

Use of demineralized bone matrix in spinal fusion

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Abstract

Spinal fusion remains the gold-standard treatment for several pathological spine conditions. Although, autologous Iliac Crest Bone Grafting is considered the gold-standard graft choice to promote spinal fusion; however, it is associated with significant donor site morbidity and a limited graft quantity. Therefore, several bone graft alternatives have been developed, to augment arthrodesis. The purpose of this review is to present the results of clinical studies concerning the use of demineralized bone matrix (DBM), alone or as a composite graft, in the spinal fusion. A critical review of the English-language literature was conducted on Pubmed, using key word "demineralized bone matrix", "DBM", "spinal fusion", and "scoliosis". Results had been restricted to clinical studies. The majority of clinical trials demonstrate satisfactory fusion rates when DBM is employed as a graft extender or a graft enhancer.

Limited number of prospective randomized controlled trials (4 studies), have been performed comparing DBM to autologous iliac crest bone graft in spine fusion. The majority of the clinical trials demonstrate comparable efficacy of DBM when it used as a graft extender in combination with autograft, but there is no clinical evidence to support its use as a standalone graft material. Additionally, high level of evidence studies are required, in order to optimize and clarify the indications of its use and the appropriate patient population that will benefit from DBM in spine arthrodesis.

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Key words: Bone grafts; Demineralized bone matrix; Spinal fusion; Scoliosis

Core tip: It is widely accepted that autologous iliac crest bone graft (ICBG) is considered the gold-standard for spinal fusion surgery, although it is associated with a series of complications and a morbidity rate. Demineralized bone matrix (DBM) could be successfully used as a potential graft extender, enhancer or substitute. Spinal surgeons can take advance of DBMs osteoinductivity and osteoconductivity and achieve good results in spinal fusion, with a significantly lower complication rate and results similar to these of ICBG. The most significant drawbacks to DBM may be the difference between and within products so, it is important the surgeon to remain updated of the product properties to optimize the successful use of DBM, and the fact that it is not useful as a structural graft material because of its amorphous consistency, so it has to be used in combination with other type of grafts or scaffolds increasing the cost.

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INTRODUCTION

Spinal fusion remains the gold-standard treatment for several pathological spine conditions, such as; spine trauma, tumors, degenerative disorders, and discogenic back pain. It is estimated that the number of spinal fusions performed in the United States, could be greater than 200000 per annum, with the majority of these being lumbar fusions^[1,2]. Although spinal fusion is a widely accepted successful procedure, offering acceptable clinical results, pseudarthrosis following spine surgery remains a major clinical challenge. Rates of pseudarthrosis have been reported to be as high as 48% in posterolateral inter-transverse process lumbar fusions^[3], with an increasing risk in multi-level fusions.

The high rate of non-union necessitates the use of various bone graft materials and substitutes, ceramics, and augmentation with growth factors such as bone morphogenetic protein-2 (BMP-2). It is widely accepted that autologous iliac crest bone graft (ICBG) is considered the gold-standard for spinal fusion surgery^[4-7].

ICBG demonstrates a reliably high fusion rate, and additionally, being autologous, does not carry the risk of rejection or disease transmission^[8].

However, harvesting bone from the iliac crest is associated with a series of complications and a morbidity rate^[9], that have made spine surgeons to employ alternatives to ICBG such as bone graft substitutes or extenders^[10-20]. Ideally these bone graft substitutes or extenders should have both osteoinductive and osteoconductive characteristics, in order to promote comparable fusion rates to autologous bone graft.

Demineralized bone matrix (DBM) is bone that has been acid treated to have the mineralized portion removed while maintaining the organic matrix and growth factors. Approximately 93% of DBM consists of collagen, whereas only 5% consists of other growth factors, a fraction of which are BMPs. It is weakly osteoconductive because the organic portions of bone, such as collagen, remain. The small quantity of BMPs provides osteoinductive capabilities^[21-26] as well, but has no osteogenic capacity because of its processing. Osteoinductivity may be variable within a single manufacturer's product and between manufacturers, because the osteoinductive capacity of DBM can be affected by storage, demineralization process, washing procedure, sterilization method and the source of the bone, which depends on the individual donor and the site of harvest^[27-33]. DBM has no immunological rejection as the antigenic surface structure of the bone is destroyed during demineralization by acid^[34], but, in the other hand, various studies have shown that any allograft bone can induce host immune responses^[35-38] despite its processing. Unfortunately, there are no studies, referred whether available DBM products could differ in immunogenicity issues, or whether immunogenicity issues would influence the osteoconductive and osteoinductive potentials of DBM.

Since DBM was found to be effective and safe as an option of bone grafting, it has been used to induce bone

formation in various clinical applications.

The purpose of this review is to present the results of clinical studies concerning the use of DBM, alone or as a composite graft, in the spinal fusion, and the Grades of Recommendation^[39] of use of DBM in different situations, like cervical fusion, lumbar fusion and at the treatment of scoliosis.

LITERATURE RESEARCH

A critical review of the English-language literature was conducted on MEDLINE using Pubmed. Various combinations of search key and MeSH terms including “demineralized bone matrix”, “DBM”, “spinal fusion”, “scoliosis” and “cervical spine fusion” were employed to generate a broad literature base. The two senior authors K.T and D.G conducted the search independently, and there were not any discrepancies in their findings. Results had been restricted to clinical studies in English language. Abstracts, supplements, editorials, correspondence, book reviews, and articles on aspects of DBM unrelated to efficacy and outcome were excluded. Clinical studies of use of DBM in non-spinal surgery were excluded as well. Papers that were included were full-length original research articles in peer-reviewed journals that investigated fusion efficacy. The Grades of Recommendation and the levels of evidences (LOEs) are presented. The Oxford centre for evidence based medicine classification is used in order to classify LOEs of individual studies^[40]. Clinical studies, authors, and their main outcomes presented in Table 1, and described by category of use.

