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# Demineralized Bone Matrix and Fibers in Spinal Fusion

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## ABSTRACT

Formation of bony fusion after arthrodesis depends on osteoinduction, osteoconduction, and osteogenesis. Traditionally, the patient's own bone, or autograft, has been used to provide biological material necessary for these steps. However, the amount of autograft obtainable is often inadequate. Modern spine surgery has adopted the use of many autograft extenders or replacements, such as demineralized bone matrix or fibers. The present article covers the history of bone grafting, the production and technical details of demineralized bone matrix, and the evidence supporting its use in spine fusions.

Biologics

Keywords: spinal fusion, demineralized bone matrix, demineralized bone fibers, allograft, autograft, implants

## HISTORY

Bone grafting for healing bony wounds or defects has been described since 1668 when Dr. Job van Meekeren performed the first xenograft from canine to human for a Russian soldier's skull fracture (the Catholic Church excommunicated the soldier because he was considered part dog and because Dr. van Meekeren was unable to remove the canine donor bone pieces since they had fully integrated into the soldier's skull).<sup>1–4</sup> Following this early experience, Dr. Philips von Walter published the first report of autologous grafting in 1820, using a patient's own bone fragment after trepanation. The term "bone graft" was first described in 1861 by Dr. Leopold Ollier. Thereafter, the study of bone grafting and healing accelerated rapidly, with Dr. William MacEwan performing the first allograft (using a tibia from a child with rickets to repair a mandibular fracture in another child in 1879) and Dr. Senn reporting the first use of decalcified bone grafts in canines and humans in 1889.

In the early 20th century, Hibbs and Albee published the first accounts of bone autograft for spine fusion. While Hibbs used spinous process and lamina fragments, Albee used tibial grafts placed alongside resected spinous processes. Albee noted that autografts had better rates of healing and fusion compared with allografts. Further work expanded the bone grafts used for various segments of spinal fusion (Radulesco used rib with intact periosteum in place of Albee's tibial graft for posterior spinal fusions in 1921, Robinson and Smith used iliac crest graft for anterior cervical discectomy and fusion in 1955, and Boucher used iliac crest for posterior lumbosacral fusions in 1959).

Understanding of the components and drivers of bone growth expanded in the late 20th century. Urist described bone morphogenic proteins (BMPs) in 1965, which were then able to be harnessed and placed in fusion cavities in impregnated collagen sponges. Lindholm further characterized the use of demineralized bone grafts to enhance spine fusion in the 1980s, roughly a century after Dr. Senn's initial work. In 1991, the Grafton gel (demineralized bone matrix [DBM] in a glycerol carrier) became the first widely available commercial DBM product in the United States.

## TECHNICAL DETAILS OF DEMINERALIZED BONE MATRIX AND FIBERS

Bone healing occurs through 3 processes: osteoconduction, osteoinduction, and osteogenesis. The gold standard substrate for bone healing is iliac crest autograft, which participates in all 3 processes.<sup>5</sup> However, its use is limited due to need for additional surgical access, postoperative pain, and donor site complications.<sup>6–8</sup> DBM has both osteoconductive and osteoinductive properties.<sup>4,5,9</sup> Its organic collagen matrix allows for osteoconduction, while growth factors such as bone morphogenetic proteins, transforming growth factor-beta, and fibroblast growth factors provide osteoinduction.<sup>9–11</sup>

DBM is procured exclusively from deceased donors and is considered an alloimplant (rather than allograft) as it does not contain viable cells.<sup>4,12</sup> This cell-free matrix is a composite of primarily type-I collagen

with some IV and X collagens, non-collagenous proteins, growth factors, and residual calcium phosphate mineral.<sup>4</sup> The donor procurement process is overseen by the US Food and Drug Administration in accordance with American Association of Tissue Banks guidelines to mitigate the risk of disease transmission. The process involves rigorous donor family interviews, physician examination of procedure specimens, and serologic testing for infectious diseases.

