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Systematic Reviews /Meta-analyses

Does conflict of interest affect the reported fusion rates of bone graft substitutes and extenders?

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ABSTRACT

Background: Bone graft extenders are being used more in spine surgery as a substitute for iliac crest bone graft. However, potential conflict of interest could impact average fusion rates. The purpose of this study was to evaluate whether fusion rates reported in the literature were different in papers evaluating bone graft substitutes and extenders when there was potential conflict of interest versus no potential conflict of interest.

Methods: Pubmed was searched for studies evaluating fusion rates when bone graft extenders including demineralized bone matrix, hydroxyapatite, and tricalcium sulfate were used. Studies were screened for one or two level fusions and for degenerative spinal conditions. The average fusion rates of subgroups were compared using unpaired Student's t-tests.

Results: 1928 studies were evaluated. 86 studies were included in the study. The fusion rates varied from 4 to 100%. There were 24 studies with a potential conflict of interest and 62 studies with no conflict of interest. The average fusion rate of all the studies was 84.63% with standard deviation of 18.33%. The average fusion rates of those studies with conflict of interest was 80.93% versus 86.06% without conflict of interest. This was not statistically significant ($p>0.07$). The average fusion rate of studies evaluated by CT scan was 79.8% versus 87.9% without CT. The average fusion rate of studies that employed an independent reviewer to evaluate the fusion was 82.61% versus 85.63% for studies with no independent reviewer.

Conclusion: There is a great variability in the reported fusion rates of bone graft extenders. Counter to expectations, average fusion rates were lower in the studies where there was a potential conflict of interest. The use of CT scans and an independent reviewer seem to account for the lower reported fusion rates, and may be a means of negating the potential conflicts of interest in fusion studies.

Level of Evidence: 2

Introduction

Autologous bone graft is the gold standard for bone grafting material. Studies show fusion rates of 90–100% when autologous bone graft is used for lumbar fusions [1–4]. However, the harvesting of bone graft has considerable morbidity (8% to 39%).[1-4] Also, the amount of bone that can be harvested is finite. This poses a problem in cases where long fusions are necessary. Because of the limitations of autologous bone graft, bone graft extenders and alternatives have been developed.

Demineralized bone matrix (DBM) has been used as a bone graft extender and substitute. DBM is processed allogeneic bone that has been demineralized by a decalcification process [5,6]. DBM also goes through chemical and radiation processes to reduce immunogenic response and infection risk [5,6]. There have been many studies that have demonstrated the efficacy of DBM as a bone graft extender and substitute [7–11]. Similarly, synthetic bone graft substitutes (hydroxyapatite, beta tricalcium phosphate) have also been developed. Studies have shown good clinical results with the use of synthetic bone graft substitutes [12,13].

The use of DBM and synthetic bone graft substitutes in orthopaedic surgery and spine surgery has expanded as a result of positive clinical data. Consequently, the number of commercially available DBM and synthetic bone graft substitute products is constantly increasing. But subsequent studies of DBM and synthetic bone graft substitutes have shown a relatively wide range of fusion rates [7–13]. There are many

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potential reasons for this. Some reasons include the variable amounts of bone growth factors in different DBMs, the indications for which it is used, and the overall health and bone forming capability of the patient [7–11]. One other reason is the potential risk that conflict of interest could play in the reporting of fusion rates when DBM and calcium based substitutes are used. Physicians and investigators could be consultants for, serve on the advisory boards of, or hold stock interest in companies. In these cases, there is the risk that conflict of interest could affect the reporting of the fusion rates when bone graft substitutes and extenders are used.

Therefore, the purpose of this study was to evaluate if fusion rates reported in the literature were different in papers evaluating bone graft substitutes and extenders when there was a potential conflict of interest compared to those that had no reported conflict of interest.

Materials and methods

Search strategy

A comprehensive search of the PubMed database for studies using MeSH terms “demineralized bone matrix”, “DBM”, “bone graft extenders”, “calcium sulfate,” and “spinal fusion" was completed. The results were last updated on December 29, 2019. All qualified studies were screened by three independent investigators. The counsel of a fourth reviewer was considered when there was no consensus.

Study selection criteria

Article inclusion criteria included: age 18 to 80 years, lumbar degenerative diseases requiring one or two level lumbar fusion and use of a bone graft extender. Randomized controlled trials and retrospective reviews were included in the study. Case reports and case series were not included in the study.

Exclusion criteria were: patients presenting with fractures, tumors or infections, scoliosis, and if there was incomplete follow-up data.

Data extraction

Three investigators extracted the relevant data including: study design, characteristics of patients, sample size, details of interventions, follow-up rate and duration, fusion rate, the use of regular X-rays, use of flexion/extension X-rays, use of CT scans, use of independent reviewers, and whether or not a conflict of interest existed. Fusion success was defined as bridging bone on CT scans in the interbody space or posterolateral gutter. Fusion was defined as successful if there was <5° of angulation on flexion–extension radiographs and translation of less than 3mm.

Quality assessment

Conflict of interest was assessed by two investigators that reviewed the disclosures noted in the paper. A paper was at risk of conflict of interest if the authors were consultants, served on advisory boards, or received grants for the study.