Requirements of extensive bone grafting in spinal fusion and the subsequent morbidity of the donor site, are making iliac crest not the most accessible option for graft harvesting. This fact leads the spinal surgeons to employ different type of bone graft substitutes in order to cover their needs.

DBM has, performed successfully in long bones operative procedures requiring bone grafts, such as repairing segmental defects^[41-44]. However, there are limited clinical data to support the efficacy of any DBMs in spinal arthrodesis.

The literature has supported the use of DBM as a potential graft extender, enhancer or substitute, but there was no clinical evidence to support its use as a stand-alone graft material. On top of that there are studies that demonstrate, that in younger and healthier patients, use of DBM may be unnecessary, since harvesting autograft from local sources, like laminae and spinous processes after destruction of facet joints and decortication, shows excellent results and a fusion rate of 94% without implant failure, infection or loss of correction^[45]. It seems that spinal surgeons can take advance of DBMs osteoinductivity and osteoconductivity and achieve good results in spinal fusion but unfortunately, it is not useful as a structural graft material because of its amorphous consistency which is a draw back, since in has to be used in combination with other type of grafts or scaffolds which

Table 1 Clinical studies of demineralized bone matrix used in spinal fusion

Ref.	Study design	Diagnosis/procedures	Type of graft	Main outcomes	Level of evidence
Cervical spine					
An <i>et al</i> ^[48]	2-Center randomized prospective control trial	Patients undergone anterior cervical fusion for degenerative disc disease, <i>n</i> = 77	Freeze-dried allograft augmented with DBM (Grafton®), <i>n</i> = 39. Iliac Crest Autograft, <i>n</i> = 38	Pseudarthrosis rate was 46.2% in DBM-allograft Group <i>vs</i> 26.3% in autograft group, but with no significant differences. Graft collapse ≥ 2 mm occurred in 39.7% in DBM-allograft group than 24.4% in autograft group (<i>P</i> = 0.09)	II
Vaidya <i>et al</i> ^[49]	Retrospective comparative study	Patients treated with anterior cervical discectomy and fusion, <i>n</i> = 46	PEEK cages + morphogenetic protein-2 (rhBMP-2), <i>n</i> = 22 Allograft spacers + DBM, <i>n</i> = 24	No significant difference in pain scores between groups. Probable fusion at latest follow up in 23/24 of DBM group <i>vs</i> 22/22 in rhBMP-2 group. 85% of rhBMP-2 and 56% of DBM reported difficulty in swallowing. The cost of implants in patients treated with rhBMP-2 and PEEK spacers was more than three times the cost of the other group	III
Park <i>et al</i> ^[52]	Prospective, case series study	Patients undergoing anterior cervical discectomy and fusion	PEEK cages and DBM (Grafton®), <i>n</i> = 31	97% fusion rate (41/42 levels), neck and arm pain improved after surgery and significantly improved in 12/12 follow-up, <i>P</i> < 0.05	IV
Topuz <i>et al</i> ^[50]	Retrospective, case series study	Patients underwent 2-level contiguous anterior cervical discectomy and fusion	PEEK cages and DBM (Grafton®) and autologous blood, <i>n</i> = 79	87.3% "excellent" and "good" clinical outcomes, final fusion rate 91.7% (145/158 levels)	IV
Moon <i>et al</i> ^[51]	Retrospective case series	Patients undergone 2-level, non-instrumented cervical fusion for degenerative disk disease, <i>n</i> = 27 (54 levels)	PEEK cages and DBM	Fusion rate was 88.9% of levels. All patients showed improvements in clinical outcomes (VAS score, neurologic pain and JOA myelopathy score)	IV
Demircan <i>et al</i> ^[53]	Prospective case series	Patients undergone non-instrumented anterior cervical fusion for degenerative disk disease, <i>n</i> = 16 (42 levels)	Polyetheretherketone cages packed with autologous blood, curettage microchip material, and DBM (Grafton®)	Fusion rate was 90.5% of levels, at 18 mo after surgery with improved clinical outcomes using JOA score (<i>P</i> = 0.004)	IV
Lumbar spine					
Kang <i>et al</i> ^[54]	Prospective multicenter randomized clinical trial	Patients undergoing single-level posterior lumbar fusion	DBM (Grafton®) + local bone, <i>n</i> = 30. Autologous iliac crest bone graft, <i>n</i> = 16	Fusion rates were 86% (Grafton®) <i>vs</i> 92% (autologous graft). Grafton showed consistently higher physical function scores at 24 mo. There was a greater mean intraoperative blood loss in the autologous group.	I
Cammisa <i>et al</i> ^[31]	Prospective multicenter control trial	Patients undergone posterolateral lumbar, instrumented fusion, <i>n</i> = 120	Iliac Crest Autograft on one side DBM (Grafton®) + Iliac crest autograft on contralateral side of same patient	Radiographic fusion rates at 24 mo after surgery in Grafton DBM side was 52% and in Iliac Crest Bone Autograft side was 54%	II
Vaccaro <i>et al</i> ^[55]	Prospective, comparative study	Patients undergone instrumented posterolateral lumbosacral spinal fusion	DBM (Grafton®) + Bone Marrow, <i>n</i> = 19, DBM + Iliac crest autograft, <i>n</i> = 27 Autograft, <i>n</i> = 27	Fusion rates were 63% with DBM + Bone Marrow, 70% DBM + autograft and 67% with autograft	III
Sassard <i>et al</i> ^[56]	Retrospective comparative study	Instrumented posterolateral lumbar spinal fusion with rigid pedicle screw fixation (<i>n</i> = 108)	Iliac crest bone graft (<i>n</i> = 52). Local autograft-Grafton® (<i>n</i> = 56)	Fusion rates at 24 mo after surgery: In Iliac crest bone graft group: 56% and in local autograft-Grafton group: 60%	III

