



Bone Void Fillers

A Technology Overview

**Adopted by the American Academy of Orthopaedic Surgeons
Board of Directors
March 8, 2010**

This *Technology Overview* was prepared by an AAOS physician task force using systematic review methodology, and summarizes the findings of studies published as of October 8, 2009 on bone void fillers. As a summary, this document does not make recommendations for or against the use of bone void fillers. It should not be construed as an official position of the American Academy of Orthopaedic Surgeons. Readers are encouraged to consider the information presented in this document and reach their own conclusions concerning the use of synthetic bone void fillers.

The American Academy of Orthopaedic Surgeons has developed and is providing this *Technology Overview* as an educational tool. Patient care and treatment should always be based on a clinician's independent medical judgment given the individual patient's clinical circumstances.

Disclaimer

This technology overview was developed by an AAOS physician volunteer task force based on a systematic review of the current scientific and clinical information and accepted approaches to treatment and/or diagnosis. This technology overview is not intended to be a fixed protocol, as some patients may require more or less treatment or different means of diagnosis. Clinical patients may not necessarily be the same as those found in a clinical trial. Patient care and treatment should always be based on a clinician's independent medical judgment, given the individual patient's clinical circumstances.

Disclosure Requirement

In accordance with AAOS policy, all individuals whose names appear as authors or contributors to this technology overview filed a disclosure statement as part of the submission process. All panel members provided full disclosure of potential conflicts of interest prior to developing the key questions contained within this technology overview.

Funding Source

This technology overview was funded exclusively by the American Academy of Orthopaedic Surgeons who received no funding from outside commercial sources to support the development of this document.

FDA Clearance

Some drugs or medical devices referenced or described in this technology overview may not have been cleared by the Food and Drug Administration (FDA) or may have been cleared for a specific use only. The FDA has stated that it is the responsibility of the physician to determine the FDA clearance status of each drug or device he or she wishes to use in clinical practice.

Copyright

All rights reserved. No part of this technology overview may be reproduced, stored in a retrieval system, or transmitted, in any form, or by any means, electronic, mechanical, photocopying, recording, or otherwise, without prior written permission from the AAOS.

Published 2010 by the American Academy of Orthopaedic Surgeons

6300 North River Road

Rosemont, IL 60018

First Edition

Copyright 2010 by the American Academy of Orthopaedic Surgeons

Bone Void Fillers

A Technology Overview

SUMMARY OF PUBLISHED RESULTS

The available literature on synthetic bone void fillers is not expansive enough to be conclusive. Bearing this in mind, summaries of the data that pertain to the five key questions addressed in this Technology Overview are summarized below:

KEY QUESTION 1

Do patients treated with synthetic bone void fillers (alone) as a graft material have different clinical results when compared to patients treated with iliac crest bone grafts (autografts but not local autograft) in a posterolateral spine fusion?

To answer this question we included one Level II study (n= 40 patients) and one Level IV study (n= 90 patients) that compared synthetic bone void fillers to autogenous iliac crest grafts. The Level II study addressed adolescent patients with idiopathic scoliosis. The level IV study addressed adult patients diagnosed with degenerative spondylolisthesis, isthmic spondylolisthesis, disk herniation with instability, or canal stenosis. In addition, the studies reported different surgical instrumentation. Outcomes for these studies are summarized by patient population.

Of the five outcomes reported for adolescents, there was a statistically significant difference favoring synthetic bone void filler in overall VAS pain at hospital discharge but not at longer term follow-up. Donor site pain, a common complaint in patients treated with autogenous iliac crest grafting, was also reported at hospital discharge and 48 months postoperatively; the difference in overall VAS pain scores was statistically significantly improved at 48 months. Adolescents had more intraoperative complications in the iliac crest bone graft group.

The adult population in the Level IV study was reported to have operating times and blood loss that was statistically significant in favor of synthetic bone void filler. This study also reported that “the roentgenographic analysis appeared insufficient to determine the quality of fusion”.

KEY QUESTION 2

Do patients treated with synthetic bone void fillers that are supplemented with autograft have different clinical results than patients treated with local autografts alone in a posterolateral spine fusion?

Our literature searches did not identify any peer reviewed data that addressed this question.

KEY QUESTION 3

Do patients with metaphyseal defects as a result of fractures have different clinical outcomes if they are treated with synthetic bone void filler, allograft, or autograft in the defect?

We included three Level II studies (n=161 patients) that compared synthetic bone void filler to autogenous bone in patients with metaphyseal defects as a result of fractures. There was no statistically significant difference between groups in any of the eight outcome measures. Two studies reported donor site pain, a common complain of patients undergoing autogenous iliac crest grafting. Dickson, et al. reported that no patients experienced donor site pain 6 and 12 months after surgery. Russell, et al. reported that all patients had donor site pain at hospital discharge. Of the eighteen complications reported, there was a statistically significant difference between groups in two complications (implant site infection and stitch abscess) both in favor of the autograft group.

Our literature searches did not identify any data that compare synthetic bone void fillers to allografts.

KEY QUESTION 4

Do patients with contained defects from tumor (or other benign bone cysts) have different clinical outcomes when treated with synthetic bone void filler, autograft, or allograft?

Our literature searches did not identify any peer reviewed data that addressed this question.

KEY QUESTION 5

Do patients with contained defects from peri-prosthetic bone loss have different clinical outcomes when treated with synthetic bone void filler, allograft, or autograft?

Our literature searches did not identify any peer reviewed data that addressed this question.

Table of Contents

BONE VOID FILLERS	1
A TECHNOLOGY OVERVIEW	1
Summary of Published Results	3
Key Question 1	3
Key Question 2	3
Key Question 3	4
Key Question 4	4
Key Question 5	4
TABLE OF CONTENTS	5
I. INTRODUCTION	7
II. METHODS	8
Methods Overview.....	8
Included Articles.....	8
Quality of the Literature	8
Outcomes Considered.....	8
Minimal Clinically Important Improvement.....	9
III. KEY QUESTIONS AND SUPPORTING EVIDENCE	11
Key Question 1	11
Studies Considered	15
Study Quality	16
Study Data	18
Key Question 2	19
Key Question 3	20
Studies Considered	27
Study Quality	28
Study Data	31
Key Question 4	32
Table 20 Excluded Studies	33
Key Question 5	34
Disclaimer.....	35
IV. APPENDIXES	36
Appendix I	36
Inclusion Criteria	36
Appendix II	37

Databases Searched and Search Strategies	37
Appendix III.....	39
Study Attrition	39
Appendix IV	40
Study Quality Checklists	40
Appendix V	42
Documentation of Approval	42
AAOS Bodies that Approved this Technology Overview	42
Appendix VI.....	43
Task Force	43
Conflict of Interest.....	44
Appendix VII	45
Excluded Studies	46

List of Tables

Table 1 MCII of outcomes.....	9
Table 2 Descriptive terms for results with MCII.....	9
Table 3. Bone Void Filler vs. Autogenous Iliac Crest – Patient Characteristics/Surgery Detail.....	12
Table 4. Bone Void Filler vs. Autogenous Iliac Crest – Summary Results.....	13
Table 5. Donor site pain measured on the VAS in the Autograft group.....	14
Table 6. Bone Void Filler vs. Autogenous Iliac Crest - Results Complications	14
Table 7. Included Studies.....	15
Table 8. Excluded Studies.....	15
Table 9. Study Quality	16
Table 10. Study Data.....	18
Table 11 Excluded Studies.....	19
Table 12. Bone void filler for fractures- patient characteristics/surgery details.....	21
Table 13 Bone void filler for fractures- results.....	22
Table 14. Percent of patients reporting Iliac Crest Donor Site Pain.....	24
Table 15 Bone void filler vs. autograft - Complications	24
Table 16. Included Studies.....	27
Table 17. Excluded Studies.....	27
Table 18. Study quality.....	28
Table 19. Study data	31
Table 20 Excluded Studies.....	33

I. INTRODUCTION

Synthetic bone void fillers (SBVF) are available for a variety of indications in orthopaedic surgery. The number of available products and information complicates surgical decisions regarding bone graft substitutes. Graft substitutes may be grouped as synthetic (predominantly osteo-conductive) or biological (predominantly osteo-inductive). The scope of this Technology Overview is to evaluate the synthetic or predominantly osteo-conductive graft materials. The task force that prepared the present report posed question 1 to address the use of synthetic bone void fillers alone. We posed question 2 to determine if synthetic bone void fillers could work as graft extenders and thus eliminate the need for Iliac Crest Bone Graft. Questions 3, 4 and 5 included the use of allografts as a comparison because clinical results with allografts are perceived as much closer to autografts in these areas of the spine. The task force limited the scope to materials that had some degree of structural integrity to support loading in the indications of fracture, tumor reconstruction and periprosthetic reconstruction and as such, this overview does not include demineralized products.

Volunteers were sought to assemble a task force to frame questions and provide guidance for this Technology Overview. These volunteers were experienced in the use of synthetic bone void fillers in subspecialty areas of spine, trauma, oncology, and adult reconstruction. This technology overview was done in an attempt to inform the membership of the current knowledge of clinical results using synthetic bone void fillers for common clinical problems.

II. METHODS

METHODS OVERVIEW

This report was developed using the methods of a systematic review. We began by having a panel of physicians frame five key questions, and next developed rules (inclusion criteria) for determining what information we would include (The full list of criteria appears in Appendix I). Finally, we conducted comprehensive literature searches (Appendix II) to ensure that the data we considered are not biased in favor of any particular point of view. Thereafter, we evaluated the quality of the relevant studies, including their methods of analysis, considered their results, and summarized this information in graphs and tables.

INCLUDED ARTICLES

Our searches identified 1508 citations. Of these, five met the inclusion criteria and were used to address two of the five key questions. This information forms the dataset that we used to address the key questions.

We emphasize that this is a Technology Overview of synthetic bone void fillers alone. Therefore, our dataset does not include studies that combined bone void fillers with bone morphogenic proteins or demineralized bone matrices.

QUALITY OF THE LITERATURE

Assessing the quality of evidence is an important step in a systematic review. Readers can have more confidence in the results of high quality studies than low quality studies. To assess quality, we used a Levels of Evidence System. Many such systems examine only study design. Design alone, however, does not adequately reflect the quality of a study. Therefore, we assessed study quality using a system that considers not only design, but also several aspects of how well a study was conducted. Details about this system are provided in Appendix I. We evaluated quality on a per outcome basis rather than a per study basis because quality is not necessarily the same for all outcomes and all follow-up times reported in a study.