Statistical analysis

Unpaired Student’s t-test were used to compare the means of the study groups. The average and standard deviation of each study group is reported. P-values for each comparison are reported.

Results

Demographics (Table 1)

1928 studies were evaluated. 86 studies were included in the study (Supplemental Table 3). There were 24 studies where there was a potential conflict of interest and 62 studies where there was no conflict of interest. 39 of the studies evaluated demineralized bone matrix and 47 studies evaluated hydroxyapatite or beta-tricalcium phosphate. Laminectomy bone was included with the bone graft extender in all of these cases. All of the cases were limited to one or two level lumbar fusions for adult degenerative conditions to help control for variations in disease entity and number of levels fused. Studies where follow-up was less than a year were excluded.

There were 1308 total patients in the studies with a potential conflict of interest and 3696 patients the in studies without a potential conflict of interest. The average age of patients in the studies with potential conflict of interest was 66.8 years old. The average age of patients in the studies without potential conflict of interest was 67 years old. The male to female ratio in the studies with a potential conflict of interest was 11:27 versus 13:28 in those studies without a potential conflict of interest. The average follow-up duration was 16.8 months.

Fusion rate (Table 2)

The fusion rates varied from 4 to 100%. The average fusion rate of all the studies combined was 84.63% with a standard deviation of 18.33%. The average fusion rate of those studies with a potential conflict of interest was 80.93% (standard deviation 18.64%) versus 86.06% (standard deviation 18.16%) for those without conflict of interest. This was not statistically significant (p=0.07). There were 18 studies where iliac crest bone graft was also evaluated. The average fusion rate for studies that evaluated iliac crest bone graft was 83% (standard deviation 13.66%). The average fusion rate of the studies that evaluated demineralized bone matrix was 84.8% (standard deviation 9.18%). The average fusion rate of the studies that used HA and beta tricalcium phosphate substitutes was 89.1% (standard deviation 18.58%)

There were 6 studies evaluating hydroxyapatite and laminectomy bone which had a potential a conflict of interest; the average fusion rate of this subgroup was 90.4% (standard deviation 13.8%). There were 26 studies evaluating hydroxyapatite and laminectomy bone which did not have a conflict; the average fusion rate of this subgroup was 92.3% (standard deviation 23.23%). This difference was not statistically significant ($P = 0.89$).

There were 6 studies evaluating demineralized bone matrix and laminectomy bone which had a potential conflict with an average fusion rate of 79.4% (standard deviation 14.74%). There were 18 studies evaluating demineralized bone matrix and laminectomy bone which did not have a potential conflict with an average fusion rate of 86.6% (standard deviation 9.33%). This difference was not statistically significant ($P = 0.7$).

Independent reviewer (Table 2)

The average fusion rates when there was an independent reviewer was 82.61% (standard deviation 12.64%) versus 85.63% (standard deviation 19.75%) when there was no independent reviewer. This difference was not statistically significant (P=0.21).

CT scans and flexion/extension X-rays (Table 2)

There were 35 studies using CT scans to evaluate fusion, and their average fusion rate was 79.8% (standard deviation 20.14%). There were 51 studies that used CT scans to evaluate fusion, and their average fusion rate was of 87.9% (standard deviation 19.77%). This was statistically significant ($P = 0.05$).

There were 27 studies using flexion/extension X-rays to evaluate fusion, and their average fusion rate was 79.9% (standard deviation 17.06%). There were 57 studies that did not use flexion/extension X-rays to evaluate fusion, and their average fusion rate was 87.7%. This difference was statistically significant ($P = 0.01$).

Table 1
Demographics.

Demographics	
Total Number of Studies	86
All cases were for 1 to 2 levels of lumbar fusion for adult degenerative conditions	
Studies with COI	24
Studies with no COI	62
Studies evaluating DBM	39
Studies evaluating HA or BTP	47
Total number of patients in studies with potential COI	1308
Total number of patients in studies without potential COI	3696
Average follow-up duration	16.8 months
Average age of patients in studies with potential COI	66.8
Average age of patients in studies without potential COI	67
M:F Ratio in studies with potential COI	11:27
M:F Ratio in studies without potential COI	13:28

Abbreviations: COI, Conflict of Interest; DBM, Demineralized Bone Matrix; HA,Hydroxyapatite; BTP, Beta Tricalcium Phosphate

Table 2
Subgroups.

