International Journal of Clinical Science and Medical Research

ISSN(print): 2770-5803, ISSN(online): 2770-582X

Volume 06 Issue 06 June 2026

DOI: https://doi.org/10.55677/IJCSMR/V6I6-10/2026, Impact Factor: 8.005

Page No : 210-215

The Role of Biologics and Bone Graft Substitutes in Spinal Fusion: Current Evidence and Future Directions

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Published Online: June 18, 2026

ABSTRACT

Successful spinal arthrodesis requires a biologically active environment, mechanical stability, and sufficient graft material. Autologous iliac crest bone remains the reference standard because it provides osteogenic cells, osteoinductive signals, and an osteoconductive scaffold, but harvest related pain, limited volume, and additional operative morbidity have accelerated the use of osteobiologics and bone graft substitutes. This narrative review evaluates current evidence for local autograft, allograft, demineralized bone matrix, ceramics, recombinant human bone morphogenetic protein-2, cellular bone matrices, bone marrow aspirate, peptide enhanced grafts, and emerging delivery systems. Recombinant human bone morphogenetic protein-2 has the strongest comparative evidence for improving fusion in selected lumbar procedures, although dose, containment, surgical approach, and adverse event profiles remain central concerns. Demineralized bone matrix and synthetic ceramics are useful graft extenders but generally depend on host biology or an additional osteogenic source. Cellular products and autologous cell concentrates are conceptually attractive, yet supporting studies remain heterogeneous and frequently industry associated. Product selection should therefore be individualized according to fusion risk, anatomic site, graft volume, regulatory status, cost, and the quality of clinical evidence. Future progress will depend on lower dose and spatially controlled growth factor delivery, reproducible cell characterization, comparative effectiveness trials, and value-based assessment rather than fusion rate alone.

KEYWORDS: spinal fusion, osteobiologics, bone graft substitute, bone morphogenetic protein, demineralized bone matrix, cellular bone matrix, ceramics

1. INTRODUCTION

Spinal fusion is performed to restore stability, correct deformity, and relieve pain in selected degenerative, traumatic, neoplastic, and deformity related conditions. The procedure succeeds only when the mechanical construct and local biology permit bridging bone to form across the intended motion segment. Pseudarthrosis remains clinically important because it can produce persistent pain, implant failure, deformity progression, and revision surgery. Smoking, diabetes, osteoporosis, malnutrition, multilevel constructs, prior nonunion, and large fusion beds further increase biological demand.

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****Cite this Article: Mubarak, M.H., Ali, M., Mubarak, M.H. (2026). The Role of Biologics and Bone Graft Substitutes in Spinal Fusion: Current Evidence and Future Directions. International Journal of Clinical Science and Medical Research, 6(6), 210-215.***

https://doi.org/10.55677/IJCSMR/V6I6-10/2026

Autologous iliac crest bone graft has traditionally been regarded as the benchmark because it combines living osteogenic cells, osteoinductive proteins, and an osteoconductive matrix. Its disadvantages are equally familiar: limited quantity, harvest time, blood loss, and donor site morbidity. Local bone obtained during decompression avoids a second surgical site, but volume and quality may be inadequate in long constructs or revision settings. These limitations created a large and increasingly complex market for graft extenders, substitutes, and biologic enhancers (Khan et al., 2023; Cheers et al., 2024).

The term osteobiologic covers materials with very different mechanisms and levels of evidence. Some products provide only a scaffold. Others supply growth factors, viable cells, or cell binding signals. The clinically relevant question is not whether a material is biologically plausible, but whether it improves durable fusion and patient outcomes without disproportionate complications or cost. This review therefore compares major classes of biologics, identifies where evidence is strongest, and outlines future directions for safer and more rational use.

2. BIOLOGICAL REQUIREMENTS FOR FUSION

Bone formation is commonly described through three complementary properties. Osteoconduction is the capacity of a scaffold to support cellular attachment and vascular ingrowth. Osteoinduction refers to signals that recruit and direct progenitor cells toward an osteoblastic lineage. Osteogenesis requires viable cells capable of producing new bone. Autograft can provide all three, whereas most substitutes supply only one or two. Mechanical stability, vascularity, surface area, graft containment, and host health remain essential regardless of the selected product.

A useful graft should also handle predictably, resist migration, maintain volume during early healing, and degrade at a rate matched to new bone formation. These characteristics vary not only between material classes but also between commercial products within the same class. Consequently, evidence for one formulation cannot automatically be transferred to another product with a different carrier, processing method, cell content, or growth factor concentration.