We assessed the quality of treatment studies using a two step process. First, we assigned a level of evidence to all results reported in a study based solely on that study's design. Accordingly, all data presented in randomized controlled trials were initially categorized as Level I evidence, all results presented in non-randomized controlled trials and other prospective comparative studies were initially categorized as Level II. We next assessed each outcome at each reported time point using a quality questionnaire and, when quality standards were not met, downgraded the level of evidence (for this outcome at this time point) by one level.

OUTCOMES CONSIDERED

This overview only includes patient-oriented outcomes. This is because patient-oriented outcomes are outcomes that matter to patients and indicate, without the need for extrapolation, whether an intervention is effective.¹ Patient-oriented outcomes include

outcomes like pain, quality of life, ability to perform activities of daily living, and revision surgery. Unlike use of patient-oriented outcomes, use of surrogate outcomes such as imaging results or laboratory test results can be misleading, and can even make harmful treatments look beneficial.²

Because donor site pain is a common complaint among patients treated with an autogenous iliac crest graft, we have reported donor site pain where available. We have also reported any other complications that were reported by the authors.

MINIMAL CLINICALLY IMPORTANT IMPROVEMENT

Wherever possible, we considered the effects of treatments in terms of the minimal clinically important improvement (MCII) in addition to whether their effects were statistically significant. The MCII is the smallest clinical change that is important to patients, and recognizes the fact that there are some treatment-induced statistically significant improvements that are too small to matter to patients. The values we used for MCII are derived from a published study investigating the Visual Analogue Scale, the Numerical Rating Scale, the Oswestry Disability Index, and the Roland Disability Questionnaire.³

Table 1 MCII of outcomes

Outcome Measure	MCII (points)
Pain – VAS (0-100)	15

The associated descriptive terms in this guideline and the conditions for using each of these terms, are outlined in the following table:

Table 2 Descriptive terms for results with MCII

Descriptive Term	Condition for Use
Clinically Important	Statistically significant and lower confidence limit > MCII
Possibly Clinically Important	Statistically significant and confidence intervals contain the MCII
Not Clinically Important	Statistically significant and upper confidence limit < MCII
Negative	Not statistically significant and upper confidence limit < MCII
Inconclusive	Not statistically significant but confidence intervals contain the MCII

To determine if a study was sufficiently powered to detect the MCII, we consulted Cohen, J., “Statistical Power Analysis for the Behavioral Sciences”, 1st Edition, Lawrence Erlbaum Associates, Hillsdale (2nd Edition, 1988). For these calculations, we assumed that the statistical test was a 2-tailed paired t-test on pre- and post-treatment results and determined whether the number of patients in the study was sufficient to detect a significant difference while assuming an alpha of 0.05 as the significance level and 80% power. All outcomes that are not statistically significant with the exception of two (malunion in Russel et al.⁴ and delayed deep wound infection in Fujibayashi, et al.⁵) are underpowered.

III. KEY QUESTIONS AND SUPPORTING EVIDENCE

KEY QUESTION 1

Do patients treated with synthetic bone void fillers (alone) as a graft material have different clinical results when compared to patients treated with iliac crest bone grafts (autografts but not local autograft) in a posterolateral spine fusion?

To answer this question we included one Level II⁶ study and one Level IV⁵ study that compared synthetic bone void fillers to autogenous iliac crest grafts (please see Table 9 for further information about the quality of these studies). The Level II study addressed adolescent patients with idiopathic scoliosis. The level IV study addressed adult patients diagnosed with degenerative spondylolisthesis, isthmic spondylolisthesis, disk herniation with instability, or canal stenosis (Table 3). In addition, the studies report different surgical instrumentation. Outcomes for these studies are summarized by patient population. Please see Table 4, Table 5, Table 6, and Table 10 for the results of these studies.

Of the five outcomes reported for adolescents, there was a statistically significant but not clinically important difference favoring synthetic bone void filler in overall VAS pain at hospital discharge but not at longer term follow-up (Table 4). Donor site pain, a common complaint in patients treated with autogenous iliac crest grafting, was also reported at hospital discharge and 48 months postoperatively; the difference in overall VAS pain scores was statistically significantly improved but not clinically important at 48 months (see Table 5). Adolescents had more intraoperative complications in the iliac crest bone graft group (Table 6).

The adult population in the Level IV study was reported to have operating times and blood loss that was statistically significant in favor of synthetic bone void filler (Table 4). There was also a 10.3 point difference on the JOA scale in adults at 33.5 months in favor of the synthetic bone void filler group; however, there was not enough data available in the study to determine whether this difference was statistically significant (Table 5). This study also reported that “the roentgenographic analysis appeared insufficient to determine the quality of fusion”.⁵ The raw data extracted from each study can be found in Table 10.

Table 3. Bone Void Filler vs. Autogenous Iliac Crest – Patient Characteristics/Surgery Detail

Author	LOE	N	Age	Comparison (Type of Bone Void Filler)	Instrumentation	Surgery	Indication for Surgery
Lerner, et al. 2009	II	40	18.5 yrs autograft 19.5 yrs BVF	ultra porous β - tricalcium phosphate versus autograft from the posterior iliac crest	Posterior corrective using titanium pedicle screw and rod system and fusion with additional grafting	Posterior Correction and Fusion	Adolescent Idiopathic Scoliosis
Fujibayashi, et al. 2001	IV	90	55.3 yrs	HAP-TCO, a biphasic calcium phosphate ceramic containing hydroxyapatite and beta-tricalcium phosphate in microporous form versus autogenous iliac crest	Transpediculare instrumentation	Single level posterolateral spinal fusion (16 cases with isthmic spondylolisthesis and severe instability required a combination of posterior underbody fusion with designed HAP-TCP)	Degenerative spondylolisthesis, isthmic spondylolisthesis, Disk herniation with instability, Canal stenosis

Table 4. Bone Void Filler vs. Autogenous Iliac Crest – Summary Results

Author	LOE	N	Outcome	Duration	Results
Lerner, et al. 2009	II	40	Difference between groups in overall VAS	Hospital Discharge	● ‡ BVF
Lerner, et al. 2009	II	40	Difference between groups in overall VAS	48 months	○
Lerner, et al. 2009	II	40	Difference between groups in VAS back	Hospital Discharge	○
Lerner, et al. 2009	II	40	Difference between groups in VAS back	48 months	○
Lerner, et al. 2009	II	40	Use of analgesics	Hospital Discharge	○*
Lerner, et al. 2009	II	40	Use of analgesics	48 months	○*
Lerner, et al. 2009	II	40	Operating Time	Intraoperative	○
Lerner, et al. 2009	II	40	Blood Loss	Intraoperative	○
<hr/>					
Fujibayashi, et al 2001	IV	90	Operating Time	Intraoperative	● BVF
Fujibayashi, et al 2001	IV	90	Blood Loss	Intraoperative	● BVF
Fujibayashi, et al 2001	IV	90	JOA	33.9 months (range 26-50 months)	mean change 10.3 points**

*= AAOS calculated using arcsin transform

●BVF= statistically significant in favor of Bone Void Filler group

○= No statistically significant difference between groups

**= There was not enough data provided to determine whether results are statistically significant.

●‡= Statistically significant but not clinically important

Table 5. Donor site pain measured on the VAS in the Autograft group

Author	LoE	N	Outcome	Duration	Mean (SD)
Lerner, et al. 2009	II	40	VAS Pain Iliac Crest- Change from hospital discharge to 48 months	48 months	$p= 0.003^*$ BVF

*AAOS calculated using t-test

BVF= Statistically significant in favor of Bone Void Filler Group but not clinically important

Table 6. Bone Void Filler vs. Autogenous Iliac Crest - Results Complications

Author	LoE	N	Complication	Duration	Results
Lerner, et al. 2009	II	40	Intraoperative Complications: Prolonged wake-up test (>30 minutes) including one patient with extensive bleeding diathesis and blood loss	In hospital	$p=0.001^*$ Autograft
Lerner, et al. 2009	II	40	Pleural Effusion without the need for pleuracentesis	48 months	$p=.63^*$
Lerner, et al. 2009	II	40	Subcutaneous seroma requiring puncture	48 months	$p= 1^*$
Lerner, et al. 2009	II	40	Revision of one screw which was placed in close proximity to the aorta	48 months	$p=0.15^*$
Lerner, et al. 2009	II	40	Pseudarthrosis which was revised	48 months	$p=0.15^*$
Fujibayashi, et al. 2001**	III	90	Delayed deep wound infection resulting in removal of the instrument and graft bone	1 year	$p=0.23^*$

* AAOS Calculated using arcsin transform

Autograft= Statistically Significant in favor of Autograft group

** Per this study⁵, page 216, “Roentgenographic analysis appeared insufficient to determine the quality of fusion.”

STUDIES CONSIDERED

Table 7. Included Studies

Author	Title
Fujibayashi, et al. 2001	Lumbar posterolateral fusion with biphasic calcium phosphate ceramic
Lerner, et al. 2009	A level-1 pilot study to evaluate of ultra porous beta-tricalcium phosphate as a graft extender in the posterior correction of adolescent idiopathic scoliosis

Table 8. Excluded Studies

Author	Title	Reason for Exclusion
McConnell, et al. 2003	A prospective randomized comparison of coralline hydroxyapatite with autograft in cervical interbody fusion	Less than 80% underwent posterolateral fusion
Neen, et al. 2006	Healos and bone marrow aspirate used for lumbar spine fusion: a case controlled study comparing healos with autograft	Cervical Interbody Fusion