Schizas <i>et al</i> ^[57]	Retrospective case control study	Patients undergone posterolateral, one or two-level, instrumented, lumbar fusion, <i>n</i> = 59 (78 levels)	DBM (Accell Connexus [®] putty) with Iliac crest autograft or local decompression material, <i>n</i> = 33 Iliac crest autograft or local decompression material, <i>n</i> = 26	Fusion rate was 69.7% with DBM <i>vs</i> 76.9% without DBM. There were no differences in complication rates, ODI or VAS pain score	III
Epstein <i>et al</i> ^[58]	Prospective, clinical study	Patients undergone multilevel lumbar laminectomies, 1-level (<i>n</i> = 95) and 2-levels (<i>n</i> = 45)	Lamina autograft + DBM (Osteofil), <i>n</i> = 140	1-level fusion rates: 98%, 2-levels fusion rates: 96%. Revealed essentially comparable outcomes on 6 of 8 Health Scales of SF-36	IV
Thalgott <i>et al</i> ^[61]	Prospective case series study	Patients undergone lumbar interbody fusion (<i>n</i> = 50)	Titanium mesh cages filled with coralline hydroxyapatite (ProOsteon [™] 500R) and DBM (Grafton [®])	96% fusion rate, decrease in mean pain scores by 60% from baseline	IV
Girardi <i>et al</i> ^[60]	Retrospective case series study	Instrumented lumbar spinal fusion for various diagnoses (<i>n</i> = 65)	Combination of autologous bone graft and allograft DBM (AlloMatrix [®] Injectable Putty)	Gradual and constant improvement based on radiographic measurements taken 1, 3, 6 and 12 mo after surgery	IV
Thalgott <i>et al</i> ^[62]	Retrospective case series	Patients undergone instrumented posterolateral lumbar fusion, <i>n</i> = 40	Coralline hydroxyapatite (Pro Osteon [™] 500) + DBM (Grafton [®]), <i>n</i> = 28 Pro Osteon [™] 500 alone, <i>n</i> = 12.	Radiographic fusion rates was 100% with coralline hydroxyapatite alone, than 89.3% with Grafton added.	IV
Epstein ^[59]	Prospective case series	Geriatric patients undergone posterolateral non-instrumented lumbar fusion, <i>n</i> = 75	Lamina autograft mixed with DBM (Osteofil) in 1:1 ratio	Fusion rate was 82.7% of levels. Improved clinical outcomes using SF-36 score.	IV
Idiopathic scoliosis Weinzapfel <i>et al</i> ^[63]	Retrospective comparative study	Anterior thoracic discectomies with video Assisted thoracoscopic surgery in idiopathic scoliosis	Morselized allograft bone, <i>n</i> = 12. DBM (Grafton [®]), <i>n</i> = 28	Curve correction was similar for both groups (68% <i>vs</i> 67%). Radiological fusion fusion: 82% in allograft group <i>vs</i> 92% in DBM group	III

DBM: Demineralized bone matrix; PEEK: Polyetheretherketone; JOA: Japanese-orthopaedic-association; BMP: Bone morphogenetic protein; ODI: Oswestry disability index; VAS: Visual analogue scale.

increases the cost.

The most significant drawback to DBM may be the difference between and within products. The osteo-inductive potential of DBM may be variable within a single manufacturer's product and among manufacturers, because the osteoinductive capacity of DBM can be affected by storage, demineralization process, washing procedure, sterilization method and the source of the bone, which depends on the individual donor and the site of harvest and affects the quantity and type of BMPs preserved. There are numerous DBM composites in many forms, from gels, pastes, putties, and sheets available currently for clinical use.

Bae *et al*^[27] have pointed out that the variability of BMP concentrations among different lots of the same DBM formulation was higher than the inter-product variability or concentrations of BMP among different DBM formulations.

Another important factor that could influence efficacy of DBMs is the choice of the carrier. As opposed to the neutral pH of hyaluronic acid (DBX) carriers, negative effects have been observed in relation to the use of glycerol carriers (Grafton), which generate a highly

acidic environment for host tissues, especially when used in large quantities at the fusion site^[46]. Moreover, the amount of DBM applied does not necessarily correlate with outcomes and efficacy as demineralization process, and sterilization method can also affect osteoinductivity, as mentioned before^[21,47]. It is important the surgeon to remain updated of the product properties to optimize the successful use of DBM.

DBM USED IN CERVICAL FUSION

There are a few clinical trials in literature, which evaluated the use of DBM in fusion in cervical spine. In one of the first reports, An *et al*^[48] in a two-center prospective randomized controlled clinical trial (Level 2), found that freeze-dried allograft with DBM (Grafton[®]) mixed, shown higher nonunion and graft collapse rates than iliac crest autograft. Thirty-nine patients undergoing anterior cervical fusion for degenerative disc disease had randomly selected to take freeze-dried allograft augmented with DBM (Grafton[®]), while 38 patients took autologous ICBG. Pseudarthrosis developed in 33.3% of levels (46.2% of patients) in the allograft-DBM group, than

22% of levels (26.3% of patients) in autograft group, but with no significant difference between groups ($P = 0.23$). In addition, graft collapse > 2 mm occurred in 39.7% of the allograft-DBM group compared with 24.4% of the autograft group ($P = 0.09$). Authors suggested the use of autograft in cervical fusion for better outcomes.

