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REVIEW

Research Progress of Bone Grafting: A Comprehensive Review

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Abstract: Bone tissue, the second most transplanted tissue after blood, is utilized in over 2.2 million bone grafts annually to address various bone-related conditions including fractures, tumors, bone infections, scoliosis, congenital defects, osteoporosis, osteoarthritis, and osteogenesis imperfecta. According to incomplete statistics, $4.3 billion was spent on bone graft materials in 2015 alone, with projections suggesting this figure may reach $66 billion by 2026. The limited availability of autogenous bone graft considered the gold standard due to their three critical biological properties: osteoconduction, osteoinduction, and osteogenesis-alongside the increasing global aging population, may be contributing to this rising expenditure. Furthermore, advancements in biomaterials and engineering technologies have created opportunities for the exploration of new bone graft substitutes. In this review, we will examine the fundamental structure of natural bone and the characteristics of ideal bone graft, highlighting common bone graft materials currently available, such as true bone ceramics, decalcified bone matrix, freeze-dried bone and demineralized freeze-dried bone, bioactive glasses, bone marrow aspirate concentrate, polymer nanocomposites, which have different characteristics in osteogenic, osteoconductivity, osteoinductivity, biocompatibility, mechanical properties, and resorption. How to utilize its advantages to maximize the osteogenic effect will be the focus of this review, and some of the current challenges in the field of bone grafting will be identified, outlining potential directions for future development. In conclusion, the choice of bone graft is critical to bone repair and regeneration, and a comprehensive understanding of the advantages and disadvantages of bone graft materials can improve the effectiveness of related surgical interventions.

Keywords: bone graft, true bone ceramics, decalcified bone matrix, freeze-dried bone, bone regeneration

Introduction

Over a decade ago, the National Center for Health Statistics reported that 4,392,000 orthopedic-related surgeries were performed in 2010 alone. Among these, approximately 1 million involved surgical interventions on cranial bones, extremities, ribs and sternum affected by trauma, postoperative deformities, oncological conditions, and inflammatory diseases. Additionally, 139,400 surgeries were lower extremity joint replacements, with at least 20–25% of these cases requiring bone graft material, the majority of which utilized bone substitute materials. Consequently, the total number of surgeries involving bone graft material is estimated to be between 1.3 and 1.5 million.[1] Nowadays, the aging global population, increased life expectancy, enhanced access to advanced health care services and a heightened incidence of sports injuries among youth contribute to an annual rise in these figures. Bone defects resulting from trauma, disease, surgery or congenital malformations represent a significant health challenge worldwide, necessitating improved methods for the repair and regeneration of bone tissue.[2,3] Furthermore, bone is the second most transplanted tissue after blood, with over 2.2 million bone grafts performed each year to address various bone-related diseases, including fractures, tumors, bone infections, scoliosis, congenital defects, osteoporosis, osteoarthritis and osteogenesis imperfecta.[4,5] This substantial demand for bone replacement materials has spurred the growth of the orthopedic implant market, which was valued at $4.3 billion in 2015 and is projected to reach $66.0 billion by 2026.[6,7] Bone grafting is frequently employed in the fields of traumatology, orthopedics and maxillofacial surgery. The treatment approach is primarily influenced by the degree and nature of the pathological condition

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that results in the bone defect. Bone graft materials are predominantly utilized in traumatology and orthopedics for applications involving the spine, significant bone defects, and degenerative diseases affecting major joints. Additionally, these materials are employed in dentistry and maxillofacial surgery to address atrophy in both the upper and lower alveolar ridges.[8] Among the various types of bone grafts, autologous bone grafts, which are obtained in the form of bone fragments or pellets, are considered the gold standard due to their three critical biological properties: osteoconduction, osteoinduction and osteogenesis.[9,10] However, autografts have notable limitations, primarily due to the restricted availability of donor sites, which are mainly the ilium, tibia, and fibula.[11] Furthermore, complications related to bone collection occur in approximately 20.6% of cases and may include issues such as limited availability, the necessity for additional surgeries, bleeding at the donor site, deformities, scarring, infection, inflammation, chronic pain, and increased costs. Moreover, autografts may not be suitable for larger bone defects.[12–14] While inert non-bioactive metal implants have been employed to address large bone defects. However, issues related to the integration and compatibility of these grafts with surrounding tissues and natural bone have hindered their widespread clinical application.[15] In contrast, allograft bone exhibits similar properties, offering excellent osteogenic and osteoconductive characteristics without the complications and issues associated with donor sites, thereby serving as an effective alternative to autologous bone. However, allograft bone also has its own limitations, which includes risks of disease transmission, antigenicity, osteochondrosis, limited availability, lack of uniformity, graft resorption, and high costs.[16–18] The development of biomaterials and advancements in engineering technology have opened new avenues for modern bone tissue engineering (BTE). Both natural and synthetic biomaterials have been utilized for tissue repair, with various porous structures enhancing cell adhesion, differentiation, and proliferation, thus promoting better integration and improving the physical properties of implants. However, how do common xenografts compare to the ideal bone graft? This review aims to provide a detailed examination of the advantages and limitations of prevalent xenografts, highlight the challenges currently faced in the field of bone grafts, and outline potential directions for future development.