STUDY QUALITY

Table 9. Study Quality

Author	Outcome	Duration	Level of Evidence	RCT-Stochastic randomization	RCT- Allocation concealment	RCT- Patients blinded	RCT-Assessor blinded	RCT-80% Follow-up	RCT-Equal outcomes at entry	Retro Comparative- Less than 20% completion rate difference	Retro Comparative- Groups treated concurrently	Retro Comparative- Same Treatment in both groups	Retro Comparative- Same outcomes measured in both groups	Retro Comparative- Same follow-up time in both groups	Retro Comparative- Follow-up 80% in both groups	Retro Comparative- Patients treated at the same center
Lerner, et al. 2009	Difference between groups in VAS back	48 months	II	NR	Y	NR	NR	Y	Y	NA	NA	NA	NA	NA	NA	NA
Lerner, et al. 2009	Use of analgesics	Hospital Discharge	II	NR	Y	NR	NR	Y	Y	NA	NA	NA	NA	NA	NA	NA
Lerner, et al. 2009	Use of analgesics	48 months	II	NR	Y	NR	NR	Y	Y	NA	NA	NA	NA	NA	NA	NA
Lerner, et al. 2009	Operating Time	Intraoperative	II	NR	Y	NR	NR	Y	Y	NA	NA	NA	NA	NA	NA	NA
Lerner, et al. 2009	Blood Loss	Intraoperative	II	NR	Y	NR	NR	Y	Y	NA	NA	NA	NA	NA	NA	NA
Fujibayashi S, et al. 2001	Operating Time	Intraoperative	IV	NA	NA	NA	NA	NA	NA	Y	N	Y	Y	N	Y	Y
Fujibayashi S, et al. 2001	Blood Loss	Intraoperative	IV	NA	NA	NA	NA	NA	NA	Y	N	Y	Y	N	Y	Y

Author	Outcome	Duration	Level of Evidence	RCT-Stochastic randomization	RCT- Allocation concealment	RCT- Patients blinded	RCT-Assessor blinded	RCT-80% Follow-up	RCT-Equal outcomes at entry	Retro Comparative- Less than 20% completion rate difference	Retro Comparative- Groups treated concurrently	Retro Comparative- Same Treatment in both groups	Retro Comparative- Same outcomes measured in both groups	Retro Comparative- Same follow-up time in both groups	Retro Comparative- Follow-up 80% in both groups	Retro Comparative- Patients treated at the same center
Fujibayashi S, et al. 2001	JOA	33.9 months	IV	NA	NA	NA	NA	NA	NA	Y	N	Y	Y	N	Y	Y

Y= Yes

N= No

NR= Not reported in study

NA= Not applicable to specific study

STUDY DATA

Table 10. Study Data

Author	LOE	N	Outcome	Duration	Group Result		Results
					BVF	AICG	
Lerner, et al. 2009	II	40	Difference between groups in overall VAS	Hospital Discharge	2.9 ± 3	3.9±4	p= 0.036 BVF
Lerner, et al. 2009	II	40	Difference between groups in overall VAS	48 months	1.9 ± 1	2.3 ±2	p= .173
Lerner, et al. 2009	II	40	Difference between groups in VAS back	Hospital Discharge	2.9 ± 3	3.5 ± 4	p= 0.169
Lerner, et al. 2009	II	40	Difference between groups in VAS back	48 months	1.9 ± 1	1.9 ± 1	p= 0.368
Lerner, et al. 2009	II	40	Use of analgesics	Hospital Discharge	9	12	p= 0.344*
Lerner, et al. 2009	II	40	Use of analgesics	48 months	4	2	p= 0.38*
Lerner, et al. 2009	II	40	Operating Time	Intraoperative	212.3 ± 205	222.5 ± 227	p= 0.167
Fujibayashi, et al 2001	II	90	Operating Time	Intraoperative	143± 31.4	158± 29.7	p= 0.03 BVF
Lerner, et al. 2009	II	40	Blood Loss	Intraoperative	1124	1020	p=0.403
Fujibayashi, et al 2001	II	90	Blood Loss	Intraoperative	291.2± 191.6	416.4± 309.3	p= 0.04 BVF
Fujibayashi, et al 2001	II	90	JOA	33.9 months (range 26-50 months)	NR	NR	mean change 10.3 points

AICG= Autogenous Iliac Crest Graft

BVF= Statistically significant in favor of Synthetic Bone Void Filler

*= AAOS calculated using the arcsine transform

KEY QUESTION 2

Do patients treated with synthetic bone void fillers that are supplemented with autograft have different clinical results than patients treated with local autografts alone in a posterolateral spine fusion?

Our literature searches did not identify any peer reviewed data that addresses this question.

This question specifically addresses the comparison of synthetic bone void fillers supplemented with autograft to local autograft alone. No studies that examined this specific comparison were identified.

Table 11 Excluded Studies

Author	Title	Reason for Exclusion
Moro-Barrero, et al. 2007	Radiographic analysis of fusion mass using fresh autologous bone marrow with ceramic composites as an alternative to autologous bone graft	Both treatment group and study group are in the same patients- Confounded study design
Chang, et al. 2008	Local autogenous bone mixed with bone expander: an optimal option of bone graft in single-segment posterolateral lumbar fusion	Autograft plus BVF vs. iliac crest
Chen, et al. 2005	The fusion rate of calcium sulfate with local autograft bone compared with autologous iliac bone graft for instrumented short-segment spinal fusion	BVF plus local autograft vs. iliac crest
Dai, et al. 2008	Single-level instrumented posterolateral fusion of lumbar spine with beta-tricalcium phosphate versus autograft: a prospective, randomized study with 3-year follow-up	BVF plus Local Bone vs. Iliac Crest
Gunzburg, et al. 2002	Use of a novel beta-tricalcium phosphate-based bone void filler as a graft extender in spinal fusion surgeries	Does not answer the question: non-comparative data
Hsu, et al. 2005	Coralline hydroxyapatite and laminectomy-derived bone as adjuvant graft material for lumbar posterolateral fusion	Iliac Crest vs. three different combinations
Gitelis, et al. 2001	Use of a calcium sulfate-based bone graft substitute for benign bone lesions	Not local autograft
Bose, et al. 2003	Results of a Calcium Sulfate Bone Graft Substitute Used to Promote Posterolateral Lumbar Spinal Fusion	Not local autograft

KEY QUESTION 3

Do patients with metaphyseal defects as a result of fractures have different clinical outcomes if they are treated with synthetic bone void filler, allograft, or autograft in the defect?

Three Level II studies^{4, 7, 8} compared synthetic bone void filler to autograft in patients with metaphyseal defects (periarticular, metaphyseal bone loss) as a result of fracture. Information about the study populations and the surgery details can be found in Table 12. Please see Table 18 for quality information and Table 12 through Table 15 and Table 19 for results reported in each of these studies.

Of the eight outcome measures reported, there was no statistically significant difference between synthetic bone void fillers and autografts (Table 13). Twelve month outcomes reported by Dickson, et al.¹ were not included in this Overview because patient loss to follow up resulted in one group with fewer than 10 patients. Patient enrollment greater than ten is an *a priori* inclusion criteria. Detailed information regarding inclusion criteria can be found in Appendix I.

Donor site pain was recorded at hospital discharge in one study and at 6 and twelve months in another. 100% of patients had donor site pain at discharge, however, at both 6 and twelve months after surgery, 0% of patients enrolled in the Dickson, et al.⁷ study reported pain at the donor site (Table 14).

Of 18 reported complications, 2 were statistically different in favor of the autograft group, stitch abscess and implant site infection (Table 15).

We did not identify any studies that compare synthetic bone void filler to allograft in this patient population.

Table 12. Bone void filler for fractures- patient characteristics/surgery details

Author	LOE	N	Age (mean)	Comparison	Fixation	Indication for Surgery
Dickson, et al. 2001	II	29	42.43	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	Internal or External*	Type I fracture of the humerus, radius, ulna, femur, tibia, or calcaneus who had a traumatic bone void
Bucholz, et al. 1989	II	40	36.7-37.5	Autogenous bone graft vs. porous hydroxyapatite	Internal Fixation	Closed tibial fracture associated metaphyseal defects
Russell, et al. 2008	II	92	43	Alpha BSM versus autogenous iliac bone graft	Internal Fixation	Acute, closed, unstable fracture of the proximal part of the tibia

* Fixation based on physician preference

Table 13 Bone void filler for fractures- results

Author	LoE	N	Comparison	Duration	Outcome	Results
Dickson, et al. 2001	II	29	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	6 months	Fracture Healing- completely healed	○
Dickson, et al. 2001	II	29	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	6 months	Fracture Healing- Partial Healed	○
Dickson, et al. 2001	II	29	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	6 months	Fracture Healing Nonunion	○
Dickson, et al. 2001	II	29	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	6 months	Pain at the defect site- None	○
Dickson, et al. 2001	II	29	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	6 months	Pain at the defect site- severe	○
Dickson, et al. 2001	II	29	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	6 months	Function of the fractured limb- maximum	○

Author	LoE	N	Comparison	Duration	Outcome	Results
Dickson, et al. 2001	II	29	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	6 months	Overall Success	○
Bucholz, et al. 1989	IV	40	Autogenous bone graft vs. porous hydroxyapatite	15.4- 34.5 months	Knee pain	○
Bucholz, et al. 1989	IV	40	Autogenous bone graft vs. porous hydroxyapatite	15.4- 34.5 months	Return to pre-injury employment	○

*= AAOS Calculated arcsine transform

○= No statistically significant difference

Table 14. Percent of patients reporting Iliac Crest Donor Site Pain

Author	LoE	N	Outcome	Duration	Mean (SD)
Dickson, et al. 2001	II	15	Donor site Pain	6 months	0%
Dickson, et al. 2001	II	12	Donor site Pain	12 months	0%
Russell, et al. 2008	II	38	Donor site Pain	Immediately following surgery	100%

Table 15 Bone void filler vs. autograft - Complications

Author	LoE	N	Comparison	Complication	Results
Dickson, et al. 2001	II	30	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	Ankylosis	$p= 0.13^*$
Dickson, et al. 2001	II	30	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	Stitch Abscess	$p= 0.03^*$ AIC
Dickson, et al. 2001	II	30	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	Implant site infection	$p=0.03^*$ AIC
Dickson, et al. 2001	II	30	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	wound drainage	$p= 0.88^*$

Author	LoE	N	Comparison	Complication	Results
Dickson, et al. 2001	II	30	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	carpal tunnel	$p= 0.13^*$
Dickson, et al. 2001	II	30	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	surgical site infection	$p= 0.13^*$
Dickson, et al. 2001	II	30	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	Skin necrosis	$p= 0.18^*$
Dickson, et al. 2001	II	30	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	granulation	$p= 0.18^*$
Dickson, et al. 2001	II	30	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	pin-track infection	$p= 0.18^*$
Dickson, et al. 2001	II	30	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	graft site infection	$p= 0.18^*$
Dickson, et al. 2001	II	30	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	fracture blister	$p= 0.18^*$