Subgroup	Number of Studies	Average Fusion Rate	Standard Deviation	*P*-value
All Studies	86	84.63%	18.33%	
Iliac Crest Bone Graft	18	83.00%	13.66%	
Demineralized Bone Matrix	24	84.80%	9.18%	
Hydroxyapatite (HA) and BTP Substitutes	37	89.10%	18.58%	
With Conflict of Interest	24	80.93%	18.64%	$P = 0.07$
No Conflict of Interest	62	86.06%	18.16%	
HA + Laminectomy Bone with COI	6	90.40%	13.80%	$P = 0.89$
HA + Laminectomy Bone without COI	26	92.30%	23.23%	
DBM + Laminectomy Bone with COI	6	79.40%	14.74%	$P = 0.7$
DBM + Laminectomy Bone without COI	18	86.60%	9.33%	
Independent Reviewer	19	82.61%	12.64%	$P = 0.21$
No Independent Reviewer	66	85.63%	19.75%	
With CT Scan	35	79.80%	20.14%	$P = 0.05$
No CT Scan	51	87.90%	19.77%	
Flexion/Extension Xrays	27	79.90%	17.06%	$P = 0.01$
No Flexion/Extension Xrays	57	87.70%	19.70%	

Abbreviations: COI, Conflict of Interest; DBM, Demineralized Bone Matrix; HA,Hydroxyapatite; BTP, Beta Tricalcium Phosphate

Discussion

Iliac crest bone graft is the gold standard graft material when performing lumbar fusion [1–4]. However, due to the risks and complications associated with harvesting autologous bone graft and its limited supply, bone graft substitutes and extenders have been developed [1–4]. But there has been considerable variability in the reported fusion rates when demineralized bone matrix, hydroxyapatite, and beta tricalcium phosphate have been used [7–13]. (Table 3)

In this study, the authors performed a literature search and analysis of studies evaluating these bone graft substitutes and extenders. The studies evaluated reported fusion rates ranging from 4 to 100%. The average fusion rate of all the studies evaluating demineralized bone matrix, hydroxyapatite, and beta tricalcium phosphate was 84.63%. The average fusion rate of the studies evaluating demineralized bone matrix was 84.80%. The average fusion rate of those studies with a potential conflict of interest was 80.93% versus an average fusion rate of 86.06% for studies without conflict of interest. This was not statistically significant ($p > 0.07$). Surprisingly, the average fusion rate of the studies with a potential conflict of interest was actually lower than the average fusion rate of the studies without a potential conflict of interest. One of the reasons for this was because 21 of the 24 studies with a potential conflict of interest used CT scans to evaluate their fusions – a more stringent test. In the other 3 studies where CT was not used, both flexion/extension radiographs and an independent reviewer were used. The average fusion rate of those three studies was 71.4%.

The use of advanced imaging was an important variable impacting average fusion rates. The use of CT scans to evaluate fusion significantly affected the average fusion rate. The average fusion rate of the studies that used CT scans was 79.8%, while the average fusion rate of the studies that did not use CT scans was 87.9%. This difference was statistically significant (P=0.05). Another important variable was the use of flexion/extension X-rays. Studies using flexion/extension X-rays to evaluation fusion had an average fusion rate of 79.9% while studies that did not use flexion/extension X-rays had an average fusion rate of 87.7%. This difference was also statistically significant ($P = 0.01$). Therefore, it appears the more demanding assessment of fusion presented by advanced imaging such as CT scan or flexion/extension X-rays lowers the average fusion rate in studies that choose to use them to appraise their results.

Another parameter that was evaluated was the use of an independent reviewer to assess the fusion. There were 19 studies that used an independent reviewer and the average fusion rate of these studies was 82.6%. In the 66 studies that did not have an independent reviewer, the reported fusion rate was 85.6%. This was not statistically significant ($P = 0.21$). It should be noted that independent reviewers were only used in cases where there was a potential conflict of interest. Consequently, the use of an independent reviewer may be another reason why the average fusion rate was lower in these studies.

When studies are supported by industry, there is the concern that the data could be influenced by bias [14–17]. While the bias is not likely to be intentional, there is the risk that financial compensation or support

Table 3
Supplemental Table.