In a level 3 study, Vaidya *et al.*^[49], evaluated the use of polyetheretherketone (PEEK) cages and morphogenetic protein-2 (rhBMP-2) against allograft spacers and DBM, in patients treated with anterior cervical discectomy and fusion. There were no significant differences in pain scores between groups. Probable fusion occurred in 23 of 24 patients of DBM group *vs* 22 of 22 patients in rhBMP-2 group. 85% of patients in rhBMP-2 group and 56% of patients in DBM group reported difficulty in swallowing. The cost of implants in patients treated with rhBMP-2 and PEEK spacers was more than three times the cost of the other group. Authors concluded that despite providing good fusion rates, they have abandoned using rhBMP-2 and PEEK cages for anterior cervical fusion, due to the side effects, high cost, and the availability of a suitable alternative.

There are also 4 series of patients in literature, which studied the use of PEEK cages and DBM (Grafton®) in patients treated with cervical discectomy and fusion. Topuz *et al.*^[50] used PEEK cages packed with Grafton® DBM and autologous blood in 79 patients, who underwent 2-levels contiguous anterior cervical discectomy and fusion. Authors found “excellent” and “good” clinical results in 87.3% of patients, while final fusion had occurred in 145 of 158 levels (91.7%). In a same case series study, Moon *et al.*^[51] used PEEK cages packed with DBM, and found that fusion rate was 88.9% of levels. All patients had clinical improvement using visual analogue scale (VAS) score, neurological pain and Japanese-orthopaedic-association (JOA) myelopathy score. Park *et al.*^[52] also found high fusion rate, up to 97% using same methods in a prospective case series study. Similar main outcomes, found Demircan *et al.*^[53] in a case series of patients undergone non-instrumented anterior cervical fusion for degenerative disc disease. Authors used PEEK cages packed with Grafton®, autologous blood and curettage microchip material. Fusion rate was 90.5% with patients had improved clinical outcomes using JOA score ($P = 0.004$).

USE OF DBM IN LUMBAR FUSION

Despite the few published clinical trials about the use of DBM in cervical fusion, there are a few more about lumbar fusion. There are two level 1 and 2, three level 3 and five level 4 available clinical trials, since the preparation of this manuscript.

In a prospective multicenter randomized controlled clinical trial, Kang *et al.*^[54] reported the efficacy of a commercial DBM graft (Grafton®) compared with iliac crest autograft in patients undergone single-level posterior lumbar fusion. In this study 46 patients were randomly assigned to receive Grafton DBM Matrix with local bone

(30 patients) or autologous ICBG (16 patients). Fifty-one patients completed the 2-year follow-up. Fusion rates were 86% for Grafton group than 92% for autologous group. Grafton showed consistently higher physical function scores at 24 mo, but this was not significant. There was a significant greater mean intraoperative blood loss in the autologous group ($P = 0.0031$). Authors concluded that fusion rate and improvement in clinical outcomes of use of Grafton in lumbar fusion were comparable with those in iliac crest autograft group.

Cammisa *et al.*^[3] investigated whether Grafton® might be able to serve the function of an autograft extender, in 120 patients undergone posterolateral instrumented lumbar fusion. In this level 2 study, Iliac crest autograft was implanted on one side of the spine and a Grafton® DBM and autograft composite was implanted on the contralateral side in the same patient. After 24-mo follow-up, Radiographic fusion rates in Grafton DBM side was 52% and in Iliac Crest Bone Autograft side was 54%, while overall percentage agreement for fusion status between sides was approximately 75% ($P < 0.001$). These results suggested that Grafton DBM gel in combination with autologous bone can provide a similar rate of successful fusion as autograft alone.

In a prospective series, Vaccaro *et al.*^[55] evaluated patients undergone instrumented posterolateral lumbosacral spinal fusion. Nineteen patients had supplemental bone grafting with DBM putty (Grafton®; Osteotech, Eatontown, NJ) enriched with aspirated bone marrow, 27 patients DBM putty combined with iliac crest autograft, and 27 patients had autograft. Fusion rate at 24 mo after surgery were 63% of levels in DBM and bone marrow group, 70% of levels in DBM and iliac crest group and 67% in ICBG group. Findings suggest that both DBM composites offer similar performance to autograft in posterolateral spinal fusion.

Sassard *et al.*^[56], in a level 3 clinical trial, examined the fusion rates of a local autograft-Grafton® construct against that of iliac crest autograft alone in one hundred and eight patients undergone instrumented posterolateral lumbar spinal fusion. Fusion rates were found not to vary between the two groups, with 60% in local autograft-DBM group and 56% in iliac crest autograft group. These findings prompted further evaluation of whether Grafton® might be able to serve as graft extender.

Schizas *et al.*^[57] found that DBM was useful as a graft extender for both local bone and ICBG. They compared 33 patients who had local bone or ICBG augmented with DBM with 26 patients who received ICBG or local bone alone, for posterolateral, one or two-level, instrumented, lumbar fusion. The groups were equivalent in radiographic fusion and clinical outcomes. Fusion rates were 69.7% with DBM augmented *vs* 76.9% without DBM. There were no differences in complication rates, Oswestry disability index or VAS pain score.