Author	LoE	N	Comparison	Complication	Results
Dickson, et al. 2001	II	30	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	pain at graft site harvest	$p= 0.18^*$
Russell, et al	II	92	alpha BSM versus autogenous iliac bone graft	Malunion	$p= 0.50^*$
Bucholz, et al. 1989	II	40	Autogenous bone graft vs. porous hydroxyapatite	loss of reduction	$p= 0.28^*$
Bucholz, et al. 1989	II	40	Autogenous bone graft vs. porous hydroxyapatite	painful, prominent plates	$p=1.00^*$
Bucholz, et al. 1989	II	40	Autogenous bone graft vs. porous hydroxyapatite	loose screws	$p= 0.28^*$
Bucholz, et al. 1989	II	40	Autogenous bone graft vs. porous hydroxyapatite	deep wound infection	$p= 0.54^*$
Bucholz, et al. 1989	II	40	Autogenous bone graft vs. porous hydroxyapatite	contiguous septic knee	$p= 0.15^*$

*= AAOS Calculated arcsine transform

AIC= In favor of Autogenous Iliac Crest Group

STUIDES CONSIDERED

Table 16. Included Studies

Author	Title
Dickson, et al. 2002	The use of hydroxyapatite cement for traumatic metaphyseal bone void filling
Bucholz, et al. 1989	Interporous hydroxyapatite as a bone graft substitute in tibial plateau fractures
Russell, et al. 2008	Comparison of autogenous bone graft and endothermic calcium phosphate cement for defect augmentation in tibial plateau fractures. A multicenter, prospective, randomized study

Table 17. Excluded Studies

Author	Title	Reason for Exclusion
Cornell, et al. 1991	Multicenter trial of Collagraft as bone graft substitute	C-porous calcium phosphate ceramic plus autogenous bone marrow aspirated from the iliac crest(Collagen) vs. Autogenous cancellous graft from iliac crest
Cornell, et al. 1992	Initial clinical experience with use of Collagraft(TM) as a bone graft substitute	C-porous calcium phosphate ceramic plus autogenous bone marrow aspirated from the iliac crest(Collagen) vs. Autogenous cancellous graft from iliac crest

STUDY QUALITY

Table 18. Study quality

Author	Outcome Measure	Duration	Level of Evidence	RCT-Stochastic randomization	RCT- Allocation concealment	RCT- Patients blinded	RCT-Assessor blinded	RCT-80% Follow-up	RCT-Equal outcomes at entry
Dickson, et al. 2001	Fracture Healing-completely healed	6 months	II	Y	Y	NR	NR	N	Y
Dickson, et al. 2001	Fracture Healing-completely healed	6 months	II	Y	Y	NR	NR	N	Y
Dickson, et al. 2001	Fracture Healing-Partially Healed	6 months	II	Y	Y	NR	NR	N	Y
Dickson, et al. 2001	Fracture Healing Nonunion	6 months	II	Y	Y	NR	NR	N	Y
Dickson, et al. 2001	Pain at the defect site-None	6 months	II	Y	Y	NR	NR	N	Y
Dickson, et al. 2001	Pain at the defect site	6 months	II	Y	Y	NR	NR	N	Y

Author	Outcome Measure	Duration	Level of Evidence	RCT-Stochastic randomization	RCT- Allocation concealment	RCT- Patients blinded	RCT-Assessor blinded	RCT-80% Follow-up	RCT-Equal outcomes at entry
Dickson, et al. 2001	Pain at the defect site-severe	6 months	II	Y	Y	NR	NR	N	Y
Dickson, et al. 2001	Function of the fractured limb-maximum/moderate	6 months	II	Y	Y	NR	NR	N	Y
Dickson, et al. 2001	Function of the fractured limb-maximum	6 months	II	Y	Y	NR	NR	N	Y
Dickson, et al. 2001	Function of the fractured limb-minimal/none	6 months	II	Y	Y	NR	NR	N	Y
Dickson, et al. 2001	Overall Success	6 months	II	Y	Y	NR	NR	N	Y
Dickson, et al. 2001	Donor Site Pain	6 months	II	Y	Y	NR	NR	N	Y
Dickson, et al. 2001	Donor Site Pain	12 months	II	Y	Y	NR	NR	N	Y

Author	Outcome Measure	Duration	Level of Evidence	RCT-Stochastic randomization	RCT- Allocation concealment	RCT- Patients blinded	RCT-Assessor blinded	RCT-80% Follow-up	RCT-Equal outcomes at entry
Russell, et al. 2007	Donor Site Pain	Immediate	II	Y	Y	NR	Y	Y	NR
Bucholz et al. 1989	Knee pain	15.4- 34.5 months	II	N	NR	NR	NR	Y	Y
Bucholz et al. 1989	Return to pre-injury employment	15.4- 34.5 months	II	N	NR	NR	NR	Y	Y

Y= Yes

NR= Not reported in study

N= No

STUDY DATA

Table 19. Study data

Author	LoE	N	Comparison	Duration	Outcome	Group Result		Results
						BVF	Autograft	
Dickson, et al. 2001	II	29	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	6 months	Fracture Healing-completely healed	11	15	$p=0.42^*$
Dickson, et al. 2001	II	29	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	6 months	Fracture Healing-Partially Healed	1	0	$p=0.13^*$
Dickson, et al. 2001	II	29	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	6 months	Fracture Healing Nonunion	0	0	$p=1.0^*$
Dickson, et al. 2001	II	29	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	6 months	Pain at the defect site-None	10	9	$p=0.23^*$
Dickson, et al. 2001	II	29	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	6 months	Pain at the defect site	3	7	$p=0.23^*$
Dickson, et al. 2001	II	29	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	6 months	Function of the fractured limb-maximum/moderate	11	15	$p=0.42^*$
Dickson, et al. 2001	II	29	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	6 months	Function of the fractured limb-minimal/none	2	1	$p=0.42^*$
Dickson, et al. 2001	II	29	Bone graft harvested from the iliac crest or other appropriate site vs. calcium phosphate	6 months	Overall Success	9	8	$p=0.29^*$
Bucholz, et al. 1988		40	Autogenous bone graft vs. porous hydroxyapatite	15.4-34.5 months	Knee pain	3	2	$p=0.63^*$

*= AAOS Calculated arcsine transform

KEY QUESTION 4

Do patients with contained defects from tumor (or other benign bone cysts) have different clinical outcomes when treated with synthetic bone void filler, autograft, or allograft?

Our literature searches did not identify any peer reviewed data that addresses this question. This question specifically addresses the comparison of synthetic bone void filler to either autograft or allograft in patients with contained defects from a tumor.

TABLE 20 EXCLUDED STUDIES

Author	Title	Reason for Exclusion
Hirata, et al. 2006	Use of purified beta-tricalcium phosphate for filling defects after curettage of benign bone tumors	Does not answer the question: non-comparative data
Uchida, et al. 1990	The use of calcium hydroxyapatite ceramic in bone tumor surgery	Does not answer the question: non-comparative data
Yamamoto, et al. 2000	Use of hydroxyapatite to fill cavities after excision of benign bone tumors. Clinical results	Does not answer the question: non-comparative data
Biau, et al. 2007	Allograft-prosthesis composites after bone tumor resection at the proximal tibia	Allograft only

KEY QUESTION 5

Do patients with contained defects from peri-prosthetic bone loss have different clinical outcomes when treated with synthetic bone void filler, allograft, or autograft?

Our literature searches did not identify any peer reviewed data that addresses this question

DISCLAIMER

As noted above, this document is not intended to convey any official AAOS position on synthetic bone void fillers versus autograft or allograft for peri-prosthetic bone loss. We provide this *Technology Overview* as a service to our members in an effort to help them identify and evaluate the available published literature on this topic. We hope that our summary will assist physicians in providing the best possible care to their patients.

AAOS would like to have feedback from its members on this *Technology Overview*. To provide your feedback, please visit <http://research.aaos.org/surveys/Tech-Feedback.htm>

IV. APPENDIXES

APPENDIX I INCLUSION CRITERIA

We used the following criteria to determine whether studies should be included in this systematic review:

- Study must be of humans, no *in vitro* or biomechanical studies will be included.
- Studies must be of adults (>18 years old) (80% or more of study population must be >18 years old)
- Study must have enrolled 10 or more patients in any arm
- Study must have been published in 1980 or later
- Study must be published in English
- Study must quantitatively express its results (e.g., studies that express results as “most patients improved” are excluded)
- The quality of studies with loss to follow up of <80% will be downgraded. Less than 50% follow-up will cause the study to be excluded.
- Retrospective case series and manufacturer marketing information are excluded.
- Studies must be prospective cohorts and have concurrent comparison groups (contemporary controls for RCTs and cohort comparisons; case control studies must have concurrent controls). Retrospective comparative studies will be included.
- Study must be a full report, published in a peer-reviewed journal. Meeting abstracts, traditional reviews, and text chapters will not be included.
- Product names are not mentioned in the technology overview.
- If there are duplicate publications of the same study, the most recent publication will be included unless the earlier publication contains information not in the later one. In this latter case, both publications will be included.
- Only studies of the highest level of available evidence will be included for any given question, assuming that there are two or more studies of that higher level. For example, if there are two Level II studies that address a question, Level III and IV studies will not be included. If there is only one Level II study, Level III studies will be included.
- Data on patient-oriented outcomes will take precedence over data on surrogate outcomes.
- We will not consider biomechanical or *in vitro* studies.