	Title	Lead Author	Journal	Year	F/U (months)	Conflict (y/n)	Sample Size	Fusion rate	Flex/Ext X-rays	CT Scan	Independent Reviewer	Bone Graft Substitute
1	Adjuncts in posterior lumbar spine fusion: comparison of complications and efficacy	Hoffmann MF	Arch Orthop Trauma Surg	2012	12 mo	No	306	86.9	No	No	No	DBM
2	Posterolateral fusion in acute traumatic thoracolumbar fractures: a comparison of demineralized bone matrix and autologous bone graft	Baumann F	Acta Chir Orthop Traumatol Cech	2015	12 mo	No	16	94	No	No	No	DBM
3	Bone Union Rate Following Instrumented Posterolateral Lumbar Fusion: Comparison between Demineralized Bone Matrix versus Hydroxyapatite	Nam WD	Asian Spine J	2016	12 mo	No	38	73	No	No	No	DBM + laminectomy bone
4	The clinical and radiological outcomes of minimally invasive transforaminal lumbar interbody single level fusion	Kim MC	Asian Spine J	2011	24 mo	No	56	95.4	No	No	No	DBM + laminectomy bone
5	Clinical and radiographic outcomes of concentrated bone marrow aspirate with allograft and demineralized bone matrix for posterolateral and interbody lumbar fusion in elderly patients	Ajiboye RM	Eur Spine J	2015	12 mo	No	31	83.6	No	No	No	DBM + BMA
6	Comparison of Posterior Lumbar Interbody Fusion and Posterolateral Lumbar Fusion in Monosegmental Vacuum Phenomenon within an Intervertebral Disc	An KC	Asian Spine J	2010	24 mo	No	46	89.4	No	No	No	DBM + laminectomy bone
7	Comparison of clinical and radiological results of posterolateral fusion, posterior lumbar interbody fusion and transforaminal lumbar interbody fusion techniques in the treatment of degenerative lumbar spine	Audat Z	Singapore Med J	2012	12 mo	No	17	88	No	No	No	DBM + laminectomy bone
8	Comparison of Clinical and Radiological Results of Posterolateral Fusion and Posterior Lumbar Interbody Fusion in the Treatment of L4 Degenerative Lumbar Spondylolisthesis	Kuraishi S	Asian Spine J	2016	12 mo	No	12	73	No	No	No	DBM + laminectomy bone
9	Transforaminal lumbar interbody fusion (TLIF) versus posterolateral instrumented fusion (PLF) in degenerative lumbar disorders: a randomized clinical trial with 2-year follow-up	Kristian Høy	Eur spine jounal	2013	24 mo	No	47	88	No	No	No	DBM + laminectomy bone
10	Circumferential lumbar spinal fusion with Brantigan cage versus posterolateral fusion with titanium Cotrel-Dubousset instrumentation: a prospective, randomized clinical study of 146 patients	Christensen FB	Spine (Phila Pa 1976)	2002	60 mo	No	148	80	No	No	No	DBM + ICBG
11	Circumferential fusion improves outcome in comparison with instrumented posterolateral fusion: long-term results of a randomized clinical trial	Videbaek TS	Spine (Phila Pa 1976)	2006	24 mo	No	148	80	No	No	No	DBM + ICBG
12	Instrumented slip reduction and fusion for painful unstable isthmic spondylolisthesis in adults	Floman Y	J Spinal Disord Tech	2008	12 mo	No	12	100	No	No	No	DBM + ICBG
13	Clinical outcomes of 3 fusion methods through the posterior approach in the lumbar spine	Kim KT	Spine (Phila Pa 1976)	2006	12 mo	No	62	92	No	No	No	DBM + laminectomy bone
14	Posterior lumbar interbody fusion versus posterolateral fusion with instrumentation in the treatment of low-grade isthmic spondylolisthesis: midterm clinical outcomes	Müslüman AM	J Neurosurg Spine	2011	18 mo	No	25	84	No	No	No	DBM + laminectomy bone
15	One, two-, and three-level instrumented posterolateral fusion of the lumbar spine with a local bone graft: a prospective study with a 2-year follow-up	Inage K	Spine (Phila Pa 1976)	2011	24 mo	No	40	88	No	No	No	DBM + laminectomy bone

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Table 3 (*continued*)

	Title	Lead Author	Journal	Year	F/U (months)	Conflict (y/n)	Sample Size	Fusion rate	Flex/Ext X-rays	CT Scan	Independent Reviewer	Bone Graft Substitute
16	Clinical and Radiological Comparison between Three Different Minimally Invasive Surgical FusionTechniques for Single-Level Lumbar Isthmic and Degenerative Spondylolisthesis: Minimally Invasive Surgical Posterolateral Fusion versus Minimally Invasive Surgical Transforaminal Lumbar Interbody Fusion versus Midline Lumbar Fusion	Elmekaty M	Asian Spine J	2018	12 mo	No	22	100	No	No	No	HA + laminectomy bone
17	Postoperative Evaluation of Health-Related Quality-of-Life (HRQoL) of Patients With Lumbar Degenerative Spondylolisthesis After Instrumented Posterolateral Fusion (PLF): A prospective Study With a 2-Year Follow-Up	Kapetanakis S	Open Orthop J	2017	24 mo	No	62	97	No	No	No	DBM + laminectomy bone
18	Posterolateral fusion versus Dynesys dynamic stabilization: Retrospective study at a minimum 5.5years' follow-up	Bredin S	Orthop Traumatol Surg Res	2017	60 mo	No	25	92	No	No	No	DBM + laminectomy bone
19	Natural hydroxyapatite as a bone graft extender for posterolateral spine arthrodesis	Garin C	Int Orthop	2016	12 mo	No	47	100	No	No	No	HA + laminectomy bone
20	The fusion rate of calcium sulfate with local autograft bone compared with autologous iliac bone graft for instrumented short-segment spinal fusion	Chen WJ	Spine (Phila Pa 1976)	2005	32.5 mo	No	39	87.2	No	No	No	Calium sulfate + laminectomy bone
21	Single-center, consecutive series study of the use of a novel platelet-rich fibrin matrix (PRFM) and beta-tricalcium phosphate in posterolateral lumbar fusion	Callanan TC	Eur Spine J	2019	12 mo	No	50	92.4	No	No	No	BTP + PRP + BMA
22	Porosity of β-tricalcium phosphate affects the results of lumbar posterolateral fusion	Wang Z	J Spinal Disord Tech	2013	12 mo	No	60	93.3	No	No	No	BTP + laminectomy bone
23	Effectiveness of nano-hydroxyapatite/polyamide-66 Cage in interbody fusion for degenerative lumbar scoliosis	Hu J	Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi (Chinese)	2019	12 mo	No	43	100	No	No	No	HA + laminectomy bone
24	Effectiveness of posterior pedicle screw system combined with interbody fusion in treating lumbar spondylolisthesis	Meng C	Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi (Chinese)	2010	12 mo	No	27	100	No	No	No	HA + laminectomy bone
25	Clinical outcomes of two types of cages used in transforaminal lumbar interbody fusion for the treatment of degenerative lumbar diseases: n-HA/PA66 cages versus PEEK cages	Deng QX	J Mater Sci Mater Med	2016	12 mo	No	266	92.45	No	No	No	HA + laminectomy bone
26	Radiological study on the n-HA/PA66 cage used in the transforaminal lumbar interbody fusion	Sang PM	Zhongguo Gu Shang (Chinese)	2014	12 mo	No	50	100	No	No	No	HA + laminectomy bone
27	Treatment of lumbar instability with transforaminal lumbar interbody fusion (with single cage) combined with unilateral pedicle screw fixation	Hua YJ	Zhongguo Gu Shang (Chinese)	2014	12 mo	No	50	100	No	No	No	HA + laminectomy bone