There are also case series available in literature, which concluded that DBM is a useful graft extender for spinal fusions, when mixed with lamina autograft, or iliac crest autograft. Epstein *et al.*^[58] reported high fusion rates

(1-level fusion rate: 98%, 2-levels fusion rate: 96%) in 140 patients undergone multilevel lumbar laminectomies and had lamina autograft augmented with DBM (Osteofil) as a graft for fusion. Radiographic followed by clinical outcomes. Same authors, reported similar results in geriatric patients undergone posterolateral non-instrumented lumbar fusion, with fusion rate up to 82.7% of levels and improved clinical outcomes, using SF-36 surveys^[59]. Girardi *et al*^[60], in a series of 65 patients who undergone instrumented spinal fusion for various diagnoses, reported a gradual and constant improvement based on radiographic measurements taken 1, 3, 6, and 12 mo after surgery. Patients had combination of autologous bone graft and DBM (AlloMatrix® Injectable Putty).

Thalgott *et al*^[61] retrospectively reviewed the radiographic and clinical results of 50 patients who had received titanium mesh cages filled with coralline hydroxyapatite (ProOsteon™ 500R) and DBM Grafton® preparation for anterior lumbar interbody fusion. The authors reported a 96% fusion rate, alongside with a decrease in mean pain scores by 60% from baseline. In the other hand, there are conflicting results on the efficacy of DBM as a graft extender by the same authors, who found a higher rate of pseudarthrosis (10.7% *vs* 0%) with the use of Grafton® gel and coralline hydroxyapatite (Pro Osteon™ 500R) as compared with coralline hydroxyapatite alone in a retrospective study of 40 patients who underwent instrumented posterolateral lumbar spinal fusion^[62].

DBM USED FOR TREATMENT OF SCOLIOSIS

Because of the extensive fusion requirements for correction of scoliosis, DBM can be an available alternative to iliac crest. Weinzapfel *et al*^[63] compared retrospectively the fusion rates between allograft bone and Grafton DBM Flex in video-assisted thoracoscopic surgery for idiopathic scoliosis. Forty patients with 1 year or more follow-up were evaluated-12 with morselized allograft bone and 28 with folded Grafton DBM Flex. Percent curve correction from before surgery to the most recent follow-up was very similar in both groups (68% in Allograft and 67% in DBM group). Sixty of 73 disc spaces (82%) in the Allograft group and 100 of 109 disc spaces (92%) in the DBM group were rated as radiographically fused.

CONCLUSION

This review demonstrates that DBM shows similar fusion rates with autologous bone graft in lumbar spine fusion, when used as a graft extender either with local autologous bone or ICBG. In addition in the only one level I study that was included in this review DBM group showed consistently higher physical function scores at 24 mo and there was a greater mean intraoperative blood loss in the autologous group.

Regarding use of DBM in cervical spine fusion, it is clear that when used as an extender with autologous bone

graft in PEEK cages, shows good results, although in a level two study where Freeze-dried allograft augmented with DBM compared with ICBG, the autograft group showed superior non-union rates (Pseudarthrosis rate was 46.2% in DBM-allograft Group *vs* 26.3% in autograft group).

For correction of scoliosis due to the extensive fusion requirements DBM shows to be a reliable alternative to autograft, especially comparing with the use of other types of allografts.

Concluding, the majority of the clinical trials demonstrate comparable efficacy of DBM when it used as a graft extender in combination with autograft, but there is no clinical evidence to support its use as a standalone graft material. Additionally, studies of high methodological quality are required, in order to optimize and clarify the indications of its use and the appropriate patient population that will benefit from DBM in spine arthrodesis.

REFERENCES

- 1 Cowan JA, Dimick JB, Wainess R, Upchurch GR, Chandler WF, La Marca F. Changes in the utilization of spinal fusion in the United States. *Neurosurgery* 2006; **59**: 15-20; discussion 15-20 [PMID: 16823295 DOI: 10.1227/01.NEU.0000219836.54861.CD]
- 2 Rajae SS, Bae HW, Kanim LE, Delamarter RB. Spinal fusion in the United States: analysis of trends from 1998 to 2008. *Spine (Phila Pa 1976)* 2012; **37**: 67-76 [PMID: 21311399]
- 3 Cammisia FP, Lowery G, Garfin SR, Geisler FH, Klara PM, McGuire RA, Sassard WR, Stubbs H, Block JE. Two-year fusion rate equivalency between Grafton DBM gel and autograft in posterolateral spine fusion: a prospective controlled trial employing a side-by-side comparison in the same patient. *Spine (Phila Pa 1976)* 2004; **29**: 660-666 [PMID: 15014276]
- 4 Goldberg VM, Stevenson S. Natural history of autografts and allografts. *Clin Orthop Relat Res* 1987; **(225)**: 7-16 [PMID: 3315383]
- 5 France JC, Yaszemski MJ, Laueran WC, Cain JE, Glover JM, Lawson KJ, Coe JD, Topper SM. A randomized prospective study of posterolateral lumbar fusion. Outcomes with and without pedicle screw instrumentation. *Spine (Phila Pa 1976)* 1999; **24**: 553-560 [PMID: 10101819]
- 6 Fischgrund JS, Mackay M, Herkowitz HN, Brower R, Montgomery DM, Kurz LT. 1997 Volvo Award winner in clinical studies. Degenerative lumbar spondylolisthesis with spinal stenosis: a prospective, randomized study comparing decompressive laminectomy and arthrodesis with and without spinal instrumentation. *Spine (Phila Pa 1976)* 1997; **22**: 2807-2812 [PMID: 9431616]
- 7 Kimura I, Shingu H, Murata M, Hashiguchi H. Lumbar posterolateral fusion alone or with transpedicular instrumentation in L4-L5 degenerative spondylolisthesis. *J Spinal Disord* 2001; **14**: 301-310 [PMID: 11481551 DOI: 10.1097/00002517-200108000-00004]
- 8 Finkemeier CG. Bone-grafting and bone-graft substitutes. *J Bone Joint Surg Am* 2002; **84-A**: 454-464 [PMID: 11886919]
- 9 Kurz LT, Garfin SR, Booth RE. Harvesting autogenous iliac bone grafts. A review of complications and techniques. *Spine (Phila Pa 1976)* 1989; **14**: 1324-1331 [PMID: 2617362]
- 10 Bagaria V. Bone morphogenic protein: current state of field and the road ahead. *J Orthop* 2005; **2**: e3
- 11 Biswas D, Bible JE, Whang PH, Miller CP, Jaw R, Miller S, Grauer JN. Augmented demineralized bone matrix: a potential alternative for posterolateral lumbar spinal fusion. *Am J Orthop (Belle Mead NJ)* 2010; **39**: 531-538 [PMID: 21623419]