APPENDIX II

DATABASES SEARCHED AND SEARCH STRATEGIES

Total # de-duplicated citations: 1508

PubMedSearch Strategies

#1

((bone[tiab] OR bony[tiab]) AND void[tiab] AND filler*[tiab]) OR bioglass[tiab] OR nanomatrix OR nanomatrices OR ((absorbable[tiab] OR reabsorbable[tiab]) AND bone[tiab] AND cement*[tiab]) OR (composite[tiab] AND bone[tiab] AND graft[tiab]) OR ((silicates[tiab] OR Silicates[mh] OR hydroxylapatite* OR hydroxyapatite*[tiab] OR Hydroxyapatites[mh] OR "Calcium Phosphate"[nm] OR "Tricalcium Phosphate"[nm] OR ((calcium[tiab] OR tricalcium[tiab]) AND phosphate*[tiab]) OR sulfate[tiab] OR Sulphates[mh] OR osteoconductive[tiab] OR (ceramic*[tiab] AND collagen[tiab]) OR "hyaluronic acid"[tiab] OR "Hyaluronic Acid"[mh] OR "poly l lactic acid" OR PLA[tiab] OR conductive[tiab]) AND (filler*[tiab] OR substitute*[tiab] OR substrate*[tiab] OR scaffold*[tiab] OR matrix[tiab] OR matrices[tiab] OR replacement*[tiab] OR void[tiab] OR voids[tiab] OR "Bone Substitutes"[mh]))

#2

("Spinal Fusion"[mh] OR ((spine[tiab] OR spinal[tiab]) AND (fused[tiab] OR fusion[tiab] OR arthrodesis[tiab])) OR "Fractures, Bone"[mh] OR fracture*[tiab] OR peri-prosthetic[tiab] OR osteolysis[tiab] OR Osteolysis[mh] OR ((tumor[tiab] OR tumors[tiab] OR lesion*[tiab] OR cyst[tiab]) AND (bone[tiab] OR bony[tiab] OR "Bone and Bones"[mh])) OR "Bone Neoplasms"[mh] OR "Bone Cysts"[mh] OR chondroblastoma[tiab] OR Chondroblastoma[mh] OR enchondroma[tiab] OR (eosinophilic[tiab] AND granuloma[tiab]) OR (chondromyxoid[tiab] AND fibroma[tiab]))

#3

English[lang] AND 1980:2009[pdat]

#4

((animal[mh] NOT human[mh]) OR cadaver[mh] OR "in vitro"[pt] OR "in vitro"[titl] OR biomechanic*[titl] OR comment[pt] OR editorial[pt] OR letter[pt] OR addresses[pt] OR news[pt] OR "newspaper article"[pt] OR "historical article"[pt] OR "case report"[title] OR "retrospective case series" OR rat[titl] OR rats[titl] OR rabbit[titl] OR rabbits[titl])

#5

(#1 AND #2 AND #3) NOT #4

EMBASE

Search strategies

#1

((bone OR bony) AND void AND filler*) OR bioglass OR nanomatrix OR nanomatrices OR ((absorbable OR reabsorbable) AND bone AND cement*) OR 'composite bone graft' OR ((silicate* OR Silicate/de OR 'calcium phosphate'/de OR 'calcium phosphate ceramic'/de OR ((calcium OR

tricalcium) AND phosphate*) OR sulfate OR sulfate/exp OR osteoconductive OR hydroxylapatite* OR hydroxyapatite* OR hydroxyapatite/de OR (ceramic* AND collagen) OR 'hyaluronic acid' OR 'hyaluronic acid'/de OR 'polylactic acid'/de OR PLA OR conductive) AND (filler* OR substitute* OR substrate* OR scaffold* OR matrix OR matrices OR replacement* OR void OR voids OR 'bone prosthesis'/de)))

#2

('spine fusion'/exp OR ((spine OR spinal) AND (fused OR fusion OR arthrodesis)) OR fracture/de OR fracture* OR peri-prosthetic OR osteolysis OR osteolysis/de OR acroosteolysis/de OR ((tumor* OR lesion* OR cyst OR cysts) AND (bone OR bony OR bone/exp)) OR 'bone tumor'/exp OR 'bone cyst'/exp OR chondroblastoma OR chondroblastoma/de OR enchondroma OR 'eosinophilic granuloma'/de OR 'eosinophilic granuloma' OR 'chondromyxoid fibroma')

#3

[article]/lim AND [English]/lim AND [1980-2009]/py AND [embase]/lim

#4

(([animals]/lim NOT [humans]/lim) OR cadaver/de OR biomechanic*:ti OR 'case report':ti OR 'abstract report'/de OR book/de OR editorial/de OR letter/de OR 'retrospective case series' OR rat:ti OR rats:ti OR rabbit:ti OR rabbits:ti)

CINAHL Search strategies

S1

((bone or bony) and void and filler*) or bioglass or nanomatrix or nanomatrices or ((absorbable or reabsorbable) and bone and cement*) or (composite and bone and graft) or ((silicates or MH Silicates+ or hydroxylapatite* OR hydroxyapatite* or MH Hydroxyapatites+ or MH "Calcium Phosphate+" or ((calcium or tricalcium) and phosphate*) or sulfate or MH Sulphates+ or osteoconductive or (ceramic* and collagen) or "hyaluronic acid" or MH "Hyaluronic Acid" or "poly lactic acid" or PLA or conductive) and (filler* or substitute* or substrate* or scaffold* or matrix or matrices or replacement* or void or voids or MH "Bone Substitutes+"))

S2

MH "spinal fusion+" or ((spine or spinal) and (fused or fusion or arthrodesis)) or MH "Fractures,Bone+" or MH osteolysis+ or ((tumor or tumors or lesion* or cyst) and (bone or bony or MH "bone and bones+")) or MH "bone neoplasms+" or MH "bone cysts" or chondroblastoma or MH "chondromblastoma" or enchondroma or (eosinophilic and granuloma) or (chondromyxoid and fibroma)

S3

PT "editorial" or PT "letter" or PT "case study" or TI "case report" or MH "in vitro" or TI "in vitro" or TI biomechanic* OR MH cadaver or "retrospective case series" or TI rat or TI rats or TI rabbit or TI rabbits or MH animals+ or MH mammals+

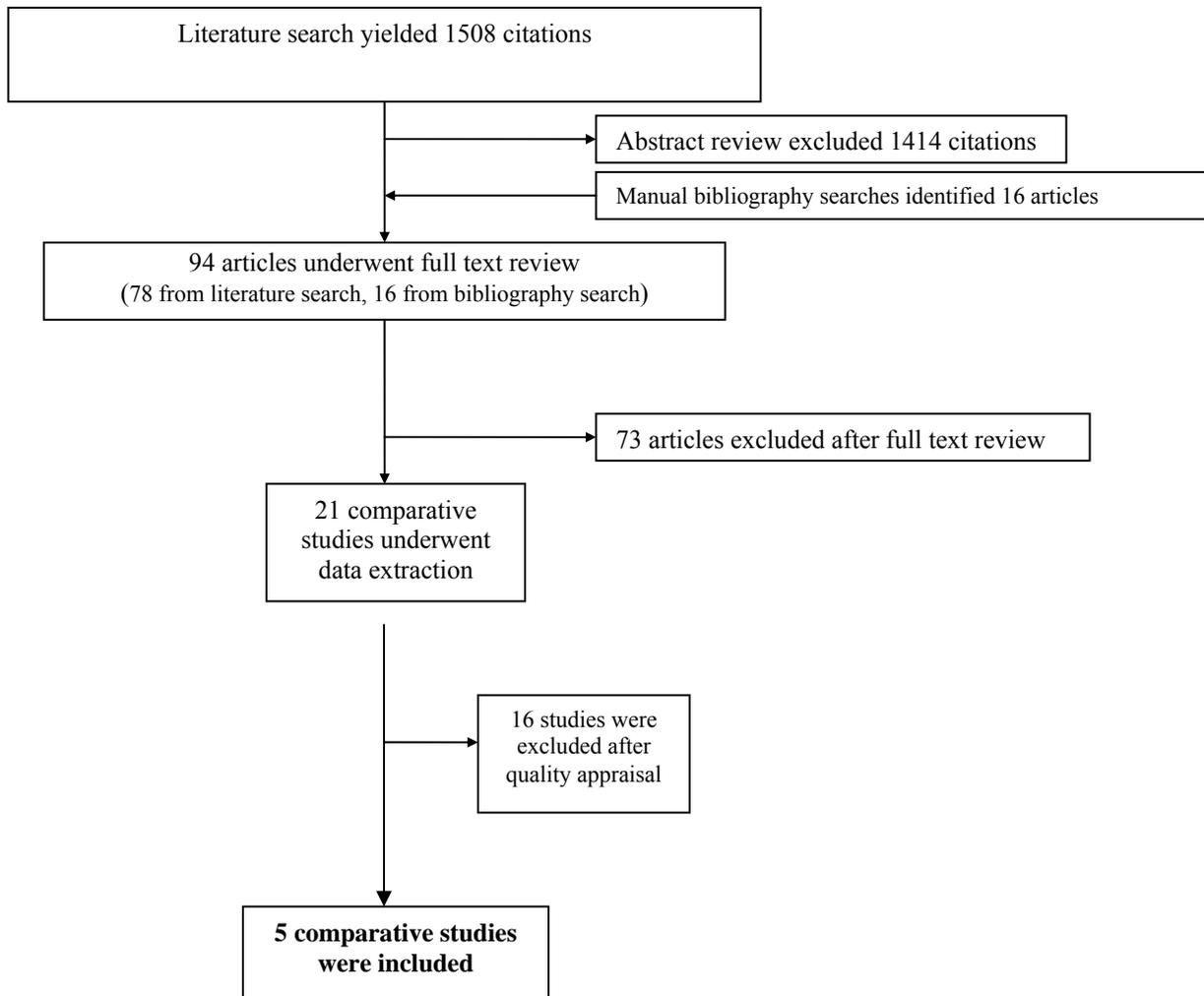
S4

(S1 and S2 and LA English and PY 1980-2009) not S3

Cochrane Library Search strategy

((bone or bony) and void and filler*) or bioglass or ((silicates or hydroxyapatite* or ((calcium or tricalcium) and phosphate*) or sulfate or osteoconductive or ceramic* or "hyaluronic acid" or "poly l lactic acid") and (filler* or substitute* or substrate* or scaffold* or matrix or matrices))

APPENDIX III STUDY ATTRITION



APPENDIX IV

We assessed the quality of each available study using a two step process. First, we assigned a Level of Evidence to each study included in this *Overview* on the basis of its design. For example, randomized controlled trials were categorized as Level I evidence, non-randomized controlled trials and other prospective comparative studies were categorized as Level II studies, retrospective comparative studies and case-control studies were initially categorized as Level III studies, and case-series studies/reports were categorized as Level IV studies. However, the quality of a study is not necessarily captured by looking only at its design. Therefore, we also used a study quality checklist (see below) and, when quality standards were not met, downgraded the Level of Evidence by one. As such, our use of Levels of Evidence ties these Levels to study quality.

When there were two or more studies of higher quality evidence that addressed a given question, we included only those higher level studies. For example, if there were two Level II articles that address a question, we did not include Level III or lower Level studies.