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Table 3 (*continued*)

	Title	Lead Author	Journal	Year	F/U (months)	Conflict (y/n)	Sample Size	Fusion rate	Flex/Ext X-rays	CT Scan	Independent Reviewer	Bone Graft Substitute
28	Unilateral pedicle screw fixation and transforaminal lumbar interbody fusion through paraspinal muscle approach for recurrent lumbar disc herniation combined with lumbar instability	Pan B	Zhongguo Gu Shang (Chinese)	2014	12 mo	No	35	97.1	No	No	No	HA + laminectomy bone
29	Unilateral pedicle screw fixation versus its combination with contralateral translaminar facet screw fixation for the treatment of single segmental lower lumbar vertebra diseases	Zeng ZY	Zhongguo Gu Shang (Chinese)	2015	12 mo	No	62	96.9	No	No	No	HA + laminectomy bone
30	Two different fixation methods combined with lumbar interbody fusion for the treatment of two-level lumbar vertebra diseases: a clinical comparison study	Zeng ZY	Zhongguo Gu Shang (Chinese)	2015	12 mo	No	49	96.2	No	No	No	HA + laminectomy bone
31	Case control study on two different surgical approaches combined fixation with lumbarinterbody fusion for the treatment of single segmental lumbar vertebra diseases	Zeng ZY	Zhongguo Gu Shang (Chinese)	2015	12 mo	No	86	95.6	No	No	No	HA + laminectomy bone
32	Fusion rate according to mixture ratio and volumes of bone graft in minimally invasive transforaminal lumbar interbody fusion: minimum 2-year follow-up	Yoo JS	Eur J Orthop Surg Traumatol	2015	24 mo	No	88	87.8	No	No	No	HA + laminectomy bone
33	The clinical and radiological outcomes of multilevel minimally invasive transforaminal lumbarinterbody fusion	Min SH	Eur Spine J	2013	12 mo	No	172	89.96	No	No	No	HA + laminectomy bone
34	Minimally invasive or open transforaminal lumbar interbody fusion as revision surgery for patients previously treated by open discectomy and decompression of the lumbar spine	Wang J	Eur Spine J	2011	12 mo	No	52	96.1	No	No	No	HA + laminectomy bone
35	Comparison of one-level minimally invasive and open transforaminal lumbar interbody fusion in degenerative and isthmic spondylolisthesis grades 1 and 2.	Wang J	Eur Spine J	2010	13 mo	No	85	97.6	No	No	No	HA + laminectomy bone
36	Comparison of the clinical outcome in overweight or obese patients after minimally invasive versus open transforaminal lumbar interbody fusion	Wang J	J Spinal Disord Tech	2014	13 mo	No	72	97.2	No	No	No	HA + laminectomy bone
37	Usefulness of Contralateral Indirect Decompression through Minimally Invasive Unilateral Transforaminal Lumbar Interbody Fusion	Min SH	Asian Spine J	2014	12 mo	No	30	93.3	No	No	No	HA + laminectomy bone
38	The efficacy of porous hydroxyapatite bone chip as an extender of local bone graft in posterior lumbar interbody fusion	Kim H	Eur Spine J	2012	12 mo	No	130	91.7	No	No	No	HA + laminectomy bone
39	Posterior lumbar interbody fusion using a unilateral single cage and a local morselized bone graft in the degenerative lumbar spine	Kim DH	Clin Orthop Surg	2009	12 mo	No	53	98.1	No	No	No	HA + laminectomy bone
40	Minimally Invasive Transforaminal Lumbar Interbody Fusion and Unilateral Fixation for Degenerative Lumbar Disease	Wang HW	Orthop Surg	2017	12 mo	No	58	94.8	No	No	No	HA + laminectomy bone

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Table 3 (*continued*)