Although various vendors may differ in the specifics of their DBM preparation, the process generally follows the same conceptual steps. Bone allograft is obtained from the donor and is debrided of soft tissue, blood, and lipids. The donor bone is then soaked in an antibiotic solution and morselized into particles or fibers. The bone is then subject to acid demineralization and freeze-drying, resulting in an intact organic matrix demineralized bone product that is ready for formulation. Nuances in DBM processing, specifically with regard to the demineralization process, may impact DBM's clinical and safety efficacy. In a mouse model, Honsawek et al showed that the osteoinductive potential of the bone matrix increased with decreased mineralization, suspected to be due to less trapping of BMPs.<sup>13</sup> To this point, Glowacki et al also found that osteoinduction was a function of the surface area of the DBM with smaller particles creating more bone per area than large particles in a rat model.<sup>14</sup> Demineralization also has an important function in muting the host graft inflammatory response.<sup>15</sup>

Sterilization of the DBM product is tightly regulated by the US Food and Drug Administration (via 510[K] sterility review guidance K90-1) with a standard of no more than 1 in 1 million devices failing sterility testing.<sup>4</sup> Traditional sterilization techniques using ethylene oxide reduced or completely abolished osteoinduction and BMP activity in numerous studies,<sup>16-19</sup> and thus, most commercially available DBM preparations use gamma irradiation for sterilization.<sup>17,19-21</sup> Despite improvements in modern preparation of DBM to maintain native BMP activity, a recent study by Bae et al demonstrated significant variability in both BMP concentrations (22–110 pg of BMP-2 per milligram of product and 44–125 pg of BMP-7 per milligram of product) and in vivo fusion rates (0%–75%) in rats between lots of a single DBM product (InterGro DBM Putty).<sup>22</sup> Of note, the measured amounts of BMP were positively correlated with fusion rates in a dose-dependent manner.

Once processed, the resultant powder must be converted to a handleable formulation to facilitate clinical application. Early formulations of DBM had numerous

pitfalls. The small size of the particles made it difficult to handle in the operating room, allowed for graft migration, and offered little mechanical support. The DBM powder was combined with glycerol by O'Leary and McBrayer in 1981 to form a viscous gel facilitating delivery to the site via handling; however, preventing graft migration remained challenging.<sup>23,24</sup> The most common modern formulation of DBM is in a putty, using either viscous, water-soluble polymers (eg, sodium hyaluronate and carboxymethylcellulose) or anhydrous water-miscible solvents (eg, glycerol) to "carry" the DBM into a moldable, packable form that resists dispersion from blood or irrigation.<sup>4</sup> Other carriers commonly used for DBM include collagen, hydroxyapatite, calcium sulfate, and bioactive glass.<sup>25</sup> The putty and paste formulations may be packaged in vials or syringes and can be placed directly into the site of desired fusion or mixed with other auto- or allograft first. Other forms of DBM, such as strips, may be moldable to fill bony defects, such as those created by osteotomies during spine fusions. Depending on the manufacturer and particular formulation, the total percentage of DBM in these products ranges between 20% and 100%.<sup>25,26</sup>

Dowd and Dyke built upon these designs in 1993 and integrated the morselized bone with elongated fibers that could be molded into any shape, which improved handleability, mechanical strength, and resistance to graft migration.<sup>27</sup> These products are termed demineralized bone fibers (DBF) and have been shown to have similar osteoinduction as DBM with improved osteoconduction due to its elongated shape. Preclinical work by Martin et al in 1999 demonstrated improved osteoconductive capabilities in a rabbit model by removing the BMP component and comparing DBM gel and DBF.<sup>28</sup> They found that DBM in sheets and putty formations were still able to support fusion, whereas the DBM in gel formation did not, which they believed was caused by the mechanical structure of the 2 formulations acting as a scaffold for osteoblast migration. Although these carriers improve the handling of DBM in the operating room, increasing the carrier to DBM ratio has been shown to reduce osteoinductivity of the implant, which has led some manufacturers to develop carrier-free DBM or DBF products.<sup>29</sup>