STUDY QUALITY CHECKLISTS

When determining the quality of the evidence, we begin by considering study design. Better study designs are given higher ratings (i.e. randomized control trials are initially evaluated as Level I studies and non-comparative case series are initially evaluated as Level IV studies). The quality checklist is then used to determine if there are flaws that could influence the outcomes in a study. The checklist is completed for each outcome the study reports. It is also completed for each time point that a study reports. For example, if a study reports two outcomes at three different times, the checklist is completed six times.

Items are answered “Yes”, “No”, or “Not Reported”. “Not applicable” is not an acceptable answer for any of the items except when evaluating a crossover trial and the question is about such a trial.

To score the checklist for a study that is a randomized controlled trial, prospective, non-randomized controlled study, retrospective comparative (i.e., controlled) study, or a case series, each “No” answer is scored as -1 , and each “Not Reported” as -0.5 . If 1 or more points is deducted, the study is downgraded by one Level *for that outcome*. Studies can only be downgraded by one level. We never downgrade two (or more) levels. Preference is always given to patient-oriented outcomes. If data for surrogate outcomes is examined, the data should be downgraded one level for the surrogate outcome.

To score the checklist for prognostic studies, prospective multiple regression studies start at Level I and retrospective multiple regression studies start at Level II. They are scored as indicated above using the checklist for prognostic studies.

For joint registries, if the reviewer answers “no” to any question or “unclear” to two or more questions, the registry is downgraded one level.

RANDOMIZED CONTROLLED TRIALS

1. Did the study employ stochastic randomization?
2. Was there concealment of allocation?
3. Were subjects blinded to the treatment they received?

4. Were those who assessed/rated the patient's outcomes blinded to the group to which the patients were assigned?
5. Was there more than 80% follow-up for all patients in the control group and the experimental group on the outcome of interest?
6. Did patients in the different study groups have similar levels of performance on ALL of the outcome variables at the time they were assigned to groups?
7. For randomized crossover studies, was there evidence that the results obtained in the study's two *experimental* groups (in period 1 and 2) did not differ?
8. For randomized crossover studies, was there evidence that the results of the two *control* groups (in period 1 and 2) did not differ?

PROSPECTIVE NON- RANDOMIZED CONTROLLED STUDIES

1. Were the *characteristics* of patients in the different study groups comparable at the beginning of the study?
2. Did patients in the different study groups have similar levels of performance on ALL of the outcome variables at baseline?
3. Were all of the study's groups concurrently treated?
4. Was there more than 80% follow-up for all patients in the control group and the experimental group on the outcome of interest?
5. Did the study avoid collecting control group data from one center and experimental group data from another?
6. For crossover studies, was there evidence that the results obtained in the study's two experimental groups (in period 1 and 2) did not differ?
7. For crossover studies, was there evidence that the results of the two control groups (in period 1 and 2) did not differ?

RETROSPECTIVE COMPARATIVE (I.E., CONTROLLED) STUDIES

1. Was there less than 20% difference in completion rates in the study's groups?
2. Were all of the study's groups concurrently treated?
3. Was the same treatment given to all patients enrolled in the experimental and control groups?
4. Were the same laboratory tests, clinical findings, psychological instruments, etc. used to measure the outcomes in all of the study's groups?
5. Were the follow-up times in all of the study's relevant groups approximately equal?
6. Was there more than 80% follow-up for all patients in the control group and the experimental group on the outcome of interest?
7. Did the study avoid collecting control group data from one center and experimental group data from another?
8. Did patients in the different study groups have similar levels of performance on ALL of the outcome variables at the time they were assigned to groups?
9. Were the *characteristics* of patients in the different study groups comparable at the beginning of the study?

CASE SERIES

1. Was enrollment in the study consecutive?
2. Was there more than 80% follow-up for all patients on the outcome of interest?
3. Were the same laboratory tests, clinical findings, psychological instruments, etc. used to measure the outcomes in all patients?
4. Were the patients instructed/not given concomitant or adjuvant treatments?
5. Were the follow-up times for all patients approximately equal?

APPENDIX V DOCUMENTATION OF APPROVAL

AAOS Task Force Draft Completed	January 8, 2010
Manufacturer Review Completed	February 4, 2010
AAOS Guidelines and Technology Oversight Committee	February 23, 2010
AAOS Evidence Based Practice Committee	February 23, 2010
AAOS Council on Research Quality Assessment and Technology	March 3, 2010
AAOS Board of Directors	March 8, 2010

AAOS BODIES THAT APPROVED THIS TECHNOLOGY OVERVIEW

Guidelines and Technology Oversight Committee

The AAOS Guidelines and Technology Oversight Committee (GTOC) consists of sixteen AAOS members. The overall purpose of this Committee is to oversee the development of the clinical practice guidelines, performance measures, health technology assessments, and utilization guidelines.

Evidence Based Practice Committee

The AAOS Evidence Based Practice Committee (EBPC) consists of ten AAOS members. This Committee provides review, planning, and oversight for all activities related to quality improvement in orthopaedic practice, including, but not limited to evidence-based guidelines, performance measures, and outcomes.

Council on Research, Quality Assessment, and Technology

To enhance the mission of the AAOS, the Council on Research, Quality Assessment, and Technology promotes the most ethically and scientifically sound basic, clinical, and translational research possible to ensure the future care for patients with musculoskeletal disorders. The Council also serves as the primary resource to educate its members, the public, and public policy makers regarding evidenced-based medical practice, orthopaedic devices and biologics regulatory pathways and standards development, patient safety, occupational health, technology assessment, and other related areas of importance.

The Council is comprised of the chairs of the AAOS Biological Implants, Biomedical Engineering, Evidence Based Practice, Guidelines and Technology Oversight, Occupational Health and Workers' Compensation, Patient Safety, Research Development, and US Bone and Joint Decade committees. Also on the Council are the AAOS second vice-president, representatives of the Diversity Advisory Board, the Women's Health Issues Advisory Board, the Board of Specialty Societies (BOS), the Board of Councilors (BOC), the Communications Cabinet, the Orthopaedic Research Society (ORS), the Orthopedic Research and Education Foundation (OREF), and three members at large.

Board of Directors

The 17 member AAOS Board of Directors manages the affairs of the AAOS, sets policy, and determines and continually reassesses the Strategic Plan.

APPENDIX VI

TASK FORCE

John S Kirkpatrick MD, Chair

University of Florida
655 W Eighth Street C-126
Jacksonville FL. 32209

Charles N Cornell MD

Hospital for Special Surgery
535 E 70th Street STE 642
New York, NY 10021

Bang H. Hoang MD

Department of Orthopaedic Surgery
University of California Irvine
101 The City Drive South Pavillion III
Orange, CA 92868

Wellington Hsu MD

Northwestern University Feinburg School of Medicine
676 N St. Clair Ste 1350
Chicago, IL 60611

J. Tracy Watson MD

St. Louis University Hospital
7th FL Desolge Towers
3635 Vista Ave.
Saint Louis MO 63110

Guidelines and Technology Oversight Chair

William C. Watters III, MD

Houston, TX 77030

AAOS Staff

Charles M. Turkelson, PhD

Director of Research and Scientific Affairs
6300 N. River Road
Rosemont, IL 60018

Janet L. Wies, MPH

Manager, Clinical Practice Guidelines

Sara Anderson, MPH

Lead Research Analyst

AAOS Medical Librarian

Kristin Hitchcock, MLS

Medical Librarian

CONFLICT OF INTEREST

All members of the AAOS task force disclosed any conflicts of interest prior to the development of the key questions for this technology overview. Conflicts of interest are disclosed in writing with the American Academy of Orthopaedic Surgeons via a private on-line reporting database.

John S Kirkpatrick, MD 1 (Cervical Spine Research Society; Southern Orthopaedic Association); 2 (Journal of surgical Orthopaedic Advances (formerly Journal of Southern Orthopaedic Association)); 5A (AAOS expert witness; Department of Health and Human Services (FDA)); 8 (Bristol-Myers Squibb; Johnson & Johnson; Pfizer; Zimmer). Submitted on: 09/21/2009. ⁺

Charles N Cornell, MD 1 (Hospital for Special Surgery); 2 (Clinical Orthopaedics and Related Research; Journal of Bone and Joint Surgery - American); 3 (Exactech, Inc); 5B (Exactech, Inc); 7 (Exactech, Inc). Submitted on: 05/18/2009. ⁺

Bang H Hoang, MD (n) Submitted on: 05/19/2009 and last confirmed as accurate on 12/15/2009. ⁺

Wellington Hsu, MD 5A (Stryker); 7 (Medtronic Sofamor Danek; Baxter Northwestern Alliance; Pioneer Surgical). Submitted on: 11/15/2009. ⁺

J Tracy Watson, MD 1 (Orthopaedic Trauma Association; Foundation for orthopaedic Trauma; National Trauma Institute); 2 (Clinical Orthopaedics and Related Research; Journal of Bone and Joint Surgery - American; orthopaedic Knowledge online trauma co-editor; journal of Trauma); 3 (DePuy, A Johnson & Johnson Company; Smith & Nephew); 5B (Smith & Nephew); 7 (Smith & Nephew). Submitted on: 09/14/2009. ⁺

⁺ **Disclosure Items Answered:** (n) = Respondent answered 'No' to all items indicating no conflicts. 1=Board member/owner/officer/committee appointments; 2= Medical/Orthopaedic Publications; 3= Royalties; 4= Speakers bureau/paid presentations; 5A= Paid consultant or employee; 5B= Unpaid consultant; 6= Research or institutional support from a publisher; 7= Research or institutional support from a company or supplier; 8= Stock or Stock Options; 9= Other financial/material support from a publisher; 10= Other financial/material support from a company or supplier.