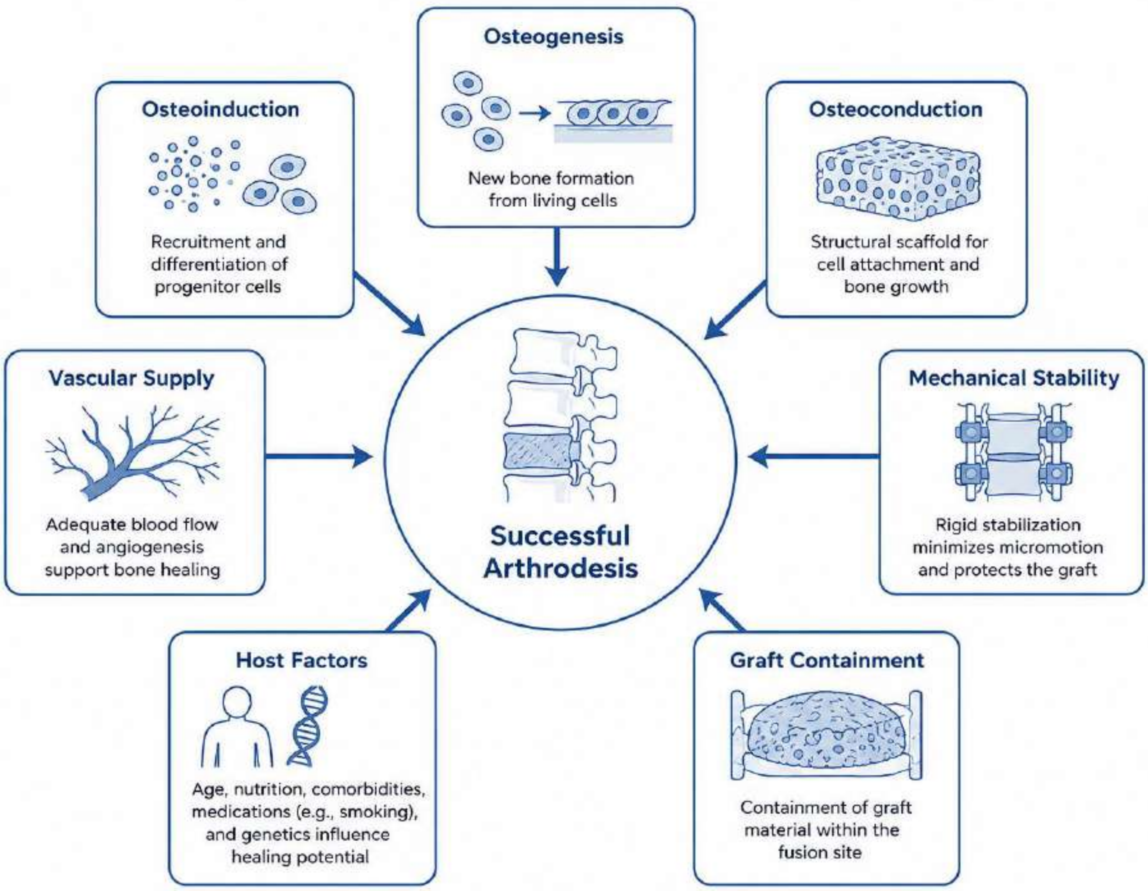

Figure 1. Biological framework for spinal fusion. Suggested elements: osteogenesis, osteoinduction, osteoconduction, vascular supply, mechanical stability, host factors, and graft containment converging on successful arthrodesis.

3. ESTABLISHED AND COMMONLY USED GRAFT OPTIONS

3.1 Autograft and Allograft

Iliac crest autograft remains a dependable reference material, especially when a high biological burden is anticipated. Local autograft is frequently sufficient for short posterior lumbar constructs and avoids harvest morbidity. Structural or morselized allograft expands graft volume and provides an osteoconductive framework, but processing reduces viable cells and may diminish osteoinductive activity. Incorporation can therefore be slower than with autograft, particularly in poorly vascularized beds. Modern donor screening has made disease transmission uncommon, although it cannot be considered impossible.