## USE IN SPINAL FUSION

### Preclinical Data

Comparison of the various carriers of DBM has been the focus of preclinical studies. Wang et al compared

Osteofil paste (Medtronic Sofamor Danek, Memphis, TN, USA), Grafton putty (Osteotech Inc., Eatontown, NJ, USA), and Dynagraft putty (GenSci Regeneration Sciences Inc., Irvine, CA, USA) in a rat model showing that Osteofil and Grafton had the highest overall fusion rate, both of which outperformed autogenous iliac crest control.<sup>30</sup> Notably, none of the rats implanted with Dynagraft fused. Acarturk and Hollinger compared several commercially available bone matrix formulations in a rat model finding Demineralized Bone Matrix (DBM) (Synthes USA, West Chester, PA, USA), DBM plus mesh, DBM (Jessup, PA, USA), and Grafton putty produced the most bone within a midline 8 mm diameter craniotomy.<sup>31</sup>

## INDICATIONS FOR SPINAL FUSION

Within modern spine surgery, bone grafting is essential for achieving bony fusion, whether in posterolateral or in interbody placement. The gold standard remains autologous iliac crest bone graft, though nonfusion is still widely reported at rates of 5% to 50%. Additionally, graft site complications, pain, and increased operative blood loss are important considerations, particularly in cases where a second incision must be made to harvest autograft. DBM is often used to extend the autograft procured from a patient, whether that is local or iliac crest. Although many groups have studied the use of DBM in spine fusion, the large variation between the study designs prevent any global conclusions regarding its use.<sup>32</sup> In general, the data suggest a lack of significant difference between DBM and autograft with regard to fusion rates and outcomes scores.<sup>33</sup> Despite this lack of significant difference and the cost of DBM

(\$1522 per level in 1 study),<sup>34</sup> the use of DBM is fairly widespread and may be particularly useful in situations where autograft is insufficient in quantity or quality to promote appropriate fusion.

## Cervical Spine

In comparison with lumbar fusion, relatively less data exist in the literature regarding the use of DBM in cervical fusions (Table 1). In 1995, An et al<sup>35</sup> prospectively compared 38 patients who received autograft from anterior iliac crest with 39 who received freeze-dried allograft-DBM for uninstrumented anterior cervical fusions, noting a higher rate of pseudoarthrosis in those receiving allograft; however, this difference was not statistically significant (33.3% vs 22%,  $P = 0.23$ ). Lee et al<sup>36</sup> retrospectively compared these 2 groups (41 patients in total, 24 receiving cortical allograft ring with DBM and 17 receiving tricortical iliac autograft) with the addition of plate fixation and found no difference in fusion rate, graft subsidence, cervical lordosis, fused segmental lordosis, and adjacent segment degeneration. Additionally, Lee noted increased operative blood loss in the patients undergoing iliac crest autograft procurement (325 vs 210 mL).

As interbody spacers became more popular, focus shifted to using DBM in combination with these products in anterior cervical surgery. Park et al prospectively followed 31 patients who underwent anterior cervical fusion with polyetheretherketone cages with Grafton DBM for 12 months and found no cases of implant-related complications.<sup>39</sup> Two recent prospective studies compared the use of different graft supplements with polyetheretherketone interbody cages. Yi et

