Systematic Reviews /Meta-analyses

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

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\textbf{A R T I C L E  I N F O}

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\textbf{A B S T R A C T}

\textbf{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.

\textbf{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.

\textbf{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.

\textbf{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.

\textbf{Level of Evidence:} 2

\textbf{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%).\textsuperscript{11–14} 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 tri-calcium 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. Laminctomy 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 in the 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 laminctomy bone which had a potential conflict of interest; the average fusion rate of this subgroup was 90.4% (standard deviation 13.8%). There were 26 studies evaluating hydroxyapatite and laminctomy 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=0.69).

There were 6 studies evaluating demineralized bone matrix and laminctomy 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 laminctomy 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).
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 evaluate 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

| 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                | 87.00%              | 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
| 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 Surg   | 2012 | 12 mo        | No            | 306         | 86.9        | No                | No      | No                   | DBM                  |
| 2 Posterior lumbar fusion in acute traumatic thoracolumbar fractures: a comparison of demineralized bone matrix and autologous bone graft   | Baumann F            | Trauma surg        | 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 transfemoral 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 Posterolateral 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 a 2-year follow-up | Krishnam Hey         | Eur spine journal  | 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 (phil 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 | Videbeak T           | Spine (phil 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 disorder  | 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 K                | Tech spine (phil 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 | Image K             | Spine (phil pa 1976) | 2011 | 24 mo        | No            | 40          | 88          | No                | No      | No                   | DBM + laminectomy bone |

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| 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                      |
|----------------------------------------------------------------------|----------------------|-----------------------|------|--------------|---------------|-------------|-------------|-----------------|--------|----------------------|--------------------------------------------|
| Clinical and Radiological Comparison between Three Different Minimally Invasive Surgical Fusion Techniques for Single-Level Lumbar Isthmic and Degenerative Spondylolisthesis: Minimally Invasive Surgical Posterior Fusion versus Minimally Invasive Surgical Transforaminal Lumbar Interbody Fusion versus Midline Lumbar Fusion | Elmekaty M           | Asian Spine J         | 2018 | 12            | No            | 22          | 100         | No              | No     | No                   | HA + laminectomy bone                     |
| Postoperative Evaluation of Health-Related Quality-of-Life (HRQoL) of Patients With Lumbar Degenerative Spondylolisthesis After Instrumented Posterior Fusion (PLF): A prospective Study With a 2-Year Follow-Up | Kapetanakis S        | Open Orthop J         | 2017 | 24            | No            | 62          | 97          | No              | No     | No                   | DBM + laminectomy bone                    |
| Posterolateral fusion versus Dynesys dynamic stabilization: Retrospective study at a minimum 5.5years’ follow-up | Bredin S             | Orthop Traumatol Surg Res | 2017 | 60            | No            | 25          | 92          | No              | No     | No                   | DBM + laminectomy bone                    |
| Natural hydroxyapatite as a bone graft extender for posterolateral spine arthrodesis | Garin C              | Int Orthop            | 2016 | 12            | No            | 47          | 100         | No              | No     | No                   | HA + laminectomy bone                     |
| 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 (Phil Pa 1976)   | 2005 | 32.5          | No            | 39          | 87.2        | No              | No     | No                   | Calcium sulfate + laminectomy bone        |
| 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            | No            | 50          | 92.4        | No              | No     | No                   | BTP + PRP + BMA                            |
| Porosity of β-tricalcium phosphate affects the results of lumbar posterolateral fusion | Wang Z               | J Spinal Disord Tech  | 2013 | 12            | No            | 60          | 93.3        | No              | No     | No                   | BTP + laminectomy bone                    |
| 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            | No            | 43          | 100         | No              | No     | No                   | HA + laminectomy bone                     |
| 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            | No            | 27          | 100         | No              | No     | No                   | HA + laminectomy bone                     |
| 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            | No            | 266         | 92.45       | No              | No     | No                   | HA + laminectomy bone                     |
| Radiological study on the n-HA/PA66 cage used in the transformal lumbar interbody fusion | Sang PM              | Zhongguo Gu Shang (Chinese) | 2014 | 12            | No            | 50          | 100         | No              | No     | No                   | HA + laminectomy bone                     |
| Treatment of lumbar instability with transformal lumbar interbody fusion (with single cage) combined with unilateral pedicle screw fixation | Hua YJ               | Zhongguo Gu Shang (Chinese) | 2014 | 12            | No            | 50          | 100         | No              | No     | No                   | HA + laminectomy bone                     |