3.2 Demineralized Bone Matrix

Demineralized bone matrix consists of processed allograft in which mineral content is removed to expose collagen and endogenous growth factors. It is available as putty, paste, fibers, or composite formulations. Demineralized bone matrix is best understood as a graft extender with variable osteoinductive potential rather than a reliable stand alone substitute. Biological activity differs by donor, processing method, carrier, sterilization, and lot. Recent systematic review evidence continues to show acceptable fusion in many applications, but product specific data and independent randomized comparisons remain limited (Butler et al., 2026).

3.3 Synthetic Ceramics and Composite Scaffolds

Calcium phosphate, hydroxyapatite, beta tricalcium phosphate, calcium sulfate, bioactive glass, and related composites mainly function as osteoconductive scaffolds. Their advantages include unlimited supply, absence of donor site morbidity, ease of storage, and no risk of human disease transmission. Porosity and degradation rate can be engineered, although brittle handling, rapid resorption, or prolonged persistence may be problematic depending on formulation. Reviews support ceramics primarily as extenders combined with local autograft or marrow derived cells rather than universal replacements for autograft (Apaydin et al., 2024; Antonacci et al., 2024).

4. GROWTH FACTORS AND POTENT OSTEOINDUCTIVE AGENTS

4.1 Recombinant Human Bone Morphogenetic Protein-2

Recombinant human bone morphogenetic protein-2 (rhBMP-2) is the most extensively studied osteoinductive agent in spinal fusion. It recruits mesenchymal progenitors and promotes osteoblastic differentiation when delivered on an absorbable collagen carrier. Comparative studies and recent evidence syntheses generally show high fusion rates and reduced need for iliac crest harvest in selected lumbar procedures. A 2025 network meta-analysis reported stronger evidence for rhBMP-2 than for most alternative osteobiologics, while emphasizing that data for other products remained sparse (Ambrosio et al., 2025).

Clinical benefit is inseparable from dose, location, and containment. Reported adverse events include inflammatory swelling, radiculitis, ectopic bone, osteolysis, seroma, and approach specific complications. Cervical use is particularly sensitive because soft tissue swelling may compromise the airway. Lower dose strategies seek to preserve fusion while reducing exposure related complications, and systematic review data indicate that the minimum effective dose may differ by procedure (Lytle et al., 2020; Lee et al., 2025). The United States Food and Drug Administration labeling should be reviewed carefully because approved indications are device and approach specific, while many patterns of use remain off label (U.S. Food and Drug Administration, 2025).

4.2 Other Growth Factors and Peptide Technologies

Platelet derived preparations, recombinant platelet derived growth factor, and peptide enhanced scaffolds have been investigated as alternatives or adjuncts. Anorganic bone mineral combined with the P-15 cell binding peptide has demonstrated clinical utility in cervical fusion and is being studied in lumbar applications. These materials may improve cellular attachment without exposing patients to supraphysiologic BMP signaling. However, direct head to head trials, consistent radiographic definitions, and long term surveillance remain less developed than for rhBMP-2.

Table 1. Comparative characteristics of major spinal fusion graft options

Material	Primary function	Principal advantage	Major limitation	Evidence position
Iliac crest autograft	Osteogenic, osteoinductive, osteoconductive	Complete biological profile	Harvest morbidity and limited volume	Reference standard
Local autograft	Complete profile with variable cell viability	No separate harvest site	Limited quantity and quality	Strong for selected short constructs
Allograft	Mainly osteoconductive	Available in structural and morselized forms	Slower incorporation and variable biology	Established adjunct
Demineralized bone matrix	Osteoconductive with variable osteoinduction	Flexible handling and graft extension	Lot and product variability	Moderate, product dependent
Ceramics and bioactive glass	Osteoconductive scaffold	Unlimited supply and no donor morbidity	Requires host biology or added cells	Moderate as extender
rhBMP-2	Strong osteoinduction	High fusion potential and avoids graft harvest	Dose and site dependent complications, cost	Strongest substitute evidence
Cellular bone matrix	Proposed osteogenic and osteoconductive activity	Ready to use viable cell product	Variable cell characterization and weak comparative evidence	Promising but limited
Bone marrow aspirate concentrate	Autologous cellular adjunct	Point of care and low immunogenicity	Cell yield varies with age and technique	Low to moderate

5. CELLULAR PRODUCTS AND AUTOLOGOUS CELL STRATEGIES

5.1 Cellular Bone Matrices

Cellular bone matrices are cryopreserved or otherwise processed allografts marketed to retain viable cells within an osteoconductive matrix. Their theoretical appeal is substantial because they aim to deliver osteogenic cells without autograft harvest. Yet viability at implantation, cell phenotype, donor variability, storage conditions, and post implantation survival are difficult to standardize. A systematic review found generally high reported fusion rates but also substantial methodological weakness, industry involvement, inconsistent definitions, and limited comparative evidence. Rare but serious safety events linked to contaminated allograft further reinforce the importance of donor screening and traceability (Lambrechts et al., 2024).

