Adolescent	88	Posterior spinal fusion	Bioglass group = 11.8 ± 2 Autograft group = 12.1 ± 1.8	Bioactive glass ($n = 48$) vs. ICBG ($n = 40$)
Lerner [60]	Prospective randomized pilot study	Adolescent	40	Posterior fusion	β-TCP = 9.9 ICBG = 9.2	β-TCP ($n = 20$) vs. ICBG ($n = 20$)
Lerner [61]	Prospective study	Adolescent	21	Posterior fusion	10	Si–CaP enriched with BMA

Luhman et al. reported a low complication rate (3/70 patients), including superficial wound dehiscence ($n = 1$), deep wound infection ($n = 1$) and wound hematoma ($n = 1$) [44]. Mulconrey et al. reported a low pseudarthrosis of 5% and only one case of subfascial hematoma [46].

Costs

In a recent cost analysis multicenter study, Jain et al. reported that the mean total cost of index surgery was significantly higher in ASD surgery with rhBMP-2 use ($60,000 ± $17,000) than without rhBMP-2 ($41,000 ± $8900) and that the mean direct cost of using rhBMP-2 in ASD surgery was $14,000 ± $6400 [51]. Similarly, Puvanesarajah et al. and Safaee et al. reported that rhBMP-2 use led to a significant increase in primary surgery costs and hospital charges [49, 50].

Synthetics

Bioceramics are biodegradable synthetic calcium-based bone graft substitutes usually used in combination with autogenous bone or bone-marrow aspirate (BMA) [52]. The available ceramics usually contain substances with varying porosity, including β-tricalcium phosphate (β-TCP), hydroxyapatite (HA), calcium phosphate, or calcium sulfate [52]. Glass ceramics are bioactive due to their composition of SiO_2, CaO, Na_2O, and P_2O_5, which attract osteoblasts and osteoprogenitor cells and stimulate bone formation and integration [53]. Silicated calcium phosphate (Si–CaP) mimics the trabecular architecture of natural cancellous bone. By enhancing vascularity in the host bone, the silicate substitute significantly improves bone formation [54, 55].

Fusion rates

With a mean follow-up period of 34.7 months, Ameri et al. reported a 90% solid fusion rate using metal-derived bioactive glass in adolescent idiopathic scoliosis (AIS) surgery and 85% solid fusion rate using ICBG (Tables 5, 6) [53]. With a mean follow-up period of 2.94 years, Harshavardhana et al. reported a 100% fusion rate by 3 months postoperatively using Si–CaP ceramic mixed with locally harvested bone graft in AIS surgery [55]. Mashoof et al. reported 100% fusion rate using coralline hydroxyapatite ceramic mixed with ICBG [56]. Muschik et al. reported a 100% fusion rate using β-TCP mixed with autograft [57].

Outcomes

Delécrin et al. compared synthetic calcium phosphate ceramic graft and ICBG and reported lower blood loss in the

Table 6 Summary of fusion rates, complications, and cost

References	Fusion rates/clinical outcomes	Complications	Costs
rh-BMP2			
Luhmann [44]	93% fusion rate in posterior fusion; 96% fusion rate in anterior fusion; 100% fusion rate in posterior compassionate-use patients	Low complication rate (3/70 patients); superficial wound dehiscence (n = 1), deep wound infection (n = 1) and wound hematoma (n = 1)	Not reported
Mulconrey [46]	91% fusion rate in anterior fusion; 97% fusion rate in posterior fusion; 100% fusion rate in high-dose posterior compassionate-use fusions	5% pseudarthrosis one case of subfascial hematoma	Not reported
Maeda [47]	95.7% fusion rate and 50.6% correction rate in BMP group; 71.9% fusion rate and 42.5% correction rate in ICBG group	Not reported	Not reported
Kim [48]	93.5% fusion rate in BMP group; 71.9% fusion rate in ICBG group; Higher Scoliosis Research Society scores within pain, function, self-image, and domains in BMP group	Not reported	Not reported
Bess [43]	Not reported	Longer operative time, greater number of osteotomies with rhBMP-2; No significant correlation between rhBMP-2 use and neurological, wound, or superficial, and deep infection	Not reported
Puvanesarajah [49]	Elderly patients with ≥ 8 fused levels are less likely to require revision surgery with BMP use	Not reported	Significant increase in primary surgery costs and hospital charges with rhBMP-2 use
Safaee [50]	11% absolute risk reduction of revision for pseudarthrosis with BMP use	Not reported	Significant increase in primary surgery costs and hospital charges with rhBMP-2 use
Jain [51]	Not reported	Not reported	Mean total cost of index surgery was significantly higher in ASD surgery with rhBMP-2 use mean direct cost of using rhBMP-2 in ASD surgery was $14,000 ± $6400
Synthetics			
Ameri [53]	90% solid fusion rate using metal-derived bioactive glass; 85% solid fusion rate using ICBG	Not reported	Not reported
Harshavardhana [55]	100% fusion rate using Si–CaP ceramic mixed with locally harvested bone graft	2/35 patients had revision surgery for deep infection (n = 1) and implant failure (n = 1)	Not reported
Mashoof [56]	100% fusion rate using coralline hydroxyapatite ceramic mixed with ICBG	Superficial infection (n = 1), deep infection requiring debridement and hardware removal (n = 1), and proximal hook dislodge (n = 1)	Not reported
Muschik [57]	100% fusion rate using β-TCP mixed with autograft	Deep infection (n = 1)	Not reported
Ploumis	91.6% fusion rate using hydroxyapatite collagen sponge/bone-marrow aspirate; 93.7% fusion rate using allograft	DVT (n = 1), superficial wound infection (n = 1)	Not reported