**Table 1.** Review of studies comparing DBM to other bone grafts or implants in cervical spine.

Study	Design	Patient Population	Groups (No. of Patients)	Follow-Up, mo	Fusion Rates	Other Outcomes	Notes
Yi et al, 2015 <sup>37</sup>	Prospective and randomized	ACDF	PEEK and HA-DBM (43) vs HA-BTP (42)	12	87% HA-DBM vs 72% HA-BTP ( $P = 0.16$ )	No difference in neck disability score or infection	Bonion
Xie et al, 2015 <sup>38</sup>	Prospective and randomized	ACDF	PEEK and calcium sulfate and DBM (35) vs autologous ICBG (33)	24	94% DBM vs 100% ICBG ( $P$ not reported)		OsteoSet2 DBM
An et al, 1995 <sup>35</sup>	Prospective	Uninstrumented anterior cervical fusion	DBM with freeze-dried allograft (39) vs autologous ICBG (38)	12		Higher rates of pseudoarthrosis with DBM/allograft and higher rates of graft collapse	Grafton DBM Gel
Lee et al, 2019 <sup>36</sup>	Retrospective	Instrumented ACDF	DBM (24) vs autologous ICBG (17)	24	94% DBM vs 96% ICBG ( $P = 0.66$ )		Orthoblast II

Abbreviations: ACDF, anterior cervical discectomy and fusion; BTP,  $\beta$ -tricalcium phosphate; DBM, demineralized bone matrix; HA, hydroxyapatite; ICBG, iliac crest bone graft; PEEK, polyetheretherketone.

**Table 2.** Review of studies comparing DBM to other bone grafts or implants in thoracolumbar spine.

Study	Design	Patient Population	Groups (No. of Patients)	Follow-Up, mo	Fusion Rates	Other Outcomes	Notes
Kang et al, 2012 <sup>40</sup>	Prospective and randomized	Single-level posterolateral fusion	DBM (30) vs autologous ICBG (16)	24	86% DBM vs 92% ICBG ( $P > 0.99$ )	No difference in ODI or physical functioning scores; increased operative blood loss with ICBG ( $P < 0.0031$ ).	Grafton DBM matrix
Schizas et al, 2008 <sup>42</sup>	Prospective	Posterolateral fusion	DBM (33) vs ICBG or LA (26)	12	70% DBM vs 77% autograft ( $P = 0.77$ )	No difference in ODI	Accell Connexus
Vaccaro et al, 2007 <sup>43</sup>	Prospective	Posterolateral fusion	DBM with bone marrow (19) vs DBM with ICBG (27 patients) vs ICBG (27 patients)	24	63% DBM-bone marrow vs 70% DBM-ICBG vs 67% ICBG ( $P = 0.88$ )		Grafton DBM
Cammisa et al, 2004 <sup>44</sup>	Prospective inpatient control	Posterolateral fusion	120 patients in total, DBM on one side, ICBG on the other	24	52% DBM vs 54% ICBG		Grafton DBM
Sassard et al, 2000 <sup>45</sup>	Prospective case control	Posterolateral fusion	DBM (56) vs autologous ICBG (52)	24	60% DBM vs 56% ICBG ( $P = 0.83$ )	15 ICBG patients reported donor site pain	Grafton DBM
Ricart et al, 2018 <sup>46</sup>	Retrospective	Posterolateral fusion	DBM (21) vs BTP (20)	12	90% DBM vs 70% BTP ( $P = 0.09$ )	No difference in revision rates or visual analog scores	Grafton DBM
Fu et al, 2016 <sup>41</sup>	Retrospective consecutive	Posterolateral fusion >3 levels	DBM (26) vs autologous ICBG (21)		81% DBM vs 86% ICBG ( $P = 0.72$ )	Increased operative blood loss with ICBG ( $P = 0.02$ )	Allomatrix DBM putty
Nam & Yi, 2016 <sup>47</sup>	Retrospective consecutive	Posterolateral fusion	DBM (38) vs HA (41)	12	73% DBM vs 58% HA ( $P = 0.15$ )	No difference in ODI or infection	Bonfuse DBM
Baumann et al, 2015 <sup>48</sup>	Retrospective	Thoracolumbar fractures	DBM (16) vs autologous ICBG (46)		94% DBM vs 100% ICBG ( $P = 0.26$ )		Synthes DBM
Thalgott et al, 2001 <sup>49</sup>	Retrospective	Posterolateral fusion	DBM (28) vs LA (12)		92.5% DBM vs 100% LA (P not reported)		Grafton DBM with coralline HA
<b>Interbody Fusions</b>							
Ko et al, 2022 <sup>50</sup>	Retrospective	Single-level PLIF	DBM (20) vs LA (20)	12	Brantigan-Steffee score 4.4 DBM vs 3.7 LA ( $P = 0.001$ )	No difference in ODI	SurFuse
Kim et al, 2016 <sup>51</sup>	Retrospective	ALIF, PLIF, and TLIF	HA-DBM (65) vs LA (65)	12	52% HA-DBM vs 62% LA ( $P = 0.21$ )	Improvement in ODI in both groups when fusion was achieved; lower rates of fusion with older age and decreased bone mineral density	Bonfuse HA-DBM
Ahn et al, 2014 <sup>52</sup>	Retrospective	PLIF	DBM (44) vs LA (70)	24	Not reported	No difference in degree of bone formation or ODI	Allomatrix DBM