APPENDIX VII

Reference List

- (1) Grimes DA, Schulz KF. Surrogate end points in clinical research: hazardous to your health. *Obstet Gynecol* 2005;105(5 Pt 1):1114-1118.
- (2) Shaughnessy AF, Slawson DC. What happened to the valid POEMs? A survey of review articles on the treatment of type 2 diabetes. *BMJ* 2003;327(7409):266.
- (3) Ostelo RW, Deyo RA, Stratford P et al. Interpreting change scores for pain and functional status in low back pain: towards international consensus regarding minimal important change. *Spine (Phila Pa 1976)* 2008;33(1):90-94.
- (4) Russell TA, Leighton RK. Comparison of autogenous bone graft and endothermic calcium phosphate cement for defect augmentation in tibial plateau fractures. A multicenter, prospective, randomized study. *J Bone Joint Surg Am* 2008;90(10):2057-2061.
- (5) Fujibayashi S, Shikata J, Tanaka C, Matsushita M, Nakamura T. Lumbar posterolateral fusion with biphasic calcium phosphate ceramic. *J Spinal Disord* 2001;14(3):214-221.
- (6) Lerner T, Bullmann V, Schulte TL, Schneider M, Liljenqvist U. A level-1 pilot study to evaluate of ultraporous beta-tricalcium phosphate as a graft extender in the posterior correction of adolescent idiopathic scoliosis. *Eur Spine J* 2009;18(2):170-179.
- (7) Dickson KF, Friedman J, Buchholz JG, Flandry FD. The use of BoneSource hydroxyapatite cement for traumatic metaphyseal bone void filling. *J Trauma* 2002;53(6):1103-1108.
- (8) Bucholz RW, Carlton A, Holmes R. Interporous hydroxyapatite as a bone graft substitute in tibial plateau fractures. *Clin Orthop Relat Res* 1989;(240):53-62.

EXCLUDED STUDIES

Dimar JR, Glassman SD, Burkus JK, Pryor PW, Hardacker JW, Carreon LY. Clinical and radiographic analysis of an optimized rhBMP-2 formulation as an autograft replacement in posterolateral lumbar spine arthrodesis. *J Bone Joint Surg Am* 2009;91(6):1377-1386.

Blom AW, Wylde V, Livesey C et al. Impaction bone grafting of the acetabulum at hip revision using a mix of bone chips and a biphasic porous ceramic bone graft substitute. *Acta Orthop* 2009;80(2):150-154.

Heo DH, Cho YJ, Sheen SH, Kuh SU, Cho SM, Oh SM. Morphological changes of injected calcium phosphate cement in osteoporotic compressed vertebral bodies. *Osteoporos Int* 2009.

Siegel HJ, Baird RC, III, Hall J, Lopez-Ben R, Lander PH. The outcome of composite bone graft substitute used to treat cavitory bone defects. *Orthopedics* 2008;31(8):754.

Newman JT, Smith WR, Ziran BH, Hasenboehler EA, Stahel PF, Morgan SJ. Efficacy of composite allograft and demineralized bone matrix graft in treating tibial plateau fractures with bone loss. *Orthopedics* 2008;31(7):649.

Carter JD, Swearingen AB, Chaput CD, Rahm MD. Clinical and radiographic assessment of transforaminal lumbar interbody fusion using HEALOS collagen-hydroxyapatite sponge with autologous bone marrow aspirate. *Spine J* 2009;9(6):434-438.

Fu TS, Chen WJ, Chen LH, Lin SS, Liu SJ, Ueng SW. Enhancement of posterolateral lumbar spine fusion using low-dose rhBMP-2 and cultured marrow stromal cells. *J Orthop Res* 2009;27(3):380-384.

Russell TA, Leighton RK. Comparison of autogenous bone graft and endothermic calcium phosphate cement for defect augmentation in tibial plateau fractures. A multicenter, prospective, randomized study. *J Bone Joint Surg Am* 2008;90(10):2057-2061.

Chang CH, Lin MZ, Chen YJ, Hsu HC, Chen HT. Local autogenous bone mixed with bone expander: an optimal option of bone graft in single-segment posterolateral lumbar fusion. *Surg Neurol* 2008;70 Suppl 1:S1-S9.

Mulconrey DS, Bridwell KH, Flynn J, Cronen GA, Rose PS. Bone morphogenetic protein (RhBMP-2) as a substitute for iliac crest bone graft in multilevel adult spinal deformity surgery: minimum two-year evaluation of fusion. *Spine (Phila Pa 1976)* 2008;33(20):2153-2159.

Dai LY, Jiang LS. Single-level instrumented posterolateral fusion of lumbar spine with beta-tricalcium phosphate versus autograft: a prospective, randomized study with 3-year follow-up. *Spine (Phila Pa 1976)* 2008;33(12):1299-1304.

Schindler OS, Cannon SR, Briggs TW, Blunn GW. Composite ceramic bone graft substitute in the treatment of locally aggressive benign bone tumours. *J Orthop Surg (Hong Kong)* 2008;16(1):66-74.

Acharya NK, Kumar RJ, Varma HK, Menon VK. Hydroxyapatite-bioactive glass ceramic composite as stand-alone graft substitute for posterolateral fusion of lumbar spine: a prospective, matched, and controlled study. *J Spinal Disord Tech* 2008;21(2):106-111.

Ilharreborde B, Morel E, Fitoussi F et al. Bioactive glass as a bone substitute for spinal fusion in adolescent idiopathic scoliosis: a comparative study with iliac crest autograft. *J Pediatr Orthop* 2008;28(3):347-351.

Lagoa AL, Wedemeyer C, von KM, Loer F, Epple M. A strut graft substitute consisting of a metal core and a polymer surface. *J Mater Sci Mater Med* 2008;19(1):417-424.

Moro-Barrero L, Acebal-Cortina G, Suarez-Suarez M, Perez-Redondo J, Murcia-Mazon A, Lopez-Muniz A. Radiographic analysis of fusion mass using fresh autologous bone marrow with ceramic composites as an alternative to autologous bone graft. *J Spinal Disord Tech* 2007;20(6):409-415.

Epstein NE. Efficacy of different bone volume expanders for augmenting lumbar fusions. *Surg Neurol* 2008;69(1):16-19.

Khoueir P, Oh BC, DiRisio DJ, Wang MY. Multilevel anterior cervical fusion using a collagen-hydroxyapatite matrix with iliac crest bone marrow aspirate: an 18-month follow-up study. *Neurosurgery* 2007;61(5):963-970.

Schwarz F, Sculean A, Bielting K, Ferrari D, Rothamel D, Becker J. Two-year clinical results following treatment of peri-implantitis lesions using a nanocrystalline hydroxyapatite or a natural bone mineral in combination with a collagen membrane. *J Clin Periodontol* 2008;35(1):80-87.

Dai LY, Jiang LS. Anterior cervical fusion with interbody cage containing beta-tricalcium phosphate augmented with plate fixation: a prospective randomized study with 2-year follow-up. *Eur Spine J* 2008;17(5):698-705.

Vaccaro AR, Whang PG, Patel T et al. The safety and efficacy of OP-1 (rhBMP-7) as a replacement for iliac crest autograft for posterolateral lumbar arthrodesis: minimum 4-year follow-up of a pilot study. *Spine J* 2008;8(3):457-465.

Biau DJ, Dumaine V, Babinet A, Tomeno B, Anract P. Allograft-prosthesis composites after bone tumor resection at the proximal tibia. *Clin Orthop Relat Res* 2007;456:211-217.

Dimar JR, Glassman SD, Burkus KJ, Carreon LY. Clinical outcomes and fusion success at 2 years of single-level instrumented posterolateral fusions with recombinant human bone morphogenetic protein-2/compression resistant matrix versus iliac crest bone graft. *Spine (Phila Pa 1976)* 2006;31(22):2534-2539.

Neen D, Noyes D, Shaw M, Gwilym S, Fairlie N, Birch N. Healos and bone marrow aspirate used for lumbar spine fusion: a case controlled study comparing healos with autograft. *Spine (Phila Pa 1976)* 2006;31(18):E636-E640.

Epstein NE. A preliminary study of the efficacy of Beta Tricalcium Phosphate as a bone expander for instrumented posterolateral lumbar fusions. *J Spinal Disord Tech* 2006;19(6):424-429.

Bibbo C, Patel DV. The effect of demineralized bone matrix-calcium sulfate with vancomycin on calcaneal fracture healing and infection rates: a prospective study. *Foot Ankle Int* 2006;27(7):487-493.

Huber FX, McArthur N, Hillmeier J et al. Void filling of tibia compression fracture zones using a novel resorbable nanocrystalline hydroxyapatite paste in combination with a hydroxyapatite ceramic core: first clinical results. *Arch Orthop Trauma Surg* 2006;126(8):533-540.

Hirata M, Murata H, Takeshita H, Sakabe T, Tsuji Y, Kubo T. Use of purified beta-tricalcium phosphate for filling defects after curettage of benign bone tumours. *Int Orthop* 2006;30(6):510-513.

Arlet V, Jiang L, Steffen T, Ouellet J, Reindl R, Aebi M. Harvesting local cylinder autograft from adjacent vertebral body for anterior lumbar interbody fusion: surgical technique, operative feasibility and preliminary clinical results. *Eur Spine J* 2006;15(9):1352-1359.

Seeherman H, Li R, Bouxsein M et al. rhBMP-2/calcium phosphate matrix accelerates osteotomy-site healing in a nonhuman primate model at multiple treatment times and concentrations. *J Bone Joint Surg Am* 2006;88(1):144-160.

Hsu CJ, Chou WY, Teng HP, Chang WN, Chou YJ. Coralline hydroxyapatite and laminectomy-derived bone as adjuvant graft material for lumbar posterolateral fusion. *J Neurosurg Spine* 2005;3(4):271-275.

Chen WJ, Tsai TT, Chen LH et al. The fusion rate of calcium sulfate with local autograft bone compared with autologous iliac bone graft for instrumented short-segment spinal fusion. *Spine (Phila Pa 1976)* 2005;30(20):2293-2297.

Lewis G. Injectable bone cements for use in vertebroplasty and kyphoplasty: state-of-the-art review. *J Biomed Mater Res B Appl Biomater* 2006;76(2):456-468.

Beadel GP, McLaughlin CE, Wunder JS, Griffin AM, Ferguson PC, Bell RS. Outcome in two groups of patients with allograft-prosthetic reconstruction of pelvic tumor defects. *Clin Orthop Relat Res* 2005;438:30-35.

Glassman SD, Dimar JR, Carreon LY, Campbell MJ, Puno RM, Johnson JR. Initial fusion rates with recombinant human bone morphogenetic protein-2/compression

resistant matrix and a hydroxyapatite and tricalcium phosphate/collagen carrier in posterolateral spinal fusion. *Spine (Phila Pa 1976)* 2005;30(15):1694-1698.

Langlais F, Lambotte JC, Collin P, Thomazeau H. Long-term results of allograft composite total hip prostheses for tumors. *Clin Orthop Relat Res* 2003;(414):197-211.