5.2 Bone Marrow Aspirate and Concentrate

Bone marrow aspirate provides autologous progenitor cells and signaling molecules, usually combined with a ceramic or allograft scaffold. Concentration can increase nucleated cell content, but the number of true mesenchymal stromal cells remains low and declines with age. Harvest site, aspiration volume, dilution with peripheral blood, and processing method influence the final product. Meta-analytic evidence suggests that autologous cells combined with graft substitutes may improve early fusion and patient reported outcomes, although study heterogeneity and small samples limit certainty (Salamanna et al., 2024).

Expanded cell products may deliver larger and more standardized populations, but they introduce manufacturing, cost, regulatory, and long term safety concerns. At present, point of care marrow derived adjuncts are more clinically accessible than culture expanded therapies, yet neither should be assumed to reproduce the biological performance of fresh iliac crest autograft.

6. CHOOSING A BIOLOGIC IN CLINICAL PRACTICE

No single graft is optimal for every fusion. Selection should begin with the baseline probability of nonunion. A healthy patient undergoing a short, well instrumented fusion may require only local bone and an inexpensive extender. A smoker with osteoporosis, prior pseudarthrosis, multilevel deformity, or limited autograft stock presents a different biological problem and may justify a stronger osteoinductive strategy. The anatomic region also matters because the consequences of graft migration, inflammatory swelling, and ectopic bone differ between cervical, thoracic, and lumbar procedures.

Economic value should include acquisition cost, harvest time, complications, length of stay, revision risk, and the cost of a failed fusion. Higher fusion rates do not automatically translate into better pain, disability, or quality of life. Comparative studies should therefore report patient centered outcomes and reoperations alongside radiographic fusion. Current value based reviews caution that several expensive products entered routine practice before robust independent evidence was available (Khan et al., 2023; Lambrechts et al., 2024).

Table 2. Practical framework for selecting an osteobiologic

Clinical domain	Questions to consider	Implication for selection
Patient biology	Smoking, diabetes, osteoporosis, nutrition, age, previous nonunion	Higher risk may justify stronger osteoinduction and optimization of modifiable factors
Procedure	Number of levels, revision status, fusion bed, surgical approach	Determines graft volume, containment, and complication profile
Material properties	Cells, signals, scaffold, resorption, handling	Match product function to the biological deficit
Evidence and regulation	Approved indication, independent trials, external validity	Avoid extrapolating results across products or off label settings
Safety	Swelling, ectopic bone, infection, migration, immune or donor risk	Use the lowest effective exposure and careful placement
Value	Product cost, harvest morbidity, revision avoidance, patient outcomes	Choose on total episode value rather than purchase price alone

7. FUTURE DIRECTIONS

The next generation of osteobiologics will likely focus on control rather than simply increasing biological potency. Sustained and spatially restricted delivery may permit lower doses of growth factors while reducing leakage into neural and soft tissue compartments. Smart scaffolds can be engineered for porosity, degradation, vascular ingrowth, and sequential release of osteogenic and angiogenic signals. Three dimensional printing may also allow patient specific graft geometry and improved contact with irregular fusion beds.

Cell based products require clearer potency assays, minimum viable cell specifications, and transparent reporting of donor and manufacturing variables. Registries and multicenter pragmatic trials are needed to detect rare adverse events and to compare products in real clinical populations. Future studies should use computed tomography based fusion criteria, blinded assessment, standardized follow up, and explicit reporting of conflicts of interest. Patient reported outcomes, time to return to function, and revision free survival should be considered co-primary outcomes rather than secondary decorations.

Predictive analytics may eventually support biologic selection by integrating patient risk, bone quality, construct features, and procedure type. Such tools should be tested prospectively and should not become a new route for uncritical product escalation. The most valuable innovation may be a system that identifies patients who need no expensive adjunct just as accurately as it identifies those at high risk of pseudarthrosis.

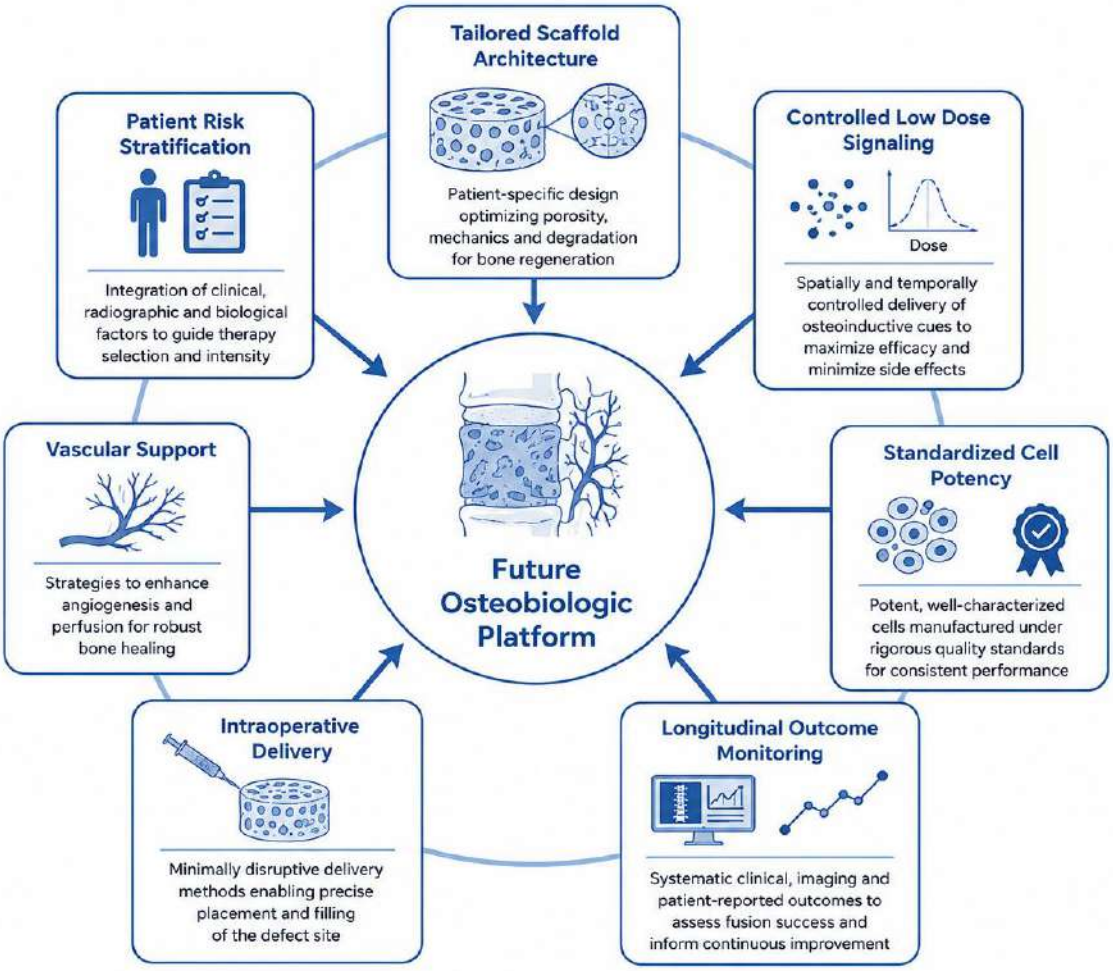

Figure 2. Future osteobiologic platform. Suggested elements: patient risk stratification, tailored scaffold architecture, controlled low dose signaling, vascular support, standardized cell potency, intraoperative delivery, and longitudinal outcome monitoring.

8. CONCLUSION

Biologics and bone graft substitutes have expanded the options available for spinal fusion, but their evidentiary foundations are not equal. Autograft remains the biological benchmark. Demineralized bone matrix, allograft, and synthetic ceramics are useful extenders, especially when combined with local bone or an osteogenic source. Recombinant human bone morphogenetic protein-2 has the strongest evidence for enhancing fusion in selected lumbar settings, although careful dosing, containment, and adherence to indication specific safety principles are essential. Cellular bone matrices, marrow derived concentrates, peptide technologies, and engineered scaffolds are promising, but many require stronger independent comparative trials. Future practice should move away from product driven selection toward a patient specific, evidence graded, and value conscious strategy that balances fusion biology with safety and meaningful clinical outcomes.

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