- 12 **Boden SD**, Kang J, Sandhu H, Heller JG. Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies. *Spine* (Phila Pa 1976) 2002; **27**: 2662-2673 [PMID: 12461392]
- 13 **Rihn JA**, Kirkpatrick K, Albert TJ. Graft options in posterolateral and posterior interbody lumbar fusion. *Spine* (Phila Pa 1976) 2010; **35**: 1629-1639 [PMID: 20628336 DOI: 10.1097/BRS.0b013e3181d25803]
- 14 **Vaccaro AR**, Patel T, Fischgrund J, Anderson DG, Truumees E, Herkowitz HN, Phillips F, Hilibrand A, Albert TJ, Wetzel T, McCulloch JA. A pilot study evaluating the safety and efficacy of OP-1 Putty (rhBMP-7) as a replacement for iliac crest autograft in posterolateral lumbar arthrodesis for degenerative spondylolisthesis. *Spine* (Phila Pa 1976) 2004; **29**: 1885-1892 [PMID: 15534410]
- 15 **Boden SD**, Martin GJ, Morone MA, Ugbo JL, Moskovitz PA. Posterolateral lumbar intertransverse process spine arthrodesis with recombinant human bone morphogenetic protein 2/hydroxyapatite-tricalcium phosphate after laminectomy in the nonhuman primate. *Spine* (Phila Pa 1976) 1999; **24**: 1179-1185 [PMID: 10382242]
- 16 **Dimar JR**, Glassman SD, Burkus KJ, Carreon LY. Clinical outcomes and fusion success at 2 years of single-level instrumented posterolateral fusions with recombinant human bone morphogenetic protein-2/compression resistant matrix versus iliac crest bone graft. *Spine* (Phila Pa 1976) 2006; **31**: 2534-259; discussion 2540 [PMID: 17047540]
- 17 **Dimar JR**, Glassman SD, Burkus JK, Pryor PW, Hardacker JW, Carreon LY. Clinical and radiographic analysis of an optimized rhBMP-2 formulation as an autograft replacement in posterolateral lumbar spine arthrodesis. *J Bone Joint Surg Am* 2009; **91**: 1377-1386 [PMID: 19487515 DOI: 10.2106/JBJS.H.00200]
- 18 **Aspenberg P**, Andolf E. Bone induction by fetal and adult human bone matrix in athymic rats. *Acta Orthop Scand* 1989; **60**: 195-199 [PMID: 2728883 DOI: 10.3109/17453678909149253]
- 19 **Heckman JD**, Boyan BD, Aufdemorte TB, Abbott JT. The use of bone morphogenetic protein in the treatment of nonunion in a canine model. *J Bone Joint Surg Am* 1991; **73**: 750-764 [PMID: 2045401]
- 20 **Tiedeman JJ**, Connolly JF, Strates BS, Lippiello L. Treatment of nonunion by percutaneous injection of bone marrow and demineralized bone matrix. An experimental study in dogs. *Clin Orthop Relat Res* 1991; **150**: 294-302 [PMID: 2060222]
- 21 **Urist MR**. Bone: formation by autoinduction. *Science* 1965; **150**: 893-899 [PMID: 5319761 DOI: 10.1126/science.150.3698.893]
- 22 **Buring K**, Urist MR. Effects of ionizing radiation on the bone induction principle in the matrix of bone implants. *Clin Orthop Relat Res* 1967; **55**: 225-234 [PMID: 4230143]
- 23 **Dubuc FL**, Urist MR. The accessibility of the bone induction principle in surface-decalcified bone implants. *Clin Orthop Relat Res* 1967; **55**: 217-223 [PMID: 4866853]
- 24 **Urist MR**, Silverman BF, Buring K, Dubuc FL, Rosenberg JM. The bone induction principle. *Clin Orthop Relat Res* 1967; **53**: 243-283 [PMID: 4870495 DOI: 10.1097/00003086-196707000-00026]
- 25 **Eriksson C**. Surface energies and the bone induction principle. *J Biomed Mater Res* 1985; **19**: 833-849 [PMID: 4077899 DOI: 10.1002/jbm.820190709]
- 26 **Jones CB**. Biological basis of fracture healing. *J Orthop Trauma* 2005; **19**: S1-S3 [PMID: 16479215 DOI: 10.1097/00005131-200511101-00001]
- 27 **Bae HW**, Zhao L, Kanim LE, Wong P, Delamarter RB, Dawson EG. Intervariability and intravariability of bone morphogenetic proteins in commercially available demineralized bone matrix products. *Spine* (Phila Pa 1976) 2006; **31**: 1299-306; discussion 1307-1308 [PMID: 16721289]
- 28 **Han B**, Tang B, Nimmi ME. Quantitative and sensitive in vitro assay for osteoinductive activity of demineralized bone matrix. *J Orthop Res* 2003; **21**: 648-654 [PMID: 12798064 DOI: 10.1016/S0736-0266(03)00005-6]