Common Xenograft Bones

Bone is a highly metabolically active, multifunctional, and complex organ characterized by unique regenerative and repair properties. In addition to its weight-bearing and auxiliary functions, bone plays a vital role in various physiological processes, including hematopoiesis, the protection of essential organs (such as the brain and heart), and the storage of minerals and various growth factors.[19] Furthermore, bone is a dynamic and highly vascularized tissue with a nanocomposite structure, exhibiting approximately 80–90% porosity and accounting for about 15% of the total body weight.[20,21] It comprises a diverse array of cells, including osteoprogenitor cells, osteoblasts, osteoclasts, and osteocytes, along with collagen, hydroxyapatite, and water. The extracellular matrix (ECM) serving as a scaffold for bone deposition, enhances the strength of bone tissue, and accommodates signaling factors critical for bone formation, growth, remodeling, and resorption (Figure 1).[22,23] The process of bone repair following a fracture is intricate, necessitating the mobilization of a continuous stream of cells and molecules regulated by both systemic and local factors.[24] Although bone tissue possesses the ability to self-repair, it can only regenerate and reshape minor injuries (less than 8 mm).[25] When a bone defect surpasses the critical size threshold (approximately greater than 2 cm) or when more than 50% of the bone circumference is compromised, it can lead to inadequate fusion, abnormal fusion, or pathological fractures.[26] To address large bone defects, surgical intervention and the use of bone substitutes are essential. The selection of appropriate bone substitutes is a critical step in resolving this challenge. Xenograft bones are emerging as an effective alternative to autologous bone grafts due to their availability, cost-effectiveness, and reduced morbidity at the donor site (Figure 2).[27,28] Moreover, xenografts are structurally and morphologically similar to properties to human bone, providing another viable option (Table 1).[29] In North America, the proportional use of bone graft materials reveals that allografts account for just over 50% of cases, while autografts constitute approximately 15%, xenografts 22%, synthetic materials 5%, and recombinant human bone morphogenetic protein (BMP)-2 also 5%.[30] Bone graft hold significant potential for the healing and regeneration of bone defects. Under the influence of BTE, bone graft materials have been vigorously developed, with an increasing emphasis on biomaterials that fulfill three primary characteristics (Table 2).[31–37] In addition to the aforementioned characteristics of replicating bone, the ideal bone replacement material should possess the following attributes:[38–40] ① a three-dimensional (3D) structure resembling real bone, with similar porosity and good biocompatibility, is suitable for cell and vascular implantation, while being cost-effective; ② the ability to maintain in vivo