Thalgott JS, Giuffre JM, Fritts K, Timlin M, Klezl Z. Instrumented posterolateral lumbar fusion using coralline hydroxyapatite with or without demineralized bone matrix, as an adjunct to autologous bone. *Spine J* 2001;1(2):131-137.

Lobo GA, Agarwal M, Puri A, D'Lima C, Duggal A. The use of irradiated allografts in reconstruction of tumor defects - the tata memorial hospital experience. *Cell Tissue Bank* 2003;4(2-4):125-132.

Cammisa FP, Jr., Lowery G, Garfin SR et al. Two-year fusion rate equivalency between Grafton DBM gel and autograft in posterolateral spine fusion: a prospective controlled trial employing a side-by-side comparison in the same patient. *Spine (Phila Pa 1976)* 2004;29(6):660-666.

Donati D, Giacomini S, Gozzi E, Di BC, Mercuri M. The results of the surgical treatment of bone tumors using massive homoplastic grafts. *Chir Organi Mov* 2003;88(2):115-122.

den Boer FC, Wippermann BW, Blokhuis TJ, Patka P, Bakker FC, Haarman HJ. Healing of segmental bone defects with granular porous hydroxyapatite augmented with recombinant human osteogenic protein-1 or autologous bone marrow. *J Orthop Res* 2003;21(3):521-528.

Price CT, Connolly JF, Carantzas AC, Ilyas I. Comparison of bone grafts for posterior spinal fusion in adolescent idiopathic scoliosis. *Spine (Phila Pa 1976)* 2003;28(8):793-798.

McConnell JR, Freeman BJ, Debnath UK, Grevitt MP, Prince HG, Webb JK. A prospective randomized comparison of coralline hydroxyapatite with autograft in cervical interbody fusion. *Spine (Phila Pa 1976)* 2003;28(4):317-323.

Dickson KF, Friedman J, Buchholz JG, Flandry FD. The use of BoneSource hydroxyapatite cement for traumatic metaphyseal bone void filling. *J Trauma* 2002;53(6):1103-1108.

Chen WM, Chen TH, Huang CK, Chiang CC, Lo WH. Treatment of malignant bone tumours by extracorporeally irradiated autograft-prosthetic composite arthroplasty. *J Bone Joint Surg Br* 2002;84(8):1156-1161.

Boden SD, Kang J, Sandhu H, Heller JG. Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies. *Spine (Phila Pa 1976)* 2002;27(23):2662-2673.

- Boden SD. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. *Spine (Phila Pa 1976)* 2002;27(16 Suppl 1):S26-S31.
- Kujala S, Raatikainen T, Ryhanen J, Kaarela O, Jalovaara P. Composite implant of native bovine bone morphogenetic protein (BMP) and biocoral in the treatment of scaphoid nonunions--a preliminary study. *Scand J Surg* 2002;91(2):186-190.
- Gunzburg R, Szpalski M. Use of a novel beta-tricalcium phosphate-based bone void filler as a graft extender in spinal fusion surgeries. *Orthopedics* 2002;25(5 Suppl):s591-s595.
- Meadows GR. Adjunctive use of ultraporous beta-tricalcium phosphate bone void filler in spinal arthrodesis. *Orthopedics* 2002;25(5 Suppl):s579-s584.
- Totoribe K, Tajima N, Chosa E, Matsumoto M, Kataoka H, Koono M. Hydroxyapatite block for use in posterolateral lumbar fusion: a report of four cases. *Clin Orthop Relat Res* 2002;(399):146-151.
- Sandhu HS, Toth JM, Diwan AD et al. Histologic evaluation of the efficacy of rhBMP-2 compared with autograft bone in sheep spinal anterior interbody fusion. *Spine (Phila Pa 1976)* 2002;27(6):567-575.
- Gitelis S, Piasecki P, Turner T, Haggard W, Charters J, Urban R. Use of a calcium sulfate-based bone graft substitute for benign bone lesions. *Orthopedics* 2001;24(2):162-166.
- Kelly CM, Wilkins RM, Gitelis S, Hartjen C, Watson JT, Kim PT. The use of a surgical grade calcium sulfate as a bone graft substitute: results of a multicenter trial. *Clin Orthop Relat Res* 2001;(382):42-50.
- Yamamoto T, Onga T, Marui T, Mizuno K. Use of hydroxyapatite to fill cavities after excision of benign bone tumours. Clinical results. *J Bone Joint Surg Br* 2000;82(8):1117-1120.
- Boden SD. Biology of lumbar spine fusion and use of bone graft substitutes: present, future, and next generation. *Tissue Eng* 2000;6(4):383-399.
- Donati D, Di LM, Zavatta M et al. Massive bone allograft reconstruction in high-grade osteosarcoma. *Clin Orthop Relat Res* 2000;(377):186-194.
- Delecrin J, Takahashi S, Gouin F, Passuti N. A synthetic porous ceramic as a bone graft substitute in the surgical management of scoliosis: a prospective, randomized study. *Spine (Phila Pa 1976)* 2000;25(5):563-569.
- Bhat AL, Lowery GL, Sei A. The use of titanium surgical mesh-bone graft composite in the anterior thoracic or lumbar spine after complete or partial corpectomy. *Eur Spine J* 1999;8(4):304-309.

- Lowery GL, Kulkarni S, Pennisi AE. Use of autologous growth factors in lumbar spinal fusion. *Bone* 1999;25(2 Suppl):47S-50S.
- Wolfe SW, Pike L, Slade JF, III, Katz LD. Augmentation of distal radius fracture fixation with coralline hydroxyapatite bone graft substitute. *J Hand Surg Am* 1999;24(4):816-827.
- Itoh H, Ebara S, Kamimura M et al. Experimental spinal fusion with use of recombinant human bone morphogenetic protein 2. *Spine (Phila Pa 1976)* 1999;24(14):1402-1405.
- Thalgott JS, Fritts K, Giuffre JM, Timlin M. Anterior interbody fusion of the cervical spine with coralline hydroxyapatite. *Spine (Phila Pa 1976)* 1999;24(13):1295-1299.
- Heidecke V, Rainov NG, Burkert W. Occipito-cervical fusion with the cervical Cotrel-Dubousset rod system. *Acta Neurochir (Wien)* 1998;140(9):969-976.
- Blaha JD. Calcium sulfate bone-void filler. *Orthopedics* 1998;21(9):1017-1019.
- Johnson EE, Urist MR. One-stage lengthening of femoral nonunion augmented with human bone morphogenetic protein. *Clin Orthop Relat Res* 1998;(347):105-116.
- Jean JL, Wang SJ, Au MK. Treatment of a large segmental bone defect with allograft and autogenous bone marrow graft. *J Formos Med Assoc* 1997;96(7):553-557.
- Bai MH, Liu XY, GE BF, Yallg C, Chen DA. An implant of a composite of bovine bone morphogenetic protein and plaster of paris for treatment of femoral shaft nonunions. *Int Surg* 1996;81(4):390-392.
- Smeele LE, Hoekstra OS, Winters HA, Leemans CR. Clinical effectiveness of 99mTc-diphosphonate scintigraphy of revascularized iliac crest flaps. *Int J Oral Maxillofac Surg* 1996;25(5):366-369.
- An HS, Simpson JM, Glover JM, Stephany J. Comparison between allograft plus demineralized bone matrix versus autograft in anterior cervical fusion. A prospective multicenter study. *Spine (Phila Pa 1976)* 1995;20(20):2211-2216.
- Subhadrabandhu T, Keorochana S, Vajaradul Y. Massive allograft implantation for limb salvage: a clinical study of 20 cases. *J Med Assoc Thai* 1994;77(10):526-533.
- Lindeque BG, Jonck LM. Ionogran--an ionomeric micro implant in bone tumour reconstruction. A clinical evaluation. *Clin Mater* 1993;14(1):49-56.
- Johnson EE, Urist MR, Finerman GA. Resistant nonunions and partial or complete segmental defects of long bones. Treatment with implants of a composite of human bone morphogenetic protein (BMP) and autolyzed, antigen-extracted, allogeneic (AAA) bone. *Clin Orthop Relat Res* 1992;(277):229-237.
- Gitelis S, Piasecki P. Allograft prosthetic composite arthroplasty for osteosarcoma and other aggressive bone tumors. *Clin Orthop Relat Res* 1991;(270):197-201.

Cornell CN, Lane JM, Chapman M et al. Multicenter trial of Collagraft as bone graft substitute. *J Orthop Trauma* 1991;5(1):1-8.

Uchida A, Araki N, Shinto Y, Yoshikawa H, Kurisaki E, Ono K. The use of calcium hydroxyapatite ceramic in bone tumour surgery. *J Bone Joint Surg Br* 1990;72(2):298-302.

Heise U, Osborn JF, Duwe F. Hydroxyapatite ceramic as a bone substitute. *Int Orthop* 1990;14(3):329-338.

Passuti N, Daculsi G, Rogez JM, Martin S, Bainvel JV. Macroporous calcium phosphate ceramic performance in human spine fusion. *Clin Orthop Relat Res* 1989;(248):169-176.

Bucholz RW, Carlton A, Holmes R. Interporous hydroxyapatite as a bone graft substitute in tibial plateau fractures. *Clin Orthop Relat Res* 1989;(240):53-62.

Lindequist S. Bone grafting in femoral neck fractures: results in 28 cases operated on with multiple pinning and cancellous bone grafting. *Arch Orthop Trauma Surg* 1989;108(2):116-118.

Johnson EE, Urist MR, Finerman GA. Bone morphogenetic protein augmentation grafting of resistant femoral nonunions. A preliminary report. *Clin Orthop Relat Res* 1988;(230):257-265.

Bucholz RW, Carlton A, Holmes RE. Hydroxyapatite and tricalcium phosphate bone graft substitutes. *Orthop Clin North Am* 1987;18(2):323-334.

Sartoris DJ, Gershuni DH, Akeson WH, Holmes RE, Resnick D. Coralline hydroxyapatite bone graft substitutes: preliminary report of radiographic evaluation. *Radiology* 1986;159(1):133-137.

Urist MR, Dawson E. Intertransverse process fusion with the aid of chemosterilized autolyzed antigen-extracted allogeneic (AAA) bone. *Clin Orthop Relat Res* 1981;(154):97-113.