Table 6 (continued)

References	Fusion rates/clinical outcomes	Complications	Costs
Delécrin [58]	Lower blood loss in the ceramic group. Both groups achieved a satisfactory maintained degree of deformity correction	Superior grips dislodgement and revision surgery (n = 1), delayed-onset localized inflammatory reactions with prominent implants and revisions (n = 1) In the ceramic group	Not reported
Ilharreborde [59]	Significantly higher mean gain of frontal balance and lower rate of loss of correction of the main thoracic curve with bioactive glass compared to ICBG	Infection (2%), mechanical failure requiring revision (2%) in the bioglass group	Not reported
Lerner [60]	Lower degree of loss of curve correction in the β-TCP group compared to the ICBG group	Not reported	Not reported
Lerner [61]	Improved health-related quality of life and a 93% rate of patients' management satisfaction with Si–CaP enriched with BMA	Not reported	Not reported

ceramic group [58]. Successful integration of the ceramic blocks into the fusion mass was achieved within 12 months and both groups achieved a satisfactory maintained degree of deformity correction. Ilharreborde et al. reported that the use of bioactive glass compared to ICBG was associated with a significantly higher mean gain of frontal balance, 8.1 vs. 0.8 mm, as well as a significantly lower rate of loss of correction of the main thoracic curve, 11% vs. 15.5% [59]. Lerner et al. reported a lower degree of loss of curve correction in the β-TCP group compared to the ICBG group, 2.6 and 4.2, respectively [60]. Using Si–CaP enriched with BMA, Lerner et al. reported a significantly improved health-related quality of life and a 93% rate of patients' management satisfaction [61].

Complications

Harshavardhana et al. reported that two out of 35 patients had revision surgery for deep infection (n = 1) and implant failure (n = 1) [55]. In the ceramic group, Delécrin et al. reported one patient with superior grips dislodgement and had revision surgery [58]. Two other patients developed delayed-onset localized inflammatory reactions with prominent implants and had revisions. Ilharreborde et al. reported infection (2%), and mechanical failure requiring revision (2%) in the bioglass group [59]. The complications reported in Mashoof et al. study included superficial infection (n = 1), deep infection requiring debridement and implant removal (n = 1), and proximal hook dislodge (n = 1) [56]. Muschik et al. reported one case of deep infection [57].

Some studies report minimal differences in complication rates between various types of biologics and alternative graft materials. In a study by Smith (2014) on treatment of adjacent segment disease in older patients (mean age 54.8), they demonstrated no significant difference (p > 0.05) in the risk of rod fracture among adult spinal deformity patients with allograft vs. autograft vs. demineralized bone matrix vs. rhBMP-2 [40]. Another study reported no significant differences between curve type, number of levels fused, postoperative infections, pseudarthrosis, reoperations, or Scoliosis Research Scoiety-30 scores across each of the types of grafts used (allograft, autogenous iliac bone crest graft, or bone substitute) in the treatment of adolescent idiopathic scoliosis. Bone substitutes included DBM (DePuy Synthes), tricalcium phosphate (Depuy Synthes), coralline hydroxyapatite (Medtronic), and Cellect (DePuy Synthes—Selective Cell Retention technology with a combination of bone-marrow aspirate with matrix [30]. Moreover, a study with similar demographics comparing allograft and a strip of flexible demineralized bone matrix (Grafton DBM Flex) reported no pseudarthrosis, anterior overgrowth, or implant failure in either of the two groups [33].

To our knowledge, there are no randomized controlled studies comparing the efficacy of biologics to autograft alone in preventing pseudarthrosis following deformity correction surgery. Lower quality comparative studies has its flaws as difference in fusion technique and deformity correction principles add on to time-dependent biases when cohorts of different eras are compared.

Nanotechnology and osteobiologics

Nanotechnology has been used in various biomedical applications, and the newer addition of nanotechnology to synthetics can have promising results in enhancing spine fusion. Nanoparticles are particles with a size between 10 and 1000 nm [62].

Scaffold materials for rBMP2 have reduced affinity for it, leading to widespread release causing complications of hematomas and seromas, as well as exaggerated inflammatory responses [63]. The use of bioactive peptide amphiphile nanofiber scaffolds was reported by Lee et al. as an effective method for localized controlled delivery of rBMP2 to the site of fusion [64]. Moreover, the mineral structure of nanophase hydroxyapatite is nearly identical to bone with enhanced osteoblastic adhesion [65].

Bioactive glass nanofibres have a higher mesenchymal stem cell activity compared to conventional bioactive glass [66]. Further high-quality comparative studies are needed to better elucidate the clinical efficacy of these newer graft material.

Conclusions

Although there are several published studies looking at the use of individual graft material and biologics for spinal deformity surgery, there is a significant paucity of randomized comparative studies due to several limitations. The gold standard efficacy of ICBG and local autografts are so well established that subsequent materials such as allografts, bone matrixes, ceramics, biologics, and bio-materials have been compared to historical data rather than direct randomized comparisons. In addition, variability among surgeon technique/expertise and the lack of standardization of graft materials used for each case invites substantial outcome variable and makes direct comparison difficult. With increasing FDA approval for newer graft materials and more industry sponsored data emerging constantly, it is important for surgeons to understand these limitations and the quality of the data when deciphering the literature on graft materials. Based on all these issues, and the lack of consistent and comparable data, we are unable to consistently recommend any one specific biological material over another for the purpose of achieving reliable fusion for spinal deformity cases.

Future high-quality comparative studies and/or continued collaborative registry data are needed to objectively compare outcomes.

Declarations

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