	Title	Lead Author	Journal	Year	F/U (months)	Conflict (y/n)	Sample Size	Fusion rate	Flex/Ext X-rays	CT Scan	Independent Reviewer	Bone Graft Substitute
41	Effect evaluation of over 5 year follow up of unilateral pedicle screw fixation with transforaminal lumbar interbody fusion for lumbar degenerative diseases	Wang C	Zhongguo Gu Shang	2016	60 mo	No	24	95.8	No	No	No	HA + laminectomy bone
42	Comparative study of microendoscope-assisted and conventional minimally invasive transforaminal lumbar interbody fusion for degenerative lumbar diseases	Dong J	Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi (Chinese)	2019	12 mo	No	53	92.9	No	No	No	HA + laminectomy bone
43	Two-year outcome of hydroxyapatite mixed with autogenous bone marrow and local bone graft for posterolateral lumbar fusion	Sathira-Angkura V	J Med Assoc Thai	2011	24 mo	No	23	4.4	No	No	No	HA + laminectomy bone
44	Clinical and CT Analysis of Lumbar Spine Arthrodesis: β-Tricalcium Phosphate Versus Demineralized Bone Matrix	Ricart PH	J Am Acad Orthop Surg Glob Res Rev	2018	12 mo	No	41	90	No	Yes	No	DBM + laminectomy bone
45	Demineralized bone matrix composite grafting for posterolateral spinal fusion	Vaccaro AR	Orthopedics	2007	24 mo	No	27	70%	No	Yes	No	DBM + ICBG
46	Comparison of Silicate-Substituted Calcium Phosphate (Actifuse) with Recombinant Human Bone Morphogenetic Protein-2 (Infuse) in Posterolateral Instrumented Lumbar Fusion	Paul Licina	Global Spine J	2015	12 mo	Yes	9	100	No	Yes	No	HA + laminectomy bone
47	Clinical and radiological comparison of posterolateral fusion and posterior interbody fusiontechniques for multilevel lumbar spinal stabilization in manual workers	Aygün H	Asian Spine J	2014	24 mo	No	42	81	No	Yes	No	DBM + laminectomy bone
48	Comparison of a calcium phosphate bone substitute with recombinant human bone morphogenetic protein-2: a prospective study of fusion rates, clinical outcomes and complications with 24-month follow-up	Parker RM	Eur Spine J	2017	12 mo	No	25	70	No	Yes	No	BTP
49	Fusion rate and clinical outcome in anterior lumbar interbody fusion with beta-tricalcium phosphate and bone marrow aspirate as a bone graft substitute. A prospective clinical study in fifty patients.	Lechner R	Int Orthop	2017	12 mo	No		77.78	No	Yes	No	BTP
50	Within Patient Radiological Comparative Analysis of the Performance of Two Bone Graft Extenders Utilized in Posterolateral Lumbar Fusion: A Retrospective Case Series.	Stewart G	Front Surg	2016	12 mo	Yes	27	92.9	No	Yes	No	HA + laminectomy bone
51	The first clinical trial of beta-calcium pyrophosphate as a novel bone graft extender in instrumented posterolateral lumbar fusion	Lee JH	Clin Orthop Surg	2011	12 mo	No	31	87	No	Yes	No	BTP + laminectomy bone
52	Evaluation of hydroxyapatite and beta-tricalcium phosphate mixed with bone marrow aspirate as a bone graft substitute for posterolateral spinal fusion	Sanjay Bansal	Indian J Orthop	2009	12 mo	No	30	100	No	Yes	No	BTP + HA + BMA
53	Early clinical effect of intervertebral fusion of lumbar degenerative disease using nano-hydroxyapatite/polyamide 66 intervertebral fusion cage	Yang B	Sheng Wu Yi Xue Gong Cheng Xue Za Zhi (Chinese)	2014	12 mo	No	27	100	No	Yes	No	HA + laminectomy bone
54	Short-term effectiveness of nano-hydroxyapatite/polyamide-66 intervertebral cage for lumbarinterbody fusion in patients with lower lumbar degenerative diseases	Yang X	Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi (Chinese)	2012	6 mo	No	20	96	No	Yes	No	HA + laminectomy bone
55	Paraspinal muscle changes of unilateral multilevel minimally invasive transforaminal interbody fusion	Yoo JS	J Orthop Surg Res	2014	12 mo	No	92	87	No	Yes	No	HA + laminectomy bone

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Table 3 (*continued*)

	Title	Lead Author	Journal	Year	F/U (months)	Conflict (y/n)	Sample Size	Fusion rate	Flex/Ext X-rays	CT Scan	Independent Reviewer	Bone Graft Substitute
56	The fusion rate of demineralized bone matrix compared with autogenous iliac bone graft for long multi-segment posterolateral spinal fusion	Fu TS	BMC Musculoskelet Disord	2016	12 mo	No	26	80	Yes	No	No	DBM + laminectomy bone
57	A comparison of posterolateral lumbar fusion comparing autograft, autogenous laminectomy bone with bone marrow aspirate, and calcium sulphate with bone marrow aspirate: a prospective randomized study	Niu CC	Spine (Phila Pa 1976)	2009	12 mo	No	43	45.5	Yes	No	No	Calium sulfate + BMA
58	Surgical outcomes after instrumented lumbar surgery in patients of eighty years of age and older	Liao JC	BMC Musculoskelet Disord	2016	24 mo	No	72	87.5	Yes	No	No	DBM + laminectomy bone
59	Surgical outcomes in the elderly with degenerative spondylolisthesis: comparative study between patients over 80 years of age and under 80 years-a gender-, diagnosis-, and surgical method-matched two-cohort analyses	Liao JC	Spine J	2018	24 mo	No	76	89.5	Yes	No	No	DBM + laminectomy bone
60	Hybrid grafting using bone marrow aspirate combined with porous β-tricalcium phosphate and trephine bone for lumbar posterolateral spinal fusion: a prospective, comparative study versus local bone grafting	Yamada T	Spine (Phila Pa 1976)	2012	24 mo	No	61	93.5	Yes	No	No	BTP + laminectomy bone + BMA
61	Fusion in degenerative spondylolisthesis: comparison of osteoconductive and osteoinductive bone graft substitutes	Kurd M	Eur Spine J	2015	18 mo	No	126	87.18	Yes	Yes	No	DBM + laminectomy bone
62	Comparison of Clinical and Radiological Outcomes of Lumbar Interbody Fusion Using a Combination of Hydroxyapatite and Demineralized Bone Matrix and Autografts for Lumbar Degenerative Spondylolisthesis	Gatam AR	Asian Spine J	2017	12 mo	No	17	76.5	Yes	Yes	No	DBM + HA
63	Matched Comparison of Fusion Rates between Hydroxyapatite Demineralized Bone Matrix and Autograft in Lumbar Interbody Fusion	Kim DH	J Korean Neurosurg Soc	2016	12 mo	yes	130	52	Yes	Yes	No	HA-DBM
64	Comparison of posterolateral lumbar fusion and posterior lumbar interbody fusion for patients younger than 60 years with isthmic spondylolisthesis	Lee GW	Spine (Phila Pa 1976)	2014	24 mo	No	39	84.6	Yes	Yes	No	DBM + laminectomy bone
65	Unidirectional porous β-tricalcium phosphate induces bony fusion in lateral lumbar interbody fusion	Kumagai H	J Clin Neurosci	2019	12 mo	Yes	11	70.9	Yes	Yes	No	BTP
66	The use of beta-tricalcium phosphate and bone marrow aspirate as a bone graft substitute in posterior lumbar interbody fusion	Thaler M	Eur Spine J	2013	12 mo	No	34	26.67	N/A	Yes	No	BTP + BMA
67	Augmenting local bone with Grafton demineralized bone matrix for posterolateral lumbar spine fusion: avoiding second site autologous bone harvest.	Sassard WR	Orthopedics	2000	12 mo	Yes	56	60	No	Yes	Yes	DBM + laminectomy bone
68	Radiographic Analysis of Instrumented Posterolateral Fusion Mass Using Mixture of Local Autologous Bone and b-TCP (PolyBone®) in a Lumbar Spinal Fusion Surgery	Park JH	J Korean Neurosurg Soc	2011	12 mo	Yes	32	83	No	Yes	Yes	BTP + laminectomy bone
69	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	Frank P. Cammisa	Spine (Phila Pa 1976)	2004	24 mo	Yes	120	52	Yes	No	Yes	DBM + ICBG
70	Posterolateral lumbar spine fusion using a novel demineralized bone matrix: a controlled case pilot study	Constantin Schizas	Arch Orthop Trauma Surg	2008	12 mo	Yes	59	69.7	Yes	No	Yes	DBM
71	Instrumented posterolateral lumbar fusion using coralline hydroxyapatite with or without demineralized bone matrix, as an adjunct to autologous bone	Thalgott JS	Spine J	2001	12 mo	Yes	40	92.5	Yes	No	Yes	Coraline HA

(*continued on next page*)

Table 3 (*continued*)

	Title	Lead Author	Journal	Year	F/U (months)	Conflict (y/n)	Sample Size	Fusion rate	Flex/Ext X-rays	CT Scan	Independent Reviewer	Bone Graft Substitute
72	Fusion rates and SF-36 outcomes after multilevel laminectomy and noninstrumented lumbar fusions in a predominantly geriatric population	Epstein NE	Journal of Spinal Disorders & Techniques	2008	12 mo	Yes	75	82.7	Yes	Yes	Yes	DBM + laminectomy bone
73	Grafton and local bone have comparable outcomes to iliac crest bone in instrumented single-level lumbar fusions	Kang J	Spine (Phila Pa 1976)	2012	24 mo	Yes	30	86	Yes	Yes	Yes	DBM + laminectomy bone
74	SF-36 outcomes and fusion rates after multilevel laminectomies and 1 and 2-level instrumented posterolateral fusions using lamina autograft and demineralized bone matrix	Epstein NE	J Spinal Disord Tech	2007	24 mo	Yes	140	96	Yes	Yes	Yes	DBM + laminectomy bone
75	Demineralized Bone Matrix (DBM) as a Bone Void Filler in Lumbar Interbody Fusion: A Prospective Pilot Study of Simultaneous DBM and Autologous Bone Grafts	Kim BJ	J Korean Neurosurg Soc	2017	12 mo	Yes	19	65	Yes	Yes	Yes	DBM + laminectomy bone
76	A prospective consecutive study of instrumented posterolateral lumbar fusion using synthetic hydroxyapatite (Bongros-HA) as a bone graft extender	Lee JH	J Biomed Mater Res A	2009	12 mo	Yes	32	86.7	Yes	Yes	Yes	DBM + laminectomy bone
77	A preliminary comparative study of radiographic results using mineralized collagen and bone marrow aspirate versus autologous bone in the same patients undergoing posterior lumbar interbody fusion with instrumented posterolateral lumbar fusion	Kitchel SH	Spine J	2006	24 mo	Yes	25	80	Yes	Yes	Yes	DBM
78	Use of Nanocrystalline Hydroxyapatite With Autologous BMA and Local Bone in the Lumbar Spine: A Retrospective CT Analysis of Posterolateral Fusion Results	Robbins S	Clin Spine Surg	2017	12 mo	Yes	46	91	Yes	Yes	Yes	HA + laminectomy bone
79	Beta tricalcium phosphate: observation of use in 100 posterolateral lumbar instrumented fusions	Epstein NE	Spine J	2009	12 mo	Yes	100	90	Yes	Yes	Yes	HA + laminectomy bone
80	A preliminary study of the efficacy of Beta Tricalcium Phosphate as a bone expander for instrumented posterolateral lumbar fusions	Epstein NE	J Spinal Disord Tech	2006	12 mo	Yes	40	92.5	Yes	Yes	Yes	BTP + laminectomy bone
81	Transforaminal Lumbar Interbody Fusion With Viable Allograft: 75 Consecutive Cases at 12-Month Follow-up	Tally WC	Int J Spine Surg	2018	12 mo	Yes	75	96	Yes	Yes	Yes	DBM + BMA
82	An analysis of noninstrumented posterolateral lumbar fusions performed in predominantly geriatric patients using lamina autograft and beta tricalcium phosphate	Epstein NE	Spine J	2008	24 mo	Yes	60	85	Yes	Yes	Yes	BTP + laminectomy bone + BMA
83	Results of lumbar spondylodeses using different bone grafting materials after transforaminal lumbar interbody fusion (TLIF)	vonderHoeh NH	Eur Spine J	2017	12 mo	Yes	48	91.7	Yes	Yes	Yes	HA + laminectomy bone
84	Efficacy of silicate-substituted calcium phosphate ceramic in posterolateral instrumented lumbarfusion	Jenis LG	Spine (Phila Pa 1976)	2010	24 mo	Yes	42	76.5	Yes	Yes	Yes	HA + laminectomy bone
85	Clinical and radiographic outcomes of extreme lateral approach to interbody fusion with β-tricalcium phosphate and hydroxyapatite composite for lumbar degenerative conditions	Rodgers WB	Int J Spine Surg	2012	12 mo	Yes	50	93.2	N/A	Yes	Yes	BTP + HA + BMA
86	A prospective comparative study of radiological outcomes after instrumented posterolateral fusion mass using autologous local bone or a mixture of beta-tcp and autologous local bone in the same patient	Kong S	Acta Neurochir	2013	12 mo	Yes	42	57.1	Yes	Yes	N/A	BTP + laminectomy bone

Abbreviations: DBM, Demineralized Bone Matrix; HA, Hydroxyapatite; BTP, Beta Tricalcium Phosphate; ICGB, Iliac Crest Bone Graft; PRP, Platelet Rich Plasma; BMA, Bone Marrow Aspirate

to the researchers could subconsciously influence the researchers [14–17]. But, industry support has become a key funding source for new studies and advancement in science [17–20]. In all likelihood, the gains that science has made recently would not have been possible without the support from industry [19–20]. Thus, if industry is going to support research or perform its own research, it is beneficial to patients, the scientific community, and industry itself to have safeguards in place to ensure that the data is not biased.

There are some limitations of this study. First, the authors may not have fully or honestly disclosed whether or not they had a conflict of interest. Also, the number of authors who had a potential conflict of interest was not evaluated. Any study that had a conflict of interest was reported as "conflicted" regardless of how many authors had a potential conflict of interest. The number of authors conflicted and the seniority of that conflicted researcher may play a role. But the number of studies where there was a potential conflict of interest was not large enough to evaluate that variable. Also, the degree of conflict was not evaluated.

Based on the results of this study, there was no statistically significant difference in the average fusion rates in studies using DBM or synthetic bone graft substitutes regardless of the presence of a potential conflict of interest. The reported fusion rates of studies with a potential conflict of interest were actually lower than the studies that did not have a potential conflict of interest. Two variables that contributed to this were the use of advanced imaging and the use of independent reviewers. Hence, advanced imaging such as CT scans and flexion/extension X-rays may have the biggest impact on the variability of average fusion rates. More studies are necessary to further evaluate if other factors may play a role in average fusion rates when there is a potential conflict of interest.

Financial disclosures and Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.xnsj.2022.100112.

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