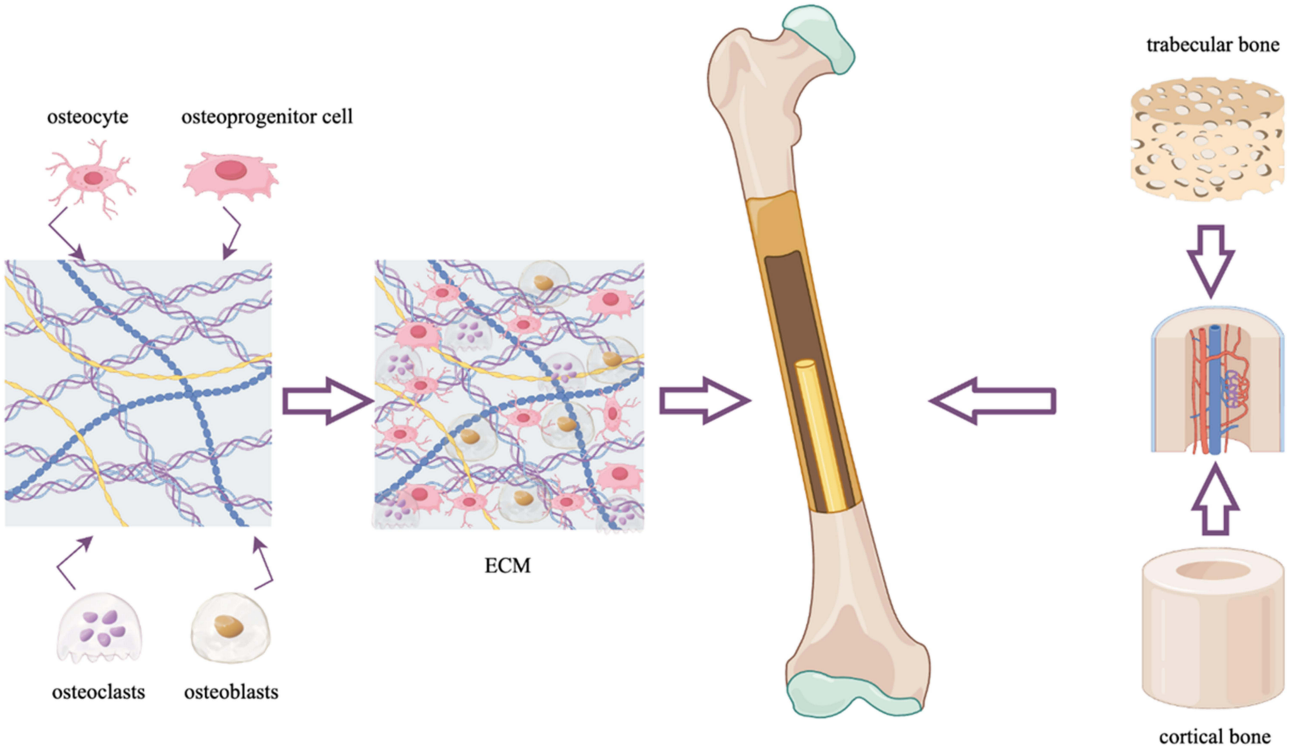

Figure 1 Schematic diagram of the anatomy and main components of natural bone.
Abbreviation: ECM, extracellular matrix.

mechanical stability and withstand physiological loads at the defect site, be radiopaque, and facilitate the use of non-invasive methods (such as X-ray or micro-computed tomography) for implant monitoring; ③ the capacity to degrade at a controlled rate that aligns with the rate of new bone formation, and be easy to handle and sterilize.

True Bone Ceramics

True bone ceramics (TBC) are organic crystals of bone minerals derived from fresh bovine cancellous bone, which are calcined at high secondary temperatures (Figure 3).[41,42] Their crystalline properties closely resemble those of artificial hydroxyapatite and other biomaterials, establishing TBC as a bone substitute material characterized by excellent biocompatibility and biological activity.[43] Specifically, TBC is completely deproteinized bone that retains the micro-skeletal structure of native bone, akin to the micropore structure of cancellous bone, and exhibits bone conduction properties.[44,45] Additionally, TBC possesses high porosity, which enhances the surface area, thereby promoting cytokine release to adjacent cells, facilitating the growth of new bone, and accelerating osteoblast proliferation.[46,47] The degradation of TBC releases calcium and phosphate ions, which are essential for new bone formation.[43] Bovine-derived xenografts are regarded as more biocompatible with human organisms. One study indicated that the use of bovine-derived grafts resulted in dense, mineralized bone encapsulated with bovine graft particles, alongside the presence of capillaries and neoplastic cells colonizing Haversian canals.[44,48] Furthermore, Tamaki et al[41] reported the findings from a study on TBC, demonstrating that TBC implanted in bone marrow exhibited good biocompatibility with surrounding bone, thus suggesting that TBC, with their natural bone structure, promoted blood vessel growth within the material and created an optimal environment for bone formation. Qiao et al[49] prepared calcined xenogeneic bone using a high-temperature calcination method and subsequently co-cultured the extract of this calcined xenogeneic bone with L929 cells in vitro. Cytotoxicity experiments indicated that the cytotoxicity of the calcined xenogeneic bone extract ranged from 0 to 1, while cytocompatibility tests demonstrated that L929 cells adhered well to the surface of the calcined xenogeneic bone and proliferated within its pores. In vivo experiments revealed varying degrees of new bone formation at 4 and 26 weeks. The advantages of TBC include its lack of antigenicity, absence of cytotoxicity, and higher alkaline