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| 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 paraspinous 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 transaminar 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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| 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 Substrate |
|----------------------------------------------------------------------|---------------------|--------------------------|------|--------------|----------------|-------------|-------------|------------------|---------|----------------------|---------------------|
| 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 |
| Comparative study of microendoscopy-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 |
| 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 |
| 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 |
| Demineralized bone matrix composite grafting for posterolateral spinal fusion | Vaccaro AR          | Orthopedics               | 2007 | 24 mo        | No             | 27          | 70%         | No               | Yes     | No                   | DBM + ICBG |
| 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 |
| Clinical and radiological comparison of posterolateral fusion and posterior interbody fusion techniques 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 |
| 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 |
| 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             | 31          | 87          | No               | Yes     | No                   | HA + laminectomy bone |
| Within Patient Radiological Comparative Analysis of the Performance of Two Bone Graft Extenders Utilized in Posteriorlumbar Lumbar Fusion: A Retrospective Case Series. | Stewart G           | Front Surg                | 2016 | 12 mo        | Yes            | 27          | 92.9        | No               | Yes     | No                   | HA + laminectomy bone |
| 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             | 3          | 87          | No               | Yes     | No                   | BTP + laminectomy bone |
| 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 |
| 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 |
| Short-term effectiveness of nano-hydroxyapatite/polyamide-66 intervertebral cage for lumbar interbody 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 |
| 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 |
| Title                                                                 | Lead Author | Journal                           | Year | F/U (months) | Conflict (y/n) | Sample Size | Fusion rate | Flex/Ext X-rays | CT Scan | Independent Reviewer | Independent Bone Graft Substitute |
|---------------------------------------------------------------------|-------------|-----------------------------------|------|--------------|---------------|-------------|-------------|-----------------|---------|---------------------|----------------------------------|
| 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          | No              | No      | No                  | DBM + laminectomy bone            |
| 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 (Phil Pa 1976)             | 2009 | 12 mo        | No            | 43          | 45.5        | Yes             | No      | No                  | Calium sul-fate + BMA             |
| 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            |
| 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            |
| Hybrid grafting using bone marrow aspirate combined with porous  \(\beta\)-tricalcium phosphate and trephine bone for lumbar posterolateral spinal fusion: a prospective, comparative study versus local bone grafting | Yamada T    | Spine (Phil Pa 1976)             | 2012 | 24 mo        | No            | 61          | 93.5        | Yes             | No      | No                  | BTP + laminectomy bone + BMA     |
| Fusion in degenerative spondylolisthesis: comparison of osteoconductive and osteoinductive bone graft substitutes | Kurt M      | Eur Spine J                       | 2015 | 18 mo        | No            | 126         | 87.18       | Yes             | Yes     | No                  | DBM + laminectomy bone            |
| 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                         |
| 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                           |
| Comparison of posterolateral lumbar fusion and posterior lumbar interbody fusion for patients younger than 60 years with ischmic spondylolisthesis | Lee GW      | Spine (Phil Pa 1976)             | 2014 | 24 mo        | No            | 39          | 84.6        | Yes             | Yes     | No                  | DBM + laminectomy bone            |
| Unidirectional porous \(\beta\)-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                               |
| 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             | No      | No                  | BTP + BMA                         |
| 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     | No                  | DBM + laminectomy bone            |
| 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            |
| 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 (Phil Pa 1976)            | 2004 | 24 mo        | Yes           | 120         | 52          | Yes             | No      | No                  | DBM + ICBG                        |
| 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      | No                  | DBM                              |
| Instrumented posterolateral lumbar fusion using coraline 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)
| 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 |
|----------------------------------------------------------------------|-------------|----------------------------------------------|------|--------------|----------------|-------------|-------------|------------------|---------|----------------------|-----------------------|
| 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 |
| 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 |
| 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 |
| 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 |
| A prospective consecutive study of instrumented posterolateral lumbar fusion using synthetic hydroxyapatite (Bongrus-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 |
| 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                    |
| 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  |
| 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  |
| 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 |
| 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               |
| 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 |
| 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  |
| 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  |
| 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          |
| 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             | N/A     | Yes                  | 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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