Abbreviations: ALIF, anterior lumbar interbody fusion; BTP,  $\beta$ -tricalcium phosphate; DBM, demineralized bone matrix; HA, hydroxyapatite; ICBG, iliac crest bone graft; LA, local autograft; ODI, Oswestry Disability Index; PLIF, posterior lumbar interbody fusion; TLIF, transforaminal lumbar interbody fusion.

al<sup>37</sup> compared DBM to beta-tricalcium phosphate in 85 patients and found similar rates of fusion at 12 months, while Xie et al<sup>38</sup> compared 68 patients who had received either calcium sulfate with DBM or iliac autograft and found similar 12- and 24-month fusion rates (100% in both groups at 24 months).

### Lumbar Spine

Several studies have examined the utility of DBM in instrumented fusion lumbar cases as an adjunct to promote fusion (Table 2). Kang et al randomly assigned 46 patients to receive either Grafton DBM matrix or autologous iliac crest graft.<sup>40</sup> There was no significant difference in fusion rates (86% DBM vs 92% iliac crest bone graft,  $P > 0.99$ ) at multiple time points at up to 2-year follow-up. Additionally, there was no difference in Oswestry Disability Index and physical function scoring, though there was

significantly decreased operative blood loss in the patients receiving DBM (512 vs 883 mL,  $P = 0.0031$ ). Similarly, Fu et al<sup>41</sup> found no significant difference in rates of fusion for 47 patients undergoing greater than 3-level fusion (26 received DBM putty [Allomatrix] and 21 received autologous iliac crest graft). Again, there was decreased blood loss in the DBM group (700 vs 1200 mL,  $P = 0.02$ ).

Sassard et al<sup>45</sup> conducted a prospective case-control study comparing 56 posterior lumbar interbody fusion (PLIF) patients who received Grafton DBM and local autograft to 52 patients who received iliac crest autograft finding similar rates of fusion between the 2 groups (60% in DBM vs 56% in control,  $P = 0.83$ ). Cammisa et al<sup>44</sup> examined the use of Grafton DBM to autograft on either side of the spine posterolaterally finding fusion mass formation in 52% of the Grafton DBM cases compared with 54% on the autograft side.

Fewer studies have examined the use of DBM in interbody fusions compared with in posterolateral fusion. Ahn et al<sup>52</sup> compared DBM (44 cases) with local autograft (70 cases) as a graft enhancer in PLIFs, but they found no significant difference in bone formation at 24-month follow-up. Kim et al similarly examined lumbar interbody fusions (including patients who received anterior, posterior, and transforaminal approaches) using hydroxyapatite mixed with DBM placed in the interbody spacer vs local autograft and found no significant difference in fusion rates (52% vs 62%, respectively,  $P = 0.21$ ). In both patient groups, ODI improved when fusion was achieved. The authors observed that older age and decreased bone density were associated with lower rates of fusion in both groups. Most recently, Ko et al<sup>50</sup> found that in 40 patients undergoing single-level PLIF (20 DBM and 20 local autograft), there was improvement in Brantigan-Steffee fusion scores in patients receiving DBM (4.4 DBM vs 3.7 local autograft,  $P = 0.001$ ) but no difference in ODI between groups.