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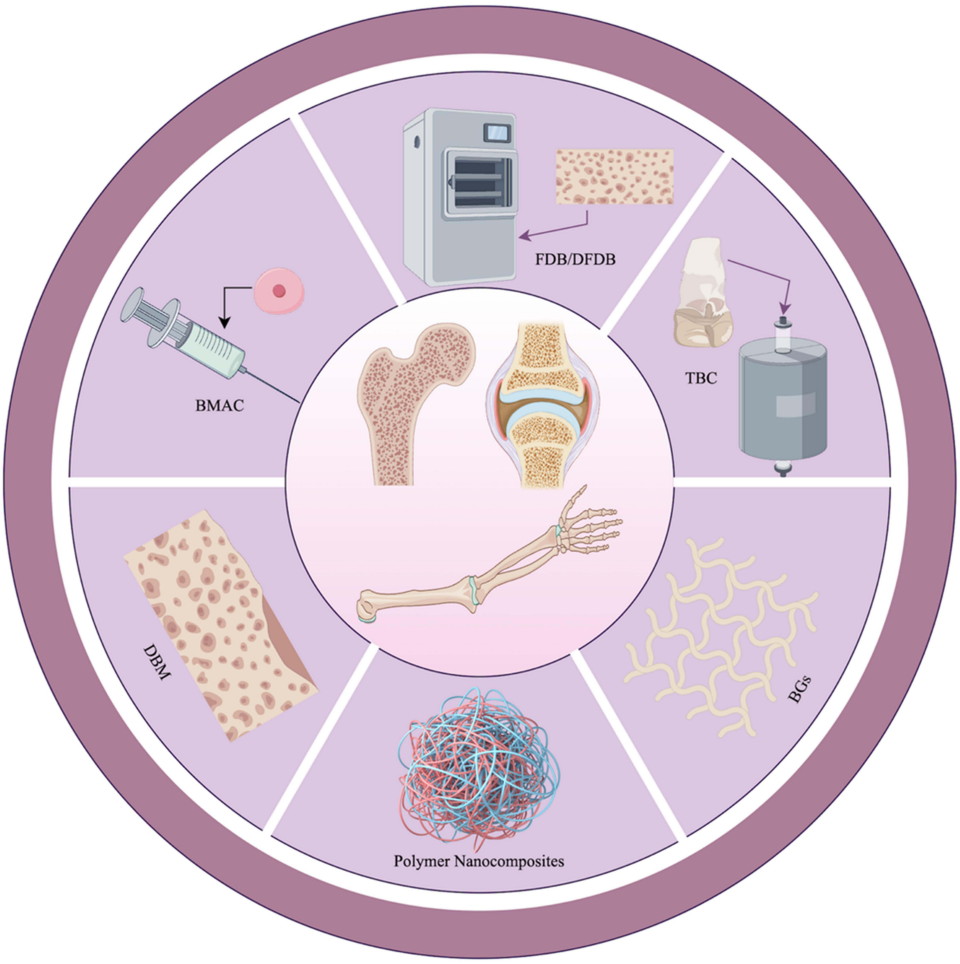

Figure 2 Schematic representation of common bone graft to facilitate bone defect repair.
Abbreviations: BMAC, bone marrow aspirate concentrate; BGs, bioactive glasses; DBM, decalcified bone matrix; DFDB, demineralized freeze-dried bone; FDB, freeze-dried bone; TBC, true bone ceramics.

phosphatase activity in osteoblasts cultured with TBC compared to those cultured with hydroxyapatite (HA) materials.[50] However, TBC alone is not an ideal bone substitute due to its poor surface activity, insufficient cell adhesion, and low osteogenic induction capacity.[51,52] With the rapid development of BTE, the surface modification of TBC have been implemented to retain its beneficial properties, enhance the biological activity of the TBC surface and improve the adhesion between seed cells and the scaffold. Consequently, the incorporation of bioactive molecules or bone-promoting metal ions, such as BMP-2-related peptide, rhBMP-2 and Sr, and (DSS)6-liposome/Casein kinase 2-interacting protein (CKIP)-1 siRNA, has been shown to possess osteoinductive properties that facilitate more effective bone defect repair (Table 3). [53–63]

Decalcified Bone Matrix

The use of decalcified bone as a substitute for treating bone defects can be traced back to Senn,[64] while Urist elaborated on the preparation of decalcified bone matrix (DBM) in 1965, highlighting the role of BMP in facilitating bone formation.[65] With the rapid advancement in bone graft technologies, DBM is now regarded as a highly processed allogeneic bone derivative, produced through standardized procedures that include acidification to remove at least 40% of the mineral content from the matrix (Figure 3). This matrix primarily consists of collagen (predominantly type I, along with types IV and X, which together account for over 93% of its total composition), proteins (including BMPs), various growth factors such as transforming growth factor-beta (TGF-β), and residual minerals (1–6%).[66,67] The surface area and

Table 1 Summary of Representative Commercial Xenograft and DBM-Based Bone Graft

Trade Name	Manufacturing Company	Characteristics	Main Ingredients	Scope of Application	Advantages
XenoBone®	Desu Medical	Pellet	Type-I ultra-pure bovine collagen, ß-TCP	Orthopaedic	Providing the osteoconductive properties required for bone filling Triggering bone regeneration and providing growth matrix for osteoblasts Completely bio-absorbable
DiaBONE	Cowellmedi	Pellet	100% bovine bone	Dentