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Techniques for cervical interbody grafting

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Object. The objective of this systematic review was to use evidence-based medicine to determine the efficacy of interbody graft techniques.

Methods. The National Library of Medicine and Cochrane Database were queried using MeSH headings and keywords relevant to cervical interbody grafting. Abstracts were reviewed and studies that met the inclusion criteria were selected. The guidelines group assembled an evidentiary table summarizing the quality of evidence (Classes I–III). Disagreements regarding the level of evidence were resolved through an expert consensus conference. The group formulated recommendations that contained the degree of strength based on the Scottish Intercollegiate Guidelines network. Validation was done through peer review by the Joint Guidelines Committee of the American Association of Neurological Surgerons/Congress of Neurological Surgeons.

Results. Autograft bone harvested from the iliac crest, allograft bone from either cadaveric iliac crest or fibula, or titanium cages and rectangular fusion devices, with or without the use of autologous graft or substitute, have been successful in creating arthrodesis after 1- or 2-level anterior cervical discectomy with fusion (Class II). Alternatives to autograft, allograft, or titanium cages include polyetheretherketone cages and carbon fiber cages (Class III). Polyetheretherketone cages have been used successfully with or without hydroxyapatite for anterior cervical discectomy with fusion. Importantly, recombinant human bone morphogenic protein-2 carries a complication rate of up to 23–27% (especially local edema) compared with 3% for a standard approach.

Conclusions. Current evidence does not support the routine use of interbody grafting for cervical arthrodesis. Multiple strategies for interbody grafting have been successful with Class II evidence supporting the use of autograft, allograft, and titanium cages. *(DOI: 10.3171/2009.2.SPINE08723)*

Key Words • athrodesis • cervical spine • fusion • practice guidelines • treatment outcome

Recommendations

Indications: 1- or 2-Level Cervical Discectomy. Autograft bone harvested from iliac crest, allograft bone from either cadaveric iliac crest or fibula, or titanium cages and rectangular fusion devices, with or without autologous graft or substitute, are recommended for use in creating an arthrodesis after 1- or 2-level ACDF (quality of evidence, Class II; strength of recommendation, C).

Technique: Autograft, Allograft, or Titanium Cage. Autograft bone harvested from the iliac crest, allograft bone from either cadaveric iliac crest or fibula, or titanium cages and rectangular fusion devices, with or without autologous graft or substitute, are recommended for creating an arthrodesis after 1- or 2-level ACDF (quality of evidence, Class II; strength of recommendation, C).

Technique: PEEK Cages, CFCs, PMMA, rhBMP-2.

Abbreviations used in this paper: ACDF = anterior cervical discectomy with fusion; CFC = carbon fiber cage; mJOA = modified Japanese Orthopaedic Association; NDI = neck disability index; PEEK = polyetheretherketone; PMMA = polymethyl-methylmethacrylate; rhBMP-2 = recombinant human bone morphogenic protein-2; VAS = visual analog scale.

If alternatives to autograft, allograft, or titanium cages are preferred, several options are recommended including PEEK cages, CFCs, PMMA, and rhBMP-2. Polyetheretherketone cages may be considered with or without the use of hydroxyapatite for ACDF. Using hydroxyapatite alone may result in more settling and fragmentation (quality of evidence, Class III; strength of recommendation, D). Carbon fiber cages are recommended for arthrodesis after ACDF with fusion rates > 50% (quality of evidence, Class III; strength of recommendation, D).

The use of PMMA is not recommended as a means to preserve interspace height after anterior discectomy. Although short-term results are similar to those obtained with bone grafts, fusion generally does not occur when PMMA is used as a spacer, and the long-term consequences have not been described (quality of evidence, Class II; strength of recommendation, B).

Although rhBMP-2 promotes fusion with rates equivalent to autograft, its use in the cervical spine carries a complication rate of up to 23–27% (especially for local edema) compared with 3% for a standard approach. This significant difference prompted a public health notification by the Food and Drug Administration (http://www.fda.gov/cdrh/safety/070108-rhbmp.html). Current evidence does not support the routine use of rhBMP-2 for cervical arthrodesis. However, the use of rhBMP-2 may have utility in the context of future studies in patients in whom cervical fusion poses a great technical challenge (quality of evidence, Class II; strength of recommendation, C).

Rationale

The purpose of this chapter is to undertake an evidence-based review of studies that have examined cervical interbody grafting. The use of fixation is discussed in Techniques for Anterior Cervical Decompression for Radiculopathy and Cervical Surgical Techniques for the Treatment of Cervical Spondylotic Myelopathy, both of which appear in this month's issue of the *Journal of Neurosurgery: Spine*. Successful arthrodesis of the cervical spine following procedures intended to promote fusion requires the development of bone bridging the space between vertebral bodies. This process is usually the result of the introduction of grafting material between the levels to be fused and develops over a period of time. Traditionally the graft material has been harvested autologous bone (autograft). Limitations of autograft include limited availability and complications at the harvest site. Allograft bone has been tried in a variety of applications, but also has potential limitations including cost, availability, infectious risks, and potentially lower fusion rates. Bone graft expanders, bone substitutes, and implantable devices have also been investigated in an attempt to address some of these concerns and maintain similar fusion rates.

Search Criteria

We searched the National Library of Medicine (Pubmed) and the Cochrane Database for the period from 1966 through 2007 using the MeSH subject headings of cervical and fusion (4231 references) and cervical and arthrodesis (2347 references). After combining the databases and eliminating duplicates, 5237 articles remained. We reviewed the titles and abstracts with attention to those titles addressing issues pertinent to obtaining fusion in the cervical spine. We also considered secondary outcomes of interest, including graft site morbidity, effect of smoking, number of levels included, and the role of surgical adjuncts if sufficient information were presented to warrant review. We reviewed the bibliographies of the selected papers for additional references of relevance.

We selected articles if they addressed issues related to cervical spine surgery, arthrodesis, and interbody grafting. We excluded articles that did not contain information regarding arthrodesis rates and/or outcomes and gave preference to articles that contained randomized or prospective data. Articles primarily included data on anterior approaches with a paucity of studies examining posterior fusion. We compiled evidentiary tables (Tables 1–4) based on the resulting list of 43 studies selected for inclusion. In general, these studies addressed different types of grafting media including autograft, allograft, and xenograft, and a multitude of different interbody prostheses. Four systematic reviews were identified.[12,19,40,42] The remainder of the studies selected for inclusion were randomized trials, prospective cohort studies, or large case series reports.

Scientific Foundation

A discussion of the process for obtaining successful arthrodesis requires an understanding of the incorporation of grafted bone into a surgical fusion site. Goldberg and Stevenson[13] divided this process into 5 stages. The initial stage is inflammation, resulting in the formation of granulation tissue. This is followed by vascularization and osteoinduction, resulting in the arrival of nutrients and osteoprogenitor cells at the grafted site. If the graft is autologous, no immune reaction is involved. If allograft is used, an acute immune response is mounted against the foreign body or cells. Osteoinduction is the process of new bone formation resulting from the arrival of the progenitor cells, and results in incorporation of the graft, or osteoconduction. Finally, remodeling occurs as the graft is transformed into stable, weight-bearing bone. Differences in the incorporation of bone graft are observed when comparing autograft and allograft sources. This is theorized to be at least in part related to the immune response or the absence of growth factors.

Clinicians have extensively debated the decision to use allograft or autograft to achieve a successful arthrodesis in cervical fusion surgery. In general, allograft has a slower and less complete incorporation than autologous bone graft; however, the harvest of autograft from the anterior iliac crest, the fibula, or rib may be associated with significant postoperative complications. Factors that have been reported to have an impact on fusion rate include smoking, number of fusion levels, and the use of cervical instrumentation.[23]

The majority of surgical studies involving the cervi-

TABLE 1: Evidentiary summary of systematic reviews for techniques on cervical interbody fusion*

Authors & Year	Study Description	Evidence Class	Conclusions
Floyd & Ohnmeiss, 2000	Meta-analysis of 1- & 2-level ACDF on data derived from peer-reviewed journal articles to determine whether there is a difference in fusion rate, graft complications, or clinical outcome in patients undergoing ACDF according to whether autograft or allograft was used. Medical literature dating from 1955 was reviewed. Of 395 titles, only 4 studies comparing autograft w/ allograft in ACDF were appropriate for this analysis. 2 studies did not report clinical results & the 2 that reported clinical results did not use a grading scheme. Graft collapse was not consistently assessed.	III	Data from 4 studies included 310 patients & 379 intervertebral levels. Radiographic union (1 level in 251 patients): autograft (n = 149) pseudarthosis 6.0%; allograft (n = 102) pseudarthrosis 14.7% (p = 0.02). Radiographic union (2 levels in 59 patients): autograft (n = 35) 20% pseudarthosis, allograft (n = 24) 46% pseudarthrosis (p = 0.034). The authors concluded that autograft had a higher rate of fusion for both 1- & 2-level procedures. They were not able to comment on clinical outcome or graft collapse. In addition, authors also recommended that patient preference & the risk of graft site morbidity be considered when selecting graft type.
Van Limbeek et al., 2000	Systematic review of clinical trials for interbody fusion. Search of Medline, Current Contents, & Cochrane. Titles numbered 214 w/ 8 studies found.	III	8 trials found via search but only 3 met criteria. 1 trial was discectomy vs PMMA. 1 study was discectomy vs fusion, & 1 trial was discectomy vs fusion vs fusion w/ plate. This review yielded no gold standard for interbody surgery. Class III due to the underlying studies, not methodology.
Wigfield & Nelson, 2001	Systematic reviews of basic science & clinical trials for interbody fusion nonautologous materials.	III	Search of Medline revealed 32 clinical & 10 basic science studies. Studies dealt w/ multiple prosthetic interbody materials. Conclusion: at present there was little evidence to support the use of alternatives to autologous bone for interbody fusion. Not all implants meet the mechanical requirements for promoting fusion & preventing collapse. Fewer w/ osteointegration or osteoconduction. Class III due to underlying studies, not methodology.
Jacobs et al., 2004	Systematic review of techniques including types of grafts. 4 studies w/ 218 patients total comparing autograft (n = 94) to use of other graft (n = 124). In general, authors found that methodological quality was low & the studies did not provide adequate homogeneous comparison groups.	II	Limited evidence that autograft results in better pain reduction than bovine allograft. No difference between biocompatible osteoconductive polymer & autograft. Limited evidence that allograft ring w/ rhBMP results in better outcome at 24 mos than autograft. Moderate evidence that autograft provides better fusion than the addition of a cage for 1- or 2-level surgery.