- 29 **Oakes DA**, Lee CC, Lieberman JR. An evaluation of human demineralized bone matrices in a rat femoral defect model. *Clin Orthop Relat Res* 2003; **(413)**: 281-290 [PMID: 12897620 DOI: 10.1097/01.blo.0000073347.50837.16]
- 30 **Takikawa S**, Bauer TW, Kambic H, Togawa D. Comparative evaluation of the osteoinductivity of two formulations of human demineralized bone matrix. *J Biomed Mater Res A* 2003; **65**: 37-42 [PMID: 12635152 DOI: 10.1002/jbm.a.10345]
- 31 **Peterson B**, Whang PG, Iglesias R, Wang JC, Lieberman JR. Osteoinductivity of commercially available demineralized bone matrix. Preparations in a spine fusion model. *J Bone Joint Surg Am* 2004; **86-A**: 2243-2250 [PMID: 15466734]
- 32 **Lee YP**, Jo M, Luna M, Chien B, Lieberman JR, Wang JC. The efficacy of different commercially available demineralized bone matrix substances in an athymic rat model. *J Spinal Disord Tech* 2005; **18**: 439-444 [PMID: 16189457 DOI: 10.1097/01.bsd.0000175696.66049.f7]
- 33 **Wildemann B**, Kadow-Romacker A, Haas NP, Schmidmaier G. Quantification of various growth factors in different demineralized bone matrix preparations. *J Biomed Mater Res A* 2007; **81**: 437-442 [PMID: 17117475 DOI: 10.1002/jbm.a.31085]
- 34 **Tuli SM**, Singh AD. The osteoinductive property of decalcified bone matrix. An experimental study. *J Bone Joint Surg Br* 1978; **60**: 116-123 [PMID: 342532]
- 35 **Bos GD**, Goldberg VM, Zika JM, Heiple KG, Powell AE. Immune responses of rats to frozen bone allografts. *J Bone Joint Surg Am* 1983; **65**: 239-246 [PMID: 6337163]
- 36 **Friedlaender GE**. Immune responses to osteochondral allografts. Current knowledge and future directions. *Clin Orthop Relat Res* 1983; **(174)**: 58-68 [PMID: 6339143]
- 37 **Horowitz MC**, Friedlaender GE. Immunologic aspects of bone transplantation. A rationale for future studies. *Orthop Clin North Am* 1987; **18**: 227-233 [PMID: 2951639]
- 38 **Friedlaender GE**, Horowitz MC. Immune responses to osteochondral allografts: nature and significance. *Orthopedics* 1992; **15**: 1171-1175 [PMID: 1409127]
- 39 **Wright JG**, Einhorn TA, Heckman JD. Grades of recommendation. *J Bone Joint Surg Am* 2005; **87**: 1909-1910 [PMID: 16140803 DOI: 10.2106/JBJS.8709.edit]
- 40 **OCEBM Levels of Evidence Working Group**. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. Available from: URL: <http://www.cebm.net/index.aspx?o=5653>
- 41 **Bolander ME**, Balian G. The use of demineralized bone matrix in the repair of segmental defects. Augmentation with extracted matrix proteins and a comparison with autologous grafts. *J Bone Joint Surg Am* 1986; **68**: 1264-1274 [PMID: 3533947]
- 42 **el Deeb M**, Hosny M, Sharawy M. Osteogenesis in composite grafts of allogenic demineralized bone powder and porous hydroxylapatite. *J Oral Maxillofac Surg* 1989; **47**: 50-56 [PMID: 2536085 DOI: 10.1016/0278-2391(89)90124-9]
- 43 **Einhorn TA**, Lane JM, Burstein AH, Kopman CR, Vigorita VJ. The healing of segmental bone defects induced by demineralized bone matrix. A radiographic and biomechanical study. *J Bone Joint Surg Am* 1984; **66**: 274-279 [PMID: 6693455]
- 44 **Gebhart M**, Lane J. A radiographical and biomechanical study of demineralized bone matrix implanted into a bone defect of rat femurs with and without bone marrow. *Acta Orthop Belg* 1991; **57**: 130-143 [PMID: 1872156]
- 45 **Milinković ZB**, Krneta O, Milicković S, Dozić D, Curčić A. Are the additional grafts necessary? *Acta Chir Iugosl* 2010; **57**: 69-72 [PMID: 20681203 DOI: 10.2298/ACI1001069M]
- 46 **Wang JC**, Kanim LE, Nagakawa IS, Yamane BH, Vinters HV, Dawson EG. Dose-dependent toxicity of a commercially available demineralized bone matrix material. *Spine* (Phila Pa 1976) 2001; **26**: 1429-1435; discussion 1435-1436 [PMID: 11458146]
- 47 **Aspenberg P**, Johnsson E, Thorngren KG. Dose-dependent