Vaidya et al<sup>53</sup> compared the use of allograft with either recombinant human bone morphogenetic protein (rhBMP-2) or DBM in both anterior lumbar interbody fusion (ALIF) and transforaminal lumbar interbody fusion (TLIF). At 12-month follow-up, in the ALIF group, patients treated with allograft/DBM had a 15% height subsidence compared with 27% in patients treated with allograft/rhBMP-2. A similar trend was seen in the TLIF group with 9 or 17 patients in the rhBMP-02 group experiencing subsidence compared with 3 or 25 in the DBM group. Hyun et al<sup>54</sup> similarly compared DBM gel with rhBMP-2 (40 patients) to DBM gel alone (36 patients) and found no difference in fusion rates, adverse device effects, or clinical outcomes.

In minimally invasive TLIFs, Park et al<sup>55</sup> showed 77% solid fusion rate at 2-year follow-up using a combination of DBM paste (OsteofilRT DBM paste; Regeneration Technologies Inc, Alachua, FL, USA) and local autograft. A recent meta-analysis by Han et al<sup>33</sup> comparing DBM to autograft in lumbar fusion cases saw no significant difference in fusion rates in posterolateral fusion (risk ratio [RR], 1.03; 95% CI, 0.90–1.17;  $P = 0.66$ ) and interbody fusion (RR, 1.13; 95% CI, 0.91–1.39;  $P = 0.27$ ).

The role of DBF specifically (in contrast to DBM) is much more poorly defined in the literature. A pre-clinical rat model demonstrated superiority of Strand Family DBF for posterolateral fusion compared with other brands of DBF, though not more than Grafton DBM or Flex.<sup>29</sup> Only 2 clinical studies (not including a

single-case series of 2 patients) were available regarding fusion rates of DBF at the time of submission. Martin Gehrchen's group examined the use of DBF in adult spinal deformity correction with<sup>56</sup> and without<sup>57</sup> 3-column osteotomies. They found decreased rates of pseudoarthrosis requiring revision in cohorts that received DBF compared with their own retrospective cohorts that did not receive DBF (RR with 3-column osteotomy, 0.38; 95% CI, 0.42–0.76;  $P < 0.01$  and RR without 3-column osteotomy, 0.43; 95% CI, 0.21–0.94;  $P = 0.016$ ).

Despite the widespread use of DBM and DBF, there remains little high-quality evidence for its comparative efficacy in spinal fusions. The only level 1 evidence regarding fusion rates available is 2 randomized controlled trials (1 in lumbar and 1 in cervical spine fusions) performed in 1995 and 2004, using Grafton DBM. Although these data have been used to support the use of many other forms and manufacturers of DBM, it is unclear to what extent the fusion and performance data are generalizable to these other products. Given the availability and convenience of commercial DBMs in the context of the morbidity of harvesting iliac crest autograft, further randomized control trials comparing additional DBMs to the gold standard iliac crest harvest are unlikely to be performed.

## CONCLUSION

DBM is a widely used and promising graft alternative, particularly for extending local autograft. There is a comparatively low amount of high-quality data regarding the use of DBM in the context of how many products are commercially available, particularly for cervical fusions. The data that are available suggest similar rates of fusion and improvements in outcome scores compared with the “gold standard” autologous iliac bone graft, with no increase in complications or safety issues. The rapid expansion of the available forms of DBM and the increasing use of DBF call attention to the need for more rigorous study and evaluation of these products and their indications, particularly in comparison with the gold standard autograft.

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