* The criteria for scoring each manuscript into a class are described in *Introduction and Methodology: Guidelines for the Surgical Management of Cervical Degenerative Disease*, which appears in this issue of the *Journal of Neurosurgery: Spine*.

cal spine have addressed the use of graft and fusion techniques accompanying an anterior cervical surgery. Posterior cervical arthrodesis studies have been infrequent. Both will be addressed in this setting.

Anterior Cervical Arthrodesis

Early studies using autograft to perform a cervical fusion from an anterior approach were nearly uniformly successful with fusion rates approaching 100%. In a series of reports, Gore[14] and Gore and Sepic[15] described fusion rates of 97–100% in > 200 patients. As clinical experience increased, concerns over donor site morbidity caused investigators to attempt the use of allograft as a substitute, but problems with graft subsidence and pseudarthrosis tempered enthusiasm.[11] Several authors have subsequently reported on their experience with a series of hybrid techniques which attempt to increase the success of arthrodesis while still avoiding autograft donor site morbidity.

Floyd and Ohnmeiss[12] published their meta-analysis of 1- and 2-level cervical interbody fusion cases with data derived from peer-reviewed articles to evaluate fusion rate, graft complications, and clinical outcome after ACDF, using either autograft or allograft. The authors reviewed 395 titles, selecting only 4 studies for inclusion. These 4 studies included 310 patients with surgery at 379 intervertebral levels. The patients undergoing 1-level fusion included 251 who received either autograft (in 149 cases) or allograft material (in 102 cases). There was a pseudarthrosis rate of 6.0% in the autograft group compared with 14.7% in the allograft group ($p < 0.02$). Radiographic evaluation of the union in the 59 patients who underwent 2-level fusion indicated a 20% pseudarthrosis rate in the autograft group (35 patients) versus a 46%

TABLE 2: Evidentiary summary of studies comparing autograft to allograft for cervical interbody arthrodesis*

Authors & Year	Study Description	Class	Conclusions
Suchomel et al., 2004	Prospective study of fusion & graft collapse rates in 79 consecutive instrumented anterior cervical fusions comparing arthrodesis using allograft fibula (n = 76), AIC (n = 37), & radiographic evaluation. Min FU 2 yrs.	III	Fusion rate at 24 mos: autograft 94.6% vs allograft 93.4% (p = NS). Collapse rate at 24 mos: autograft 8.1% vs allograft 8.3% (p = NS). Time to fusion delayed in allograft: fusion (6 mos): autograft 89.2% vs allograft 63.1% (p = 0.001). No graft migration in either group. No differential effect of smoking or number of levels on fusion rates. The authors concluded that allograft was a suitable substitute for autograft in instrumented ACDF. Class III because patients decided on graft type, introducing allocation bias.
Martin et al., 1999	Retrospective review of 317 patients undergoing ACDF w/ allogenic fibula arthrodesis after ACDF. Mean FU 33 mos w/ radiographic assessment.	III	Fusion 1-level 90% (242/269); nonsmokers 92% (182/198) vs smokers 85% (60/71; p = 0.120). 2-level 72% (13/18); smokers 50% (2/4) vs nonsmokers 79% (11/14; p = 0.53). Graft subsidence occurred in 5% (17/311). Allogenic fibula is an effective substrate for use in achieving fusion after ACDF. Cigarette smoking decreased the fusion rate w/ allogenic fibula in the anterior cervical spine (p = NS).
Bishop et al., 1996	Prospective study of 132 patients requiring interbody fusion w/o instrumentation following ACDF comparing tricortical iliac crest allograft vs autograft. Assessment of: interspace collapse, angulation, maintenance of alignment, clinical & blinded radiographic fusion success rates. Smoking impact on fusion rate examined. Median FU 31 mos.	III	Fusion (1-level): autograft 97%, allograft 87%. Fusion (multi-level): autograft 100%, allograft 89% (no statistics reported). Subsidence (single-level) autograft 1.4 mm vs allograft 2.4 mm (p = 0.004); (multi-level) autograft 1.8 mm vs allograft 3.0 mm (p = 0.005). All failed fusions were in smokers 14% (8/59). The authors concluded that autograft tricortical iliac crest bone was superior to allograft bone as an interbody fusion substrate for both 1- & multiple-level ACD procedures. Smoking had a negative impact on fusion—most significant in allograft. Class III due to no clear description of group allocation & the lack of dynamic films to assess stabilization. Also, no statistics for fusion.
An et al., 1995	Prospective study of patients undergoing noninstrumented ACDF & fusion at 2 medical centers comparing: anterior iliac crest autograft (n = 38), freeze-dried allograft augmented w/ demineralized bone matrix (n = 39). Mean FU 17.5 mos. Radiographs taken 12 mos postop were analyzed blindly.	II	Fusion rates: 1-level: autograft (n = 19) 83.7% vs allograft (n =19) 52.6% (p = 0.31). 2-levels: autograft (n = 17) 86.5% vs allograft (n = 16) 62.5% (p = NS). Pseudarthrosis developed in 46.2% in the allograft-DBM group compared w/ 26.3% in the autograft group (p = 0.11). Graft collapse of ≥3 mm was noted in 11% of the autograft group vs 19% in allograft-DBM group (p = 0.32). Graft collapse of ≥2 mm occurred in 24.4% of autograft group compared w/ 39.7% of the allograft-DBM group (p = 0.09). Smokers had increased rate of pseudarthrosis (47.1%) compared w/ nonsmokers (27.9%; p = 0.13). Allograft-DBM construct gave a higher rate of graft collapse & pseudarthrosis compared w/ autograft in a prospective series (p = NS).
McGuire & St. John, 1994	Prospective study comparing the use of autologous bone from the cervical vertebrae for grafting to the modified Smith-Robinson technique using AIC graft. 7 levels in 6 patients were fused using the VB autograft technique & 43 levels in 40 patients using the standard technique. All patients had radiculopathy & neck pain. Radiographic assessment. Min FU 2 yrs.	III	Fusion rate: VB autograft 4/7 (57%) vs AIC 40/43 (93%) (p = 0.029). Disc height maintenance (p = 0.001) & neck pain improvement (p = 0.05) were both significantly better in the iliac crest harvest group. The authors concluded that VB autograft for the Smith-Robinson technique for anterior cervical fusion following discectomy was not recommended.

(continued)

TABLE 2: Evidentiary summary of studies comparing autograft to allograft for cervical interbody arthrodesis* *(continued)*