- reduction of bone inductive properties by ethylene oxide. *J Bone Joint Surg Br* 1990; **72**: 1036-1037 [PMID: 2123200]
- 48 **An HS**, Simpson JM, Glover JM, Stephany J. Comparison between allograft plus demineralized bone matrix versus autograft in anterior cervical fusion. A prospective multicenter study. *Spine* (Phila Pa 1976) 1995; **20**: 2211-2216 [PMID: 8545714]
 - 49 **Vaidya R**, Carp J, Sethi A, Bartol S, Craig J, Les CM. Complications of anterior cervical discectomy and fusion using recombinant human bone morphogenetic protein-2. *Eur Spine J* 2007; **16**: 1257-1265 [PMID: 17387522 DOI: 10.1007/s00586-007-0351-9]
 - 50 **Topuz K**, Colak A, Kaya S, Simsek H, Kutlay M, Demircan MN, Velioglu M. Two-level contiguous cervical disc disease treated with peek cages packed with demineralized bone matrix: results of 3-year follow-up. *Eur Spine J* 2009; **18**: 238-243 [PMID: 19130094 DOI: 10.1007/s00586-008-0869-5]
 - 51 **Moon HJ**, Kim JH, Kim JH, Kwon TH, Chung HS, Park YK. The effects of anterior cervical discectomy and fusion with stand-alone cages at two contiguous levels on cervical alignment and outcomes. *Acta Neurochir* (Wien) 2011; **153**: 559-565 [PMID: 21132445 DOI: 10.1007/s00701-010-0879-z]
 - 52 **Park HW**, Lee JK, Moon SJ, Seo SK, Lee JH, Kim SH. The efficacy of the synthetic interbody cage and Grafton for anterior cervical fusion. *Spine* (Phila Pa 1976) 2009; **34**: E591-E595 [PMID: 19644317 DOI: 10.1097/BRS.0b013e3181ab8b9a]
 - 53 **Demircan MN**, Kutlay AM, Colak A, Kaya S, Tekin T, Kibici K, Ungoren K. Multilevel cervical fusion without plates, screws or autogenous iliac crest bone graft. *J Clin Neurosci* 2007; **14**: 723-728 [PMID: 17543528 DOI: 10.1016/j.jocn.2006.02.026]
 - 54 **Kang J**, An H, Hilibrand A, Yoon ST, Kavanagh E, Boden S. Grafton and local bone have comparable outcomes to iliac crest bone in instrumented single-level lumbar fusions. *Spine* (Phila Pa 1976) 2012; **37**: 1083-1091 [PMID: 22076647]
 - 55 **Vaccaro AR**, Stubbs HA, Block JE. Demineralized bone matrix composite grafting for posterolateral spinal fusion. *Orthopedics* 2007; **30**: 567-570 [PMID: 17672157]
 - 56 **Sassard WR**, Eidman DK, Gray PM, Block JE, Russo R, Russell JL, Taboada EM. Augmenting local bone with Grafton demineralized bone matrix for posterolateral lumbar spine fusion: avoiding second site autologous bone harvest. *Orthopedics* 2000; **23**: 1059-1064; discussion 1064-1065 [PMID: 11045552]
 - 57 **Schizas C**, Triantafyllopoulos D, Kosmopoulos V, Tzinieris N, Stafylas K. Posterolateral lumbar spine fusion using a novel demineralized bone matrix: a controlled case pilot study. *Arch Orthop Trauma Surg* 2008; **128**: 621-625 [PMID: 17978826 DOI: 10.1007/s00402-007-0495-4]
 - 58 **Epstein NE**, Epstein JA. SF-36 outcomes and fusion rates after multilevel laminectomies and 1 and 2-level instrumented posterolateral fusions using lamina autograft and demineralized bone matrix. *J Spinal Disord Tech* 2007; **20**: 139-145 [PMID: 17414983 DOI: 10.1097/01.bsd.0000211261.36120.3e]
 - 59 **Epstein NE**. Fusion rates and SF-36 outcomes after multilevel laminectomy and noninstrumented lumbar fusions in a predominantly geriatric population. *J Spinal Disord Tech* 2008; **21**: 159-164 [PMID: 18458584 DOI: 10.1097/BSD.0b013e318074ddaa]
 - 60 **Girardi FP**, Cammisa FP. The effect of bone graft extenders to enhance the performance of iliac crest bone grafts in instrumented lumbar spine fusion. *Orthopedics* 2003; **26**: s545-s548 [PMID: 12755222]
 - 61 **Thalgott JS**, Giuffre JM, Klezl Z, Timlin M. Anterior lumbar interbody fusion with titanium mesh cages, coralline hydroxyapatite, and demineralized bone matrix as part of a circumferential fusion. *Spine J* 2002; **2**: 63-69 [PMID: 14588290 DOI: 10.1016/S1529-9430(01)00155-3]
 - 62 **Thalgott JS**, Giuffre JM, Fritts K, Timlin M, Klezl Z. Instrumented posterolateral lumbar fusion using coralline hydroxyapatite with or without demineralized bone matrix, as an adjunct to autologous bone. *Spine J* 2001; **1**: 131-137 [PMID: 14588393 DOI: 10.1016/S1529-9430(01)00011-0]
 - 63 **Weinzapfel B**, Son-Hing JP, Armstrong DG, Blakemore LC, Poe-Kochert C, Thompson GH. Fusion rates after thoracoscopic release and bone graft substitutes in idiopathic scoliosis. *Spine* (Phila Pa 1976) 2008; **33**: 1079-1083 [PMID: 18449041]

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