Authors & Year	Study Description	Class	Conclusions
Rawlinson, 1994	Comparison study of the CP using autologous bone dowel vs xenograft bone dowel. Original group had 89.51% (45/89) available for FU.	III	Fusion rates (6-mo FU): xenograft 19% (6/31) vs autologous dowel 72% (10/14). The authors concluded that xenograft was not found to be a satisfactory substitute for autologous bone.
Young & Rosenwasser, 1993	Retrospective review of 23 cases of ACD & fusion performed w/ cadaveric fibular allograft. Compared w/ 25 cases of ACD in which AIC graft was used. No Bayesian table reported. Radiographic assessment. Min 6-mo FU.	III	Fusion rates: autograft 88% (22/25) vs allograft 92% (21/23; p = NS). The mean duration of hospital stay was less in the allograft group (5.4 vs 7.25 days), p < 0.05. Postop pain was less in the allograft group because of lack of donor site pain. The authors concluded that fibular allograft for interbody fusion after ACD can be used w/ acceptable rates of fusion & less postop pain compared w/ the use of AIC graft.
Zdeblick & Ducker, 1991	Consecutive series of 87 patients who underwent Smith-Robinson anterior cervical fusion. Either freeze-dried tricortical iliac crest bone or tricortical autograft bone was used. Surgical technique was otherwise identical.	III	Nonfusion rate at 1 yr, overall nonfusion rate of autograft 8% vs allograft 22% (p = 0.04). 1-level: autograft 4.9% vs allograft 5.3% (p = NS). 2-level: autograft 17% vs allograft 63% (p = 0.03). Graft collapse: allograft (30%) vs autograft (5%; p = 0.003). Clinical outcome (relief of neck & arm pain) was similar in both groups. The authors concluded that the use of allograft in 1-level fusion was successful but for multilevel procedures there was an increase in the rate of pseudarthrosis.
Brown et al., 1976	Retrospective radiographic review. Autograft in 53 patients (76 levels) grafted w/ frozen bone marrow–free cadaver bone. Allograft in 45 patients (63 levels) w/ iliac crest autografts for anterior cervical spine fusion. Radiographic assessment of fusion & graft collapse.	III	Fusion: allografts 94% vs autografts 97%, p = NS. 1-level (n = 32): no difference in graft collapse comparing allograft vs autograft, 16 vs 17% multilevel (n = 21): higher rate of graft collapse in allograft, allograft 36% vs autograft 6%.
Heary et al., 2002	Retrospective review of 105 patients reporting pain after iliac crest graft harvest. Physician written assessment was compared w/ an independent assessment from a structured telephone questionnaire interview. Pain assessed with VAS & categorized as no pain, acceptable pain, or unacceptable pain.	III	Incidence of iliac crest donor site pain after graft harvest procedures: independent 34% vs neurosurgeon's assessment 8% (p = 0.0001) severity (independent assessment group): no pain 66%, acceptable pain 31%, unacceptable pain 3%. The authors concluded that accurate assessment of iliac crest donor site pain may be underrated by the treating surgeon & requires independent outcome assessment.
Shamsaldin et al., 2006	Prospective single institution study of 50 patients who underwent anterior iliac crest bone harvest. No comparison group. Donor site pain assessed w/ VAS at 2, 7, & 60 days postop & telephone interview at 1 yr.	III	VAS score Day 2: >7 in 4 patients (8%); 5–7 in 27 patients (54%); <5 in 19 (38%). VAS score Day 7: >7 in 0 (0%); 6 in 1 (2%); <5 in 49 patients (98%). VAS score at 2 mos: 0 (no pain) in 45 patients; <5 in 5 patients; VAS score at 1 yr: 0 (no pain) 46 patients (1 patient was lost to FU); <5 in 3 patients (6%). The authors concluded that the harvest iliac crest bone in most patients does not result in persisting pain at the donor site.
Löfgren et al., 2000	43 patients randomized by sealed enveloped to ACD w/ autograft (n = 15), allograft (n = 14), bovine xenograft (n = 14). Radiostereometric analysis w/ tantalum beads.	III	Outcome assessed in only 33/43 for movement. All tended to fuse over time. Excess motion did not correlate w/ symptoms. Statistically stronger improvement in arm & neck pain w/ autograft compared w/ xenograft w/ greater improvement in motor & sensory function.

(continued)

TABLE 2: Evidentiary summary of studies comparing autograft to allograft for cervical interbody arthrodesis* *(continued)*

Authors & Year	Study Description	Class	Conclusions
Sawin et al., 1998	Retrospective analysis of fusion rate & donor site morbidity in 600 patients undergoing posterior cervical fusion procedures. Use of allograft rib & iliac crest bone graft were compared: rib graft in 300 posterior cervical fusions. iliac crest graft in 300: 248 for anterior & 52 for posterior fusions. Fusion criteria included bony trabeculae traversing the donor-recipient interface & long-term stability on flexion-extension radiographs. Graft morbidity was defined as any untoward event attributable to graft harvest. Statistical comparisons by Fisher exact test.	III	Rib grafts: occipitocervical (196), atlantoaxial (35), subaxial (69). Iliac crest grafts: occipitocervical (28), atlantoaxial (10), subaxial (14). Fusion rates (posterior cases only): rib 98.8% (296/300) vs iliac crest 94.2% (49/52; p = 0.056). Donor-site complications: rib graft, 3.7%: pneumonia in 8, persistent atelectasis in 2, and wound dehiscence in 1. iliac crest, 25.3%: chronic donor-site pain in 52, wound dehiscence in 8, pneumonia in 7, meralgia paresthetica in 4, hematoma requiring evacuation in 3, & iliac spine fracture in 2. More complications w/ iliac crest than rib (p < 0.00001). The authors concluded that the fusion rate & donor-site morbidity for rib autograft compare favorably w/ those for iliac crest when used in posterior cervical constructs.

* ACD = anterior cervical discectomy; AIC = autologous iliac crest; CP = Cloward procedure; DBM = demineralized bone matrix; Fu = follow-up; NS = not statistically significant; VB = vertebral body.

pseudarthrosis rate in the allograft group (24 patients; p < 0.03).[12]

The authors concluded that the use of autograft yielded a higher rate of fusion in both 1- and 2-level procedures.[12] However, because of the lack of information reported in the studies, Floyd and Ohnmeiss were unable to comment on clinical outcome, graft collapse, or patient satisfaction. The authors further commented that they were specifically unable to assess the risk and impact of graft site morbidity. They recommended that both graft harvest morbidity and patient preference be considered when selecting the type of graft for this procedure. This meta-analysis was scored Class III due to the heterogeneity of the studies included and the lack of consistency in reported outcomes. This review appropriately included randomized controlled trials, but also allowed inclusion of cohort studies and 1 large case series.[12]

Jacobs and colleagues' systematic review[19] in the Cochrane Database found 4 studies with 218 patients comparing autograft with different techniques. In general, the methodological quality of the underlying studies was low. The authors noted limited evidence that autograft results in better pain reduction than bovine allograft. They found limited evidence for no difference between a biocompatible osteoconductive polymer and autograft. There was also limited evidence that an allograft ring with rhBMP results in better outcome at 24 months postoperatively than the use of autograft. These authors also found moderate evidence that autograft alone provides better fusion than the addition of a cage for 1- or 2-level surgery.[19] The systematic reviews by van Limbeek and colleagues[40] and Wigfield and Nelson[42] did not find a gold standard, nor did they find a technique superior to the use of autograft.

Suchomel et al.[36] described their prospective study of fusion and graft collapse rates in 79 consecutive instrumented anterior cervical fusions comparing the use of allograft fibula in 76 patients versus the use of autologous iliac crest bone in 37. Radiographic evaluation was obtained with a minimum follow-up of 2 years. Fusion rates at 24 months were not significantly different between the groups, with 94.6% of the autograft group achieving fusion compared with 93.4% of the allograft group. The graft collapse rate was also not significantly different (8.1 vs 8.3%). Time to fusion was delayed in the allograft group. When assessed at 6 months, only 63.1% of the allograft group had achieved radiographic fusion compared with 89.2% of the autograft cases. There were no reports of graft migration in either group. The authors' conclusion was that allograft was a suitable substitute in instrumented ACDF. This study was graded Class III due to selection bias. Patients chose their treatment arm (autograft or allograft), permitting allocation bias.[36]

Martin et al.[24] described a retrospective series of 317 patients who underwent ACDF with allogenic fibula. The purpose of this study was to evaluate fusion in smokers versus nonsmokers, as well as the influence of the number of operated levels over a mean follow-up of 33 months. Nonsmoking patients who underwent a single-level procedure achieved a 90% fusion rate, whereas smoking resulted in a decrease to 85% (p = 0.12). In patients who

underwent 2-level procedures, the overall fusion rate was 72% (50% in smokers vs 79% in nonsmokers). The small number of cases in the study did not allow statistical significance to be achieved ($p = 0.53$). The authors concluded that allogenic fibula was an effective substrate for achieving fusion after anterior discectomy. It appeared that the best results were achieved in nonsmokers who underwent 1-level procedures. Cigarette smoking did diminish fusion rates with allogenic fibula; however, the resulting differences were not statistically significant. This study was graded Class III due to study design and its retrospective nature.[24]

Bishop and coworkers[4] described a prospective study of 132 patients who required interbody fusion after ACDF without additional instrumentation. Their study compared the use of allograft and autograft, assessing interspace collapse, angulation, maintenance of alignment, radiographic fusion, and the impact of smoking. In the 1-level cases, 97% of patients with autograft achieved fusion versus 87% with allograft. In the multilevel cases, 100% of the patients who received autograft experienced fusion versus 89.5% of the patients in the allograft group. The difference in subsidence for 1-level grafting was statistically significant (1.4 mm with autograft vs 2.4 mm with allograft; $p = 0.004$). In the multilevel group, a similar trend was observed with auto- and allograft subsidence of 1.8 and 3.0 mm, respectively ($p = 0.005$). The authors concluded that autograft iliac crest bone was superior to allograft bone as an interbody substrate for both single and multiple procedures. They observed a negative impact of smoking on fusion that was most significant in the allograft patients. This study was graded Class III because randomization was not truly undertaken without bias and because the outcome measure for fusion was not dynamic radiography.[4]

An et al.[1] detailed a prospective study of patients who underwent ACDF. They compared 38 patients who received anterior iliac crest autograft with 39 patients who received freeze-dried allograft augmented with demineralized bone matrix. A mean follow-up of 17.5 months was described with a radiographic evaluation at 12 months. Pseudarthrosis was noted in 46.2% of patients in the allograft group, compared with 22.3% in the autograft group. This difference was not statistically significant. In patients who underwent 2-level fusion, fusion did not occur in 37.5% of the allograft group compared with 23.5% in the autograft group. A graft collapse of > 3 mm was noted in 11% of the autograft group versus 19% of the allograft group. Smokers had an increased rate of pseudarthrosis (47.1%) compared with nonsmokers (27.9%; $p = 0.13$). The authors indicated that the allograft demineralized bone matrix construct resulted in a higher rate of graft collapse in pseudarthrosis compared with autograft. However, the differences were not statistically significant.[1]

Löfgren et al.[21] reported on 43 patients randomized by sealed envelope to receive autograft, allograft, or bovine xenograft for 1-level Cloward fusion. Patients were assessed using radiostereometric analysis using tantalum markers. Outcome was assessed with VAS pain scores and sensorimotor function. Only 33 of 43 patients underwent radiostereometric analysis assessment. The authors observed fusion in all types of grafts over 24 months. However, pain appeared to improve significantly better with autograft than with xenograft. Improvements in sensorimotor function were greater when autograft was used. This study was scored Class III due to limited follow-up for radiostereometric analysis and also due to the lack of modification for multigroup comparisons.[21]

McGuire and St. John[27] described their prospective series comparing autologous bone from the cervical vertebrae adjacent to the fusion with autologous iliac crest graft. Six patients underwent the autologous bone fusion technique at 7 levels, and this was compared with 40 patients undergoing the standard procedure at 43 levels. They reported fusion in only 4 of the 7 patients with vertebral body autograft (57%) compared with 40 of 43 patients in the autograft iliac crest group (93%; $p = 0.029$). In addition, disc height maintenance and neck pain improvement were both statistically significantly improved with the standard technique over the local autograft. The authors concluded that the local autograft technique could not be recommended. This study was graded Class III because of allocation bias.[27]

Rawlinson[29] described a technique of the Cloward procedure using autologous bone dowel compared with a xenograft bone dowel. They did not find xenograft bone to be a satisfactory substitute for autologous bone. This study was graded Class III due to poor follow-up (only 45 of 89 patients).[29]

Young and Rosenwasser[43] undertook a retrospective review of 23 cases of ACDF performed with cadaveric fibular allograft and compared these with 25 cases of ACDF with autologous iliac crest graft. The groups were comparable in demographic characteristics, and evidence of radiographic fusion was seen in 92% of cases regardless of the source. The mean duration of hospital stay was less in the allograft group because of iliac crest harvest was not performed (5.4 vs 7.25 days). The authors concluded that fibular allograft used for anterior cervical fusion after discectomy could be anticipated to achieve similar fusion rates to autograft with less postoperative pain from the iliac crest harvest site. This study was graded Class III because of the use of historical controls.[43]

Zdeblick and Ducker[44] reviewed 87 consecutive patients who underwent a Smith-Robinson ACDF and compared the use of freeze-dried tricortical iliac crest allograft with the use of tricortical autograft iliac crest. The results were evaluated at 3 and 12 months postoperatively looking at single and multiple levels. At 1 year, the overall nonunion rate of autograft bone was 8 and 22% for the allograft group ($p = 0.04$). One-level cases did not differ significantly, with rates of 4.9% for autograft and 5.3% for allograft (not statistically significant). For 2-level cases, however, the autograft nonunion rate was 17% compared with 63% with allograft ($p = 0.03$). The authors observed that graft collapse was significantly increased in the allograft (30%) compared with the autograft group (5%; $p = 0.003$). Clinical outcomes in terms of neck and arm pain were similar in both groups. The authors concluded that the use of allograft for 1-level fusion was successful; for multilevel procedures, however, there was an

TABLE 3: Evidentiary summary of prosthetic interbody devices and outcomes*

Authors & Year	Study Description	Class	Conclusions
Barlocher, et al., 2002	Randomized study of 125 patients undergoing surgery for 1-level cervical disc disease: Group 1 MDO: 33 patients. Group 2 discectomy & autograft bone: 30 patients. Group 3 discectomy & PMMA: 26 patients. Group 4 discectomy & TTC w/ osteoconductive bone material: 36 patients. Clinical outcome: Odom criteria. 1-year FU exam was performed in 123 patients.	III	Outcome (good/excellent) at 6 mos: Group 1, 73%; Group 2, 67%; Group 3, 92% (no fusion); Group 4, 92%. Autograft bone vs TTC ($p < 0.05$). Outcome at 12 mos: Group 1, 76%; Group 2, 80%; Group 3, 88% (no fusion); Group 4, 95%. MDO vs TTC ($p < 0.05$). The authors concluded that the threaded interbody fusion cage led to better outcome compared to discectomy alone at both 6 & 12 mos postop, & when compared to discectomy & autograft at 6 mos. PMMA resulted in similar outcomes to interbody cage fusion but did not result in fusion by 12-mo FU. Class III because Odom is a nonvalidated outcome measure, there was no correction (Bonferroni) for multiple comparisons, & no interobserver reliability for radiographs.
Van den Bent et al., 1996	Randomized study. ACDF alone (n = 39) vs ACDF & PMMA (n = 42). Odom's criteria & patients' assessment. Median FU 2 yrs.	II for fusion, III for outcome	Fusion rates: ACDF alone 63% (22/35) vs ACDF w/ PMMA 28% (11/39; $p = 0.05$). Outcome (good/excellent): ACD alone 70% (30/39) vs PMMA 70% (28/42; $p = 0.12$). The authors concluded that the fusion rates are lower w/ the use of PMMA.
Schroder et al., 2007	Prospective comparison of PMMA vs Ti cages + autograft in patients undergoing ACDF for radiculopathy. Noninstrumented. PMMA (n = 53), Ti cage (n = 54). Block-restricted randomization was applied. Clinical outcome was assessed at 2 yrs. Odom scale by an independent observer at the FU exam. Preop, postop, & FU radiographs.	II for fusion, III for outcome	Fusion rates: PMMA 66% (35/53), Ti 87% (47/54). Outcome: PMMA excellent in 26 (49%), good in 19 (36%), satisfactory in 8 (15%), & bad in 3 (6%). Ti fusion: excellent in 26 (48%), good in 16 (30%), satisfactory in 9 (17%), & bad 0 (0%). No significant difference between the 2 groups could be established w/ respect to the clinical outcome ($p = 0.011$). The radiological result of the titanium cage is superior to that of PMMA w/ respect to the fusion rate. Although the Ti cage achieves a better fusion rate, there is no difference between Ti cages & PMMA w/ respect to the clinical outcome.
Madawi et al., 1996	Prospective study in 115 patients w/ symptomatic cervical disc disease. AIC graft in 50. biocompatible osteoconductive polymer implants (contains methylmethacrylate) in 65. Smith-Robinson in 74. CP in 41. Outcome assessed w/ VAS & Odom criteria. Radiographic evaluation on plain films, CT scans & MRIs. Mean FU 17.3 mos.	III	Fusion rates: anterior iliac crest 48/50 (96%), osteconductive polymer 0/50 (0%). Clinical outcome was identical in both groups. Partial graft protrusion iliac crest (11) vs osteoconductive polymer (5), $p = 0.018$. Postop intersegmental kyphosis (>15°) iliac bone graft (5) vs osteoconductive polymer (0), $p = 0.02$. Biocompatible osteoconductive polymer resulted in pseudarthosis in 100%. Biocompatible osteoconductive polymer acts as a good spacer that reduces graft collapse & intersegmental kyphosis. However, there was no radiological evidence of biodegradation or incorporation during the FU period of 24 mos.
McConnell et al., 2003	Randomized trial comparing coralline-derived hydroxyapatite w/ tricortical iliac crest graft for cervical interbody fusion following ACD. 29 patients undergoing anterior cervical fusion & plating were randomized to receive either ProOsteon 200 (n = 13) or iliac crest grafts (n = 16). Clinical outcome measures: SF-36, ODI. Postop radiographs were analyzed for graft complications & fusion.	III	Both hydroxyapatite & iliac crest groups demonstrated significant improvement in clinical outcome scores. There was no significant difference in clinical outcome or fusion rates between the 2 groups. Graft fragmentation occurred in 89% of the hydroxyapatite grafts & 11% of the autografts ($p = 0.001$). Significant graft settling occurred in 50% of the hydroxyapatite grafts, as compared w/ 11% of the autografts ($p = 0.009$). Hydroxyapatite does not possess adequate structural integrity to resist axial loading & maintain disc height or segmental lordosis during cervical interbody fusion. However, the effect of this on clinical outcome could not be determined from this study. Class III since allocation not concealed & did not include dynamic radiography analysis.

(continued)

TABLE 3: Evidentiary summary of prosthetic interbody devices and outcomes* ***(continued)***

Authors & Year	Study Description	Class	Conclusions
Mastronardi et al., 2006	Retrospective study of 36 patients undergoing ACDF w/ PEEK cages w/ coralline hydroxyapatite at 43 levels, noninstrumented. Study objective was to determine the safety & preliminary efficiency of PEEK cages for ACDF. Clinical outcome was patient self-assessment. Radiographic assessment of fusion trabeculation & flexion-extension views. FU 17.5 mos.	III	Fusion rate 16.7% at 3 mos, 61.1% at 6 mos, & 100% at 1 yr. Good to excellent outcome in 97%. The authors concluded that PEEK cages appear to be safe & efficient for anterior cervical fusion following discectomy.
Cho et al., 2005	Randomized study of 100 patients w/ cervical spondylosis undergoing anterior discectomy w/ interbody PEEK fusion. Group A (n = 50), PEEK cage containing biphasic calcium phosphate ceramic (Triosite), Group B (n = 50), PEEK cage containing AIC bone graft. Radiographic comparison of fusion rate, fusion time, spinal curvature, neuroforamen size. Compared excess operation time, excess blood loss, hospital stay, complications, neurological recovery.	III	Fusion rates for first 6 postop months by month: Group A: 57, 67, 77, 82, 92, & 100%. Group B: 81, 86, 95, 95, 100, & 100%. Group A significantly lower than Group B in the first 5 mos ($p < 0.05$) but reached 100% in both by 6 mos. Complications: there were no donor site complications in Group A (0%), Group B 3 patients (6%) (1, wound infection; 1, numbness of thigh; & 1 subcutaneous hematoma) ($p < 0.001$). The hospital stay was shorter in Group A (4.43 ± 2.36 days) than in Group B (7.00 ± 3.77 days) ($p = 0.001$). No statistical significance in spinal curve correction, neuroforamen enlargement, neurological recovery. The authors concluded that the use of calcium phosphate ceramic (Triosite) along w/ a PEEK cage resulted in complete fusion in 6 mos while avoiding AIC harvest and yields shorter hospital stay, less blood loss, shorter op time, no donor site complications. Class III because group allocation not truly randomized or concealed.
Celik et al., 2007	Prospective comparison of cervical foraminal height changes following ACDF comparing autograft tricortical iliac crest (30 patients, 46 levels) w/ PEEK cages (35 patients, 41 levels). No fixation. Fusion status, C2–7 Cobb angle, interspace height, foraminal height assessed on radiographs. Clinical outcome evaluated by mJOA & VAS for arm & neck pain. FU 18 mos. Relatively small study, technique of randomization not described & outcome assessment not blinded.	III	Clinical recovery, fusion status, Cobb angle no difference found. Allograft: preop mean foramina height 8.2 mm, postop mean foramina height 8.1 mm (18 mos, p = NS), mJOA preop 13.4, postop 15.3 ($p < 0.05$), VAS (arm) preop 7.4, postop 0.3, ($p < 0.05$), VAS (neck) preop 8.6, postop 0.2 ($p < 0.05$). PEEK: preop mean foramina height 8.4 mm, postop mean foramina height 9.6 mm (18 mos, $p < 0.05$), mJOA preop 13.5, postop 15.8 ($p < 0.05$), VAS (arm) preop 7.3, postop 0.2, ($p < 0.05$), VAS (neck) preop 8.3, postop 0.3, ($p < 0.05$). PEEK cages maintained foraminal height for at least 18 mos. A positive effect of this on clinical outcome was not confirmed in this study. Class III for allocation bias & unblinded outcome assessment.
Cho et al., 2004	Randomized comparison in multilevel anterior cervical procedures, comparing: ACDF w/ PEEK & bone marrow aspirate (n = 60) AIC w/ plate (n = 50). AIC alone (n = 70). Radiographic assessment used. Median FU 2.5 yrs.	III	Fusion rates: ACDF w/ PEEK & bone marrow aspirate 100%, AIC w/ plate 98%, AIC alone 87% ($p = 0.01$)—comparing first 2 w/ the final group. Complications: ACDF w/ PEEK & bone marrow aspirate 3.3%, AIC w/ plate 16%, AIC alone 54% ($p < 0.05$)—comparing first 2 groups w/ the final. The authors concluded that PEEK plus marrow aspirate or autograft w/ a plate result in higher fusion rates & lower complication rates compared w/ autograft alone. Class III because group allocation not truly randomized nor concealed.

(continued)

TABLE 3: Evidentiary summary of prosthetic interbody devices and outcomes* ***(continued)***

Authors & Year	Study Description	Class	Conclusions
Thome et al., 2006	Randomized trial of 100 patients (127 cervical levels) undergoing ACDF w/ either: ABG or RTC w/ no graft. Fusion rates were assessed on standard & dynamic radiographs. VAS for regional & overall pain score, mJOA, & Nurick grading systems, Odom criteria, SF-36, & Patient Satisfaction Index scales. FU data ≥ 12-mos duration were available for 95 patients (95%).	II	Fusion rate: ABG 81%, RTC 74% (p = 0.51). Residual overall pain after 12 months: ABG 3.3, RTC 2.2 (p < 0.05). Preop neck pain: RTC 1.9, ABG 2.7. Postop pain resolved: RTC 67%, ABG 48% (p < 0.05). Myelopathy improved comparably in both groups (>80% in both, p = NS). Pain scores increased in ABG-treated patients. Good to excellent functional recovery according to Odom criteria (good to excellent): ABG 79%, RTC 75%. The authors concluded that the fusion rates & clinical outcome at 12 mos were comparable w/ either ABG or RTC fusion. However, the use of rectangular cages can avoid donor site morbidity, reduce overall pain, & be an advantageous Tx alternative. Class II because patients not blinded & intraobserver reliability not tested in radiographic assessment.
Thome et al., 2004	Prospective study of 36 consecutive patients undergoing ACDF w/ AIC, & RTC w/o autograft in 18 patients each. Outcome Odom criteria, patient satisfaction. Fusion assessed radiographically. Not blinded. 1-yr FU.	III	Fusion (1 year): iliac crest autograft group (89%), RTC (83%), (p = 1.00). Outcome: (Odom's criteria): good to excellent, 83% in both groups; (Patient Satisfaction Index): 94% (17/18) in both groups were satisfied. No significant differences in neck or arm pain. Complications: hip pain 28% (5/18) of autograft group. Implant group: no implant-related complications (p = 0.045). The authors conclude that Ti cages in ACD constitute a safe & efficient alternative to iliac crest bone autograft. Class III due to nonrandomization & absence of blinding.
Cauthen et al., 2003	Retrospective comparison BAK/C conventional ACDF w/ or w/o instrumentation. BAK/C plus local autograft was used in 30, ACDF (93.8% iliac crest autograft) in 32, and ACDF (50% iliac crest autograft) & plate in 26 patients. A retrospective clinical & radiological review was performed. Hospital & clinic chart data, flexion-extension radiographs & self-assessments (SF-36, VAS) were evaluated. Radiography FU at 2.4 yrs (range 1.0–5.5 yrs).	III	Fusion rates: BAK/C, 97% (29/30), ACDF 84% (26/31), ACDF w/ plate 85% (22/26; p < 0.0585). Iliac crest harvesting: BAK/C 6.7% (2/30), ACDF 93.8% (30/32), ACDF w/ plate 50.0% (13/26; p < 0.0001). Prolonged donor-site pain: BAK/C 0%, ACDF 25.0%, ACDF w/ plate 23.0%. SF-36 & VAS scores were comparable for all groups. The authors concluded that the BAK/C cage group had similar patient outcomes & fused at a higher rate than ACDF & ACDF w/ plate groups.
Hacker et al., 2000	Randomized multicenter trial of 344 patients w/ symptomatic cervical discogenic radiculopathy treated w/ ACD & either: ACDF (2:1 ratio) or BAK/C fusion cage(s) including 2 cage groups (hydroxyapatite-coated or not coated); 97% local autograft & 3% iliac crest harvested. Outcome assessed w/ VAS, SF-36. Independent radiographic assessment of fusion. Data analysis in 344 patients at 1 yr & 180 patients at 2 yrs.	II	Fusion (1 level at 12 mos): 97.9% for the BAK/C groups & 89.7% for the ACDF group (p < 0.05). ACDF & BAK/C groups were the same comparing all outcome factors. Complications: ACDF 20.4%, BAK/C 11.8%. No difference in complications that necessitated a 2nd op. The authors concluded that outcomes after a cervical fusion procedure w/ either a threaded cage or conventional uninstrumented bone–only ACDF were similar. Class II: allocation concealment not listed; no intraobserver reliability for radiographic assessment.

(continued)

TABLE 3: Evidentiary summary of prosthetic interbody devices and outcomes* *(continued)*

Authors & Year	Study Description	Class	Conclusions
Hacker, 2000	Single center report of larger randomized study of 54 patients undergoing ACD for radiculopathy followed by either: Iliac crest graft fusion, or Ti interspace cage w/ local autograft. Min FU 2 yrs.	II	Fusion: 1 level in both groups, 100%. Outcome: iliac crest graft fusion, good or excellent in 88%. Ti cage group: good or excellent in 97%. Complication: chronic donor site pain in 31% control group. The authors conclude that use of the interbody fusion cage avoids donor site morbidity & achieves a high rate of good or excellent results. Class II for similar reasons to above.
Ryu et al., 2006	Randomized trial of 40 patients undergoing ACDF w/ either a CFC plus morselized cancellous iliac crest autograft (n = 20) or allograft w/ plating (n = 20). Cervical radiographs were evaluated preop & at each FU for evidence of fusion & instability. Neck & arm pain & NDI were assessed at every visit. SF-36 was completed prior to operation & at 12-mo intervals. Clinical & radiographic evaluations were performed at baseline & at 6 wks, & 3, 6, 12, & 24 mos. Mean FU period 14 mos (range 6–26 mos). Small study & nonblinded assessment.	III	Fusion rate 100% in both groups at 12 & 24 mos. No differences in complications between groups. No significant difference was found between the 2 randomized groups w/ respect to preop age (mean 50 yrs), sex, employment status, duration of pain, or cervical levels affected. The clinical pain & disability improvements were similar for both Tx. Postop donor site pain was only present in the cage group, but not a significant long-term disability. Both NDI & SF-36 scores significantly improved at 12 & 24 mos. No statistically significant difference in outcomes between groups at any time. Outcomes after cervical decompression & placement of a CFC appear similar to cervical decompression w/ allograft & plating w/ Smith-Robinson technique. This was scored Class III due to the lack of description of randomization process & concealment of allocation. Furthermore, fusion criteria were not dynamic films, & intraobserver reliability was not obtained.
Peolsson et al., 2006	Randomized study of 95 patients undergoing noninstrumented ACDF comparing: CIFC (n = 51), CP (n = 52). Radiographs to assess fusion at 2 yrs. NDI, distress, quality of life, & global outcome were obtained in 83 patients (87%). Mean FU 6 yrs (56–94 mos).	III	Fusion rate (2 years): CIFC 56%, CP 85% ($p = 0.02$). There were no significant differences in any outcome variable. For both CP & CIFC, pain intensity improved ($p < 0.0001$), while NDI was unchanged at long-term FU. In the CIFC group, patients w/ fusion had significantly less mean pain (24) & NDI (26) than patients w/ pseudarthrosis (42 & 41, respectively) at 6 yrs. Mean pain & NDI reported by CIFC patients w/ a healed fusion was significantly less than in healed CP patients (24 vs 37 & 26 vs 38, $p < 0.05$). However, this was a post hoc analysis. Allocation performed by nurse, w/ 8 patients not receiving Tx in their respective arms.
Vavruch et al., 2002	Randomized study of 103 patients undergoing ACDF w/ either CIFC (n = 52) or CP (n = 51). Independent assessment of pain & functional disability (Cervical Spine Functional Score), radiographic assessment of fusion rate, segmental kyphosis, disc height. Mean FU 36 mos in 86% (89/103).	III	Fusion rate: CIFC 62% vs CP 86% ($p < 0.05$). Pain & disability did not differ. Postop donor site pain was significantly less in the CFC group. Segmental kyphosis was less & disc height increased in the CIFC cage group vs CP group. Disc height was not correlated w/ outcome. Segmental kyphosis showed a weak ($r = 0.3$, $p < 0.05$) correlation w/ improvement of the cervical spine functional score, but not w/ other outcome variables. The authors concluded that the clinical outcome using CFIC or the CP was similar. CIFC resulted in reduced donor site pain, increased lordotic alignment, & disc height, but had higher pseudarthrosis rate than CP. Class III because allocation was not blinded & outcome measure (Odom) not validated. No interobserver reliability for radiography.

* ABG = autograft bone; AIC = autograft iliac crest; CIFC = carbon intervertebral fusion cage; MDO = microdiscectomy only; ODI = Oswestry Disability Index; RTC = rectangular titanium cage; SF-36 = Short Form 36; TTC = threaded titanium cage.

increased rate of pseudarthrosis. The authors could not correlate clinical outcome with fusion or type of graft selected. This study was graded Class III because it was a cohort series with selection bias as to treatment arm selection.[44]

Brown and colleagues[6] retrospectively compared autograft bone used in 53 patients at 76 levels with allograft bone utilizing 45 patients at 63 levels. Grafts were all iliac crest grafts. The study assessed for radiographic fusion and graft collapse without clinical correlation. They reported a fusion rate in the allograft group as 94% compared with 97% in the autograft group. In the one-level cases, they did not observe any difference in graft collapse; however, in the multilevel cases, they reported a higher rate of graft collapse in the allograft group. This study was scored Class III due to selection bias and its retrospective nature.

Donor Site Morbidity

Heary et al.[18] retrospectively reviewed 105 patients, focusing on reports of iliac crest graft harvest pain in a structured interview format, comparing the neurosurgeon's assessment to their independent assessment. The authors found a significant difference between the reports generated by the neurosurgeons and the patients, with only 8% reporting iliac crest donor site pain at the time of office visit compared with 34% with the independent assessment. In terms of severity, 3% of patients independently assessed felt that the iliac crest pain was unacceptable. The authors concluded that a true evaluation of iliac crest donor site pain required an independent outcome assessment tool. This case series was graded Class III because of its lack of comparative controls and retrospective method data collection.

Shamsaldin et al.[33] described their prospective series of 50 patients who underwent procedures requiring anterior iliac crest bone harvesting. There was no comparison group, and the authors assessed donor site pain with the VAS at 2, 7, and 60 days postoperatively. As expected, donor site pain gradually decreased over the course of the study. At 1 year, 3 patients continued to have pain but rated it at < 5 on a scale of 10. The authors concluded that although significant pain results in the early postoperative period, most patients who underwent iliac crest harvest did not experience persisting pain at the donor site. This case series was rated Class III.

Alternative Modalities and Techniques

Use of PMMA

Bärlocher et al.[2] described a randomized study of 125 patients who underwent 1-level ACDF: discectomy alone (in 33 patients) discectomy with autograft (in 26), discectomy with PMMA (in 26), discectomy and a threaded titanium cage with osteoconductive bone material (in 36). Clinical outcome was assessed using the Odom criteria with a minimum 1-year follow-up in 123 of the 125 patients. Outcomes assessment at 12 months indicated that 76% of patients in the discectomy group achieved good or excellent results compared with 80% of those in the discectomy and allograft group, 88% in the PMMA group, and 95% in the threaded titanium cage group. The difference between the discectomy only and the threaded titanium cage group was statistically significant at the 1-year time point ($p < 0.05$). Of note, none of the patients in the PMMA group was felt to have radiographic fusion. The authors concluded that the threaded titanium cage achieved the best outcome of the groups studied. Although PMMA resulted in a similar outcome compared with other techniques, it did not result in fusion according to radiographic criteria. This study was graded Class III based on the lack of statistical correction for multiple comparisons (Bonferroni) and nonblinded patient allocation.[2]

Van den Bent et al.[39] reported on 81 patients randomized to anterior fusion with either discectomy alone (39 patients) or discectomy with PMMA (42 patients). The median follow-up was 2 years, with fusion rates of 63% in anterior discectomy group and 28% in the PMMA group ($p = 0.05$). Outcomes using Odom's criteria were similar. This study was graded Class III for outcomes, but Class II for fusion status.

Schroder et al.[32] published their prospective comparison of PMMA (in 53 patients) to titanium cage and local autograft (in 54 patients) for ACDF in patients with radiculopathy. Their study assessed clinical outcome at 2 years postoperatively using the Odom scale as well as radiographic features. At long-term follow-up, there was no significant difference between the 2 groups with respect to clinical outcome. Fusion rates were significantly increased in the titanium group as might be expected from the character of PMMA. The authors noted that the radiographic results with the titanium cage were superior to those of PMMA but improved clinical outcomes could not be substantiated. This was graded Class III due to nonvalidated outcome measures for function and fusion.[32]

Madawi and colleagues[22] reported a randomized study of 115 patients, comparing the use of autologous iliac bone graft in 50 patients to the use of a biocompatible osteoconductive polymer implant containing PMMA in 65. The techniques varied slightly as well with the Smith-Robinson being performed in 74 patients and the Cloward technique in 41. It is not clear what the distribution of the procedure and the choice of graft were from the data reported. The authors evaluated outcome using the VAS, Odom's criteria, and radiographic analysis. The clinical outcome was identical in both groups. An increase in graft protrusion in the iliac crest group was noted ($p = 0.018$), and postoperative kyphosis was also increased in the iliac bone graft group ($p = 0.02$). Most notable was the fact that none of the patients in the biocompatible osteoconductive polymer group achieved fusion, resulting in a 100% pseudarthrosis rate. The authors concluded that the osteoconductive polymer acted as a spacer, reducing graft collapse and intersegmental kyphosis but that it did not show any sign of radiographic incorporation during a follow-up period of 2 years. The failure of fusion did not correlate with clinical outcome. This study was graded Class III due to nonvalidated outcome measures and nonblinded assessment.[22]

TABLE 4: Evidentiary summary of rhBMP and interbody arthrodesis and outcomes*

Authors & Year	Study Description	Class	Conclusions
Baskin et al., 2003	Randomized trial comparing 33 patients who underwent instrumented ACDF w/ either fibular allograft w/ rhBMP-2 or AIC bone for cervical disc disease. rhBMP-2 dose 0.4 ml of 1.5 mg/ml (0.7 mg). The patients underwent plain radiography at 6 weeks, then at 3, 6, 12, & 24 mos, & CT scans at 3 & 6 mos after surgery.	II for fusion III for outcome	Fusion rate 100% at 6, 12, & 24 mos in both groups. At 24 mos, the investigational group had mean improvement superior to that of the control group in neck disability & arm pain scores ($p < 0.03$ each). The authors concluded that in this randomized pilot study, the feasibility of using rhBMP-2 safely & effectively in the cervical spine has been demonstrated.
Lanman & Hopkins, 2004	Prospective study of 20 patients w/ instrumented ACDF at 28 levels using rhBMP-2 applied in absorbable collagen sponge in a Cornerstone-HSR (poly-lactide co-polymer) bioabsorbable spacer. Fusion evaluated plain w/ film & CT. Outcome w/ SF-36. FU not stated, but ≥6 mos.	III	Fusion rate at 3 mos: 100%. No device-related complications. The authors concluded that the Cornerstone-HSR (a bioabsorbable interbody spacer) in combination w/ Infuse (recombinant bone morphogenic protein) results in successful fusion w/in 3 mos.
Shields et al., 2006	Retrospective review of safety & complications using rhBMP-2 in 151 patients undergoing anterior cervical fusion procedures. ACDF (n = 138) or anterior cervical vertebrectomy & fusion (n = 13); rhBMP-2 doses up to 2.1 mg/level.	III	23.2% complication rate (35 patients). Postop hematoma in 15 (11 on postop Day 4 or 5, 8 required surgical evacuation). Prolonged hospital stay (>48 hrs) or hospital readmission because of swallowing/breathing difficulties or dramatic swelling w/o hematoma occurred in 13 patients. The authors concluded that a significant complication rate was associated w/ the use of a high dose of rhBMP-2 in anterior cervical fusions & suggested further investigation to determine optimal dose of rhBMP-2 to promote cervical fusion & minimize complications.
Smucker et al., 2006	Retrospective review of 234 consecutive patients undergoing anterior cervical fusion w/ & w/o rhBMP-2 over a 2-yr period at a single institution to evaluate swelling complications. Instrumentation used in 88% of the BMP group & in 97% of the no BMP group ($p = 0.02$). ACDF w/ BMP (n = 69), ACDF w/o BMP (n = 165). Statistical comparison presented but no Bayesian table included. Groups are not statistically equivalent.	II	Significant postop edema: rhBMP-2 group 27.5%, control group 3.6% ($p < 0.0001$).

	Swelling	Nonswelling
BMP	19	50
No BMP	6	159

* OR = 19(159)/6(50) = 10.1 increased risk of swelling w/ the use of BMP. The authors conclude that the off-label use of rhBMP-2 in the anterior cervical spine was associated w/ an increased rate of clinically relevant swelling events. Postop swelling events occurred at a median of 4.2 days postop.

Use of Hydroxyapatite and PEEK

McConnell et al.[26] described a randomized study in 29 patients, 13 of whom received coralline-derived hydroxyapatite, and 16 of whom received tricortical iliac crest. Both groups demonstrated improved clinical outcome without significant difference in either clinical outcome or fusion rate between the groups. There was an 89% graft fragmentation rate in the hydroxyapatite grafts compared with 11% of the autografts ($p = 0.001$). Significant graft settling also occurred in half of the hydroxyapatite grafts compared with only 11% of the autografts ($p = 0.0009$). The authors concluded that hydroxyapatite alone did not appear to adequately support the structural requirements of ACDF; however, it did not appear to alter the clinical outcome in this small study. This study was graded Class III due to uncertainty regarding allocation concealment and the absence of dynamic films in assessing fusion.[26]

Mastronardi et al.[25] published their retrospective series of 36 patients who underwent ACDF with PEEK cages supplemented with coralline hydroxylapatite. Forty-three levels were evaluated in this preliminary study. The fusion rates gradually increased to achieve a 100% success rate at 1 year, associated with a 97% good or excellent clinical outcome. The authors concluded that the use of the PEEK cage in ACDF appeared to be safe and efficient. This study was graded Class III.[25]

Cho et al.[10] reported a randomized study of 100 patients who underwent ACDF with PEEK cages in 2 groups. The first 50 patients underwent PEEK cage fusion supplemented with biphasic calcium phosphate ceramic (Triosite). The second group of 50 patients had the PEEK cage supplemented with autologous iliac bone graft. The authors assessed fusion rate radiographically. Overall fusion rates were 100% in both groups by 6 months, although the fusion rate in the Triosite group

was significantly lower than in the autograft during the first 5 months. Three patients (6%) in the iliac crest group had donor site complications. Length of hospital stay was significantly shorter in the Triosite group as was operative time. The authors concluded that fusion rates were equivalent between techniques. Avoidance of the iliac crest resulted in a shorter hospital stay, less blood loss, a shorter operative time, and no donor site complications in these series. This study was graded Class III due to lack of allocation concealment and blinded observation.[10]

Celik et al.[8] published their prospective comparison of ACDF using either allograft tricortical iliac crest or PEEK cages. They described a random assignment of patients to these two groups including 30 patients at 46 levels undergoing allograft iliac crest and 35 patients at 41 levels undergoing PEEK intervertebral cages. Fusion status and radiographic assessment including foraminal height were obtained on follow-up radiographs. The study evaluated clinical outcome using the mJOA scale score and VAS scale for arm and neck pain. The authors found no difference in terms of clinical outcome, fusion status, or Cobb angle. The allograft group did not maintain an increase in foraminal height after surgery compared with the PEEK group, which did ($p < 0.05$). The authors concluded that a radiographic increase in foraminal height was maintained with the use of the PEEK cage. This study was graded Class III due to lack of allocation concealment (suggesting bias), and the lack of blinded outcome observers.[8]

Cho and colleagues[9] described their randomized trial of 80 patients who underwent ACDF, comparing the use of PEEK cage fusion and autologous iliac crest in 40 patients each. Outcome was assessed radiographically as well as clinically (the Prolo score). The outcomes were significantly in favor of the PEEK group with 67% with an excellent outcome compared with 29% in the iliac crest group ($p < 0.05$). All patients in the PEEK group experienced fusion compared with 93% of those in the iliac crest graft group. This finding did not reach statistical significance. Complications were significantly higher in the iliac crest group, at 17.5% compared with 2.5% in the PEEK group ($p = 0.03$). The use of the PEEK cage also resulted in improved postoperative lordosis and increased foraminal height. The authors concluded that the PEEK cage technique provided a solid fusion and increased cervical lordosis and foraminal height with fewer complications then iliac crest; the authors felt that PEEK cage fusion was an adequate substitute for anterior iliac crest graft. This study was graded Class III due to questions regarding concealment of allocation and unblinded outcome observers.[9]

Use of Titanium Cages

Thome et al.[38] reported on a randomized trial of 100 patients who underwent ACDF at 127 cervical levels, comparing the use of iliac crest autograft versus a rectangular titanium cage with no graft, in 50 patients each. The study assessed fusion rates radiographically and evaluated clinical outcome using the VAS, mJOA, and Nurick grading systems. Outcome measures included Odom criteria, the Short Form-36, and Patient Satisfaction Indexes. The follow-up period was a minimum of 12 months in 95% of patients. Fusion rates were not significantly different between the groups (81 vs 74%; $p = 0.51$). There were significant differences between the overall pain at 12 months and postoperative neck pain ($p < 0.05$). Overall outcome (based on the Odom criteria) was not significantly different—79% in the iliac crest group versus 75% in the titanium cage group. The authors concluded that the fusion rates and clinical outcomes were comparable; however use of the titanium rectangle avoided donor site morbidity. This study was graded Class II because the Odom criteria has not been validated; also, although the radiographic assessment was blinded, no intraobserver reliability was calculated.[38]

In a smaller series, Thome et al.[37] published their prospective study of 36 consecutive patients who underwent anterior cervical discectomy and fusion. The first 18 received iliac crest autograft, and the second 18 received rectangular titanium cages with no autograft. Outcome was assessed using Odom criteria, patient satisfaction, and fusion at the 1-year follow-up examination. The clinical outcome according to the Odom criteria was 83% good to excellent in both groups, and patient satisfaction index was 95% in both groups as well. Fusion rates were 89% in the iliac crest group and 83% in the rectangular fusion cage group. Hip pain was present at 1 year postoperatively in 22% of patients in the autograft group, with no similar complaints in the comparison group. The authors concluded that the titanium cage without autograft constituted a safe and efficient alternative to the use of iliac crest bone autograft–based procedures. Because of study design, this was graded Class III.

Cauthen et al.[7] retrospectively reviewed their experience with BAK-C fusion cage (in 30 patients) compared with ACDF with or without plate fixation, in 32 and 26 patients, respectively. Fusion rates were equivalent statistically ($p = 0.06$). At a median follow-up of 2.4 years, 97% of the BAK/C patients, 84% of ACDF patients and 85% of the ACDF plate were fused. In this study, 6.7% of the BAK patients underwent iliac crest harvest compared with 93.8% of the ACDF patients and 50% of the ACDF plate patients. Prolonged donor site pain was only noted in the ACDF and ACDF plate patients (> 20%). The clinical outcomes by SF-36 and VAS were comparable for all groups. The authors concluded that these treatment options were similar. This study was graded Class III due to design.[7]

Hacker et al.[17] described a randomized study of 344 patients who underwent anterior cervical discectomy for radiculopathy, comparing ACDF (allograft without fixation) with the use of the BAK fusion cage. Patients were randomized 2:1 favoring the BAK device. The BAK cages were either hydroxyapatite-coated or noncoated. At the surgeon's discretion, 3% of patients underwent iliac crest graft harvesting. Data analysis included 344 patients with 1-year follow-up, and 180 of the 344 at 2 years. The authors reported that the fusion rate at 12 months was higher in the BAK group at 98% compared with 90% in the ACDF group ($p < 0.05$). They reported an increase in the complication rate for the allograft group, 20.5%, compared with 11.8% in the BAK group. There was no

difference in terms of clinical outcome as assessed by SF-36 and patient perception. None of the patients required a second operation. The authors concluded that the threaded cage resulted in a high fusion rate and overall similar outcome to the conventional bone-only fusion. This study was graded Class II due because no intraobserver reliability was reported for radiographic outcome assessment and allocation concealment was not discussed.[17]

In a smaller study with a similar design, Hacker[16] reported on 54 patients who underwent ACDF with either iliac crest autograft or titanium cage placement. Both groups had a 100% fusion rate with good or excellent outcomes similar in both groups. Chronic donor site pain was reported in the autograft group. This study was graded Class II for reasons similar to above.[16]

Use of CFCs

Ryu et al.[30] described their randomized trial of ACDF with either a CFC or allograft with plating, in 20 patients each. The study assessed radiographic outcome along with the NDI and SF-36 for clinical evaluation. The mean follow-up period was 14 months. The fusion rate was 100% in both groups at 12 and 24 months postoperatively. The groups had similar outcomes in terms of pain and disability. Postoperative donor site pain was only present in the cage group (20% at 6 weeks) but did not result in a long-term disability at 12 months. The authors concluded that ACDF with CFC appeared similar to that of ACDF with allograft and plating. This study was graded Class III. The authors did not detail the process for randomization and whether randomization was concealed. Although radiographic outcome assessment was blinded, intra- and interobserver reliability were not detailed. Finally, the criteria for fusion was bridging bony trabeculae and did not include an assessment of dynamic movement.[30]

Peolsson et al.[28] reported on a randomized series of 103 patients with ACDF using CFCs in 51 patients versus the Cloward procedure in 52, with 2-year radiographic follow-up. The study assessed clinical outcome using NDI and quality of life measures in 87% of their patients. The mean follow-up was nearly 6 years. Fusion rates at 2 years were found to be 55% in the CFC group and 85% after the Cloward procedure ($p < 0.02$). There were no significant differences in the outcome variables between the 2 groups. Clinically for both groups the pain intensity improved significantly, whereas the NDI remained unchanged. In a further subgroup analysis, those patients with a fusion resulting from the use of the CFC had the best outcome compared with patients with CFC who did not experience fusion, and compared with the Cloward procedure. This study was graded Class III due to poor allocation methods and no reported intraobserver reliability in the outcome assessment. Furthermore, the Odom criteria has not been validated as an outcome measure in this setting.[28]

Vavruch and associates[41] detailed a randomized study of 103 patients who underwent ACDF with either a CFC in 52 patients or the Cloward procedure in 51. The study reported radiographic assessment with a mean follow-up of 36 months in 86%. The study used the cervical spine functional score to obtain an independent assessment of pain. The authors found that pain and disability ratings did not differ between these 2 groups. The fusion rate was significantly higher in the Cloward procedure group (86% vs 62%, $p < 0.05$). Clinical outcomes did not differ. Postoperative donor site pain was significantly reduced in the CFC. The authors went on to conclude that clinical outcome comparing the carbon fiber cage and the Cloward procedure group was similar. The patients in the CFC group reported less donor site pain while maintaining better lordotic alignment and disc height but at the expense of a higher pseudarthrosis rate. This study was graded Class III due to poor allocation methods and no reported intraobserver reliability in the outcome assessment. Furthermore, the Odom criteria have not been validated as outcome measures in this setting.[41]

Use of rhBMP-2

Baskin et al.[3] described their randomized study in 33 patients who underwent ACDF with either fibular allograft accompanied by rhBMP-2, or iliac crest autograft. Both groups underwent anterior cervical plating and radiographic fusion, and were assessed sequentially for up to 2 years. The fusion rate was essentially 100% from 6 months onward in both groups. At the 2-year follow-up examination, the fibular rhBMP-2 group had a mean improvement in neck disability and arm pain scores compared with the control autograft group. The authors concluded that fibula graft plus rhBMP was at least equivalent to the use of autograft in instrumented fusion patients. This study was scored Class II to assess fusion and Class III for outcome because patients and surgeons were not blinded assessors. In the radiographic assessment, no intraobserver reliability was reported.[3]

Lanman and Hopkins[20] reported on 20 patients undergoing ACDF at 28 levels using rhBMP-2 combined with an allograft spacer. The study assessed fusion radiographically and assessed clinical outcomes using the SF-36. They described a 100% fusion rate at 3 months with no device-related complications. The authors concluded that rhBMP-2, in combination with the bioabsorbable spacer, could result in successful fusion within 3 months. Boakye et al.[5] retrospectively reviewed 24 cases of ACDF using PEEK spacers with rhBMP-2. The authors reported good to excellent clinical outcomes in 95% of patients. Complications included 1 laryngeal nerve palsy, 1 C-5 root paresis, one cerebrospinal fluid leak, 2 issues of dysphagia, and 1 medical death felt unrelated to the surgery. The authors concluded that in their experience, BMP led to good clinical outcome with acceptable complications and avoided the additional complications associated with iliac crest harvest. Both of these studies were graded Class III.[20]

Shields and colleagues[34] detailed their experience with rhBMP-2 in 151 patients who underwent anterior cervical fusion procedures, focusing primarily on safety issues. Complications occurred in 35 (23.2%) of their 105 patients, including 15 postoperative hematomas, and 13 patients (9.4%) with extended hospital stay or readmission because of swelling at the operative site in the absence of hematoma. The authors concluded that a significant complication rate may be associated with the use of high dose

of rhBMP-2 as used in their clinical experience. The dosage in their study was up to 2.1 mg per level. This study was graded Class III.[34]

Smucker et al.[35] reviewed 234 consecutive patients undergoing ACDF with (69 patients) and without (165 patients) use of rhBMP-2 over a 2-year period to assess perioperative edema. Using a contingency table, the authors reported an edema risk of 27.5% with rhBMP-2 and 3.6% without ($p < 0.0001$). The odds ratio for edema associated with rhBMP-2 was 10.1. The authors concluded that the use of rhBMP-2 was associated with an increased rate of clinically relevant swelling events. The dose of rhBMP-2 used in this study was 1.5 mg per level. This study was graded Class II.

Posterior Cervical Arthrodesis

Sawin et al.[31] reported on the use of autograft bone in posterior cervical fusions. Their analysis was retrospective and included a variety of fusion regions. The entire study contrasted 300 patients with rib autograft with 300 patients who had iliac crest grafts (248 for anterior procedures and 52 for posterior procedures). Fusion criteria included radiographic evidence of bony trabeculae and long-term stability on flexion/extension radiographs. The authors used Fisher's exact test for statistical comparison. Focusing on the comparison of the 300 patients undergoing rib grafting for posterior procedures with the 52 who had iliac crest grafts for posterior fusions, their data showed no significant differences in the rate of fusion between rib (98%) and iliac crest (92%; $p = 0.056$). Donor site morbidity was greater in iliac crest group than the rib graft group with 3.8% of patients experiencing complications in the rib graft group versus 25.3% in the iliac crest group. The authors concluded that the fusion rate combined with donor site morbidity for rib autograft compared favorably with iliac crest when used in the cervical spine. This study was graded Class III due to methodology.

Summary

Class II evidence indicates that either autograft bone harvested from iliac crest, allograft bone from either cadaveric iliac crest or fibula, or titanium cages and rectangular fusion devices, with or without autologous graft or substitute are excellent interbody treatment options for obtaining cervical arthrodesis. There is an expected autograft fusion rate for noninstrumented single-level fusions better than 80% and for 2-level fusion of better than 70%. With allograft, the expected fusion rate for noninstrumented single-level fusion is > 80%, and is > 50% for 2-level fusion. The use of titanium cages carries an expectation of a fusion rate of > 70%, and often > 90% with avoidance of donor site morbidity.

In choosing a graft strategy, no single type of graft has not proven consistently superior to the other. Class III evidence suggests that the surgeon consider the increased rate of subsidence with allograft but also understand that subsidence does not correlate with clinical outcome. Class III evidence also suggests that the surgeon factor in the incidence of donor pain and decrease in patient satisfaction reported with the harvest of autograft iliac crest graft.

If alternatives to auto- and allograft are preferred, therapeutic options are as follows: PEEK may be considered with or without the use of hydroxyapatite after ACDF. There is an expectation of fusion rates > 90% with fewer complications due to the absence of graft harvesting (Class III). Carbon fiber cages may be considered as well with fusion rates ranging from 55 to 62% in the larger studies (Class III). Polymethyl-methylmethacrylate may be considered to preserve intervertebral distraction after discectomy, but is a poor fusion substrate (Class II). All of the above options appear to have similar clinical outcomes equivalent to the use of bone.

Utilization of rhBMP-2 may be considered as an adjunct to promote fusion with rates equivalent to autograft. However, the high complication rate argues against its routine use for cervical arthrodesis. The surgeon must be aware that this use of rhBMP-2 is currently off-label, and its use in the cervical spine carries a reported complication rate of up to 27% (for edema), compared with 3% for a standard approach. This significant difference prompted a public health notification by the Food and Drug Administration (http://www.fda.gov/cdrh/safety/070108-rhbmp.html).

Key Issues for Future Investigation

Key issues for the future include a focused examination of the correlation of radiographic fusion with clinical outcome. In undertaking this goal, more consistent outcome measures need to be validated and used. Given the generally high rates of improved clinical outcome with anterior cervical discectomy and fusion, regardless of methodology, the evaluation of medical-economic factors may play an important role in future studies. Biological agents such as rhBMP-2 are exciting as potential adjuncts to improve fusion rates and clinical outcomes but carry a concern for increasing complication rates. The use of these agents in the cervical spine warrants careful scrutiny and will be the basis for ongoing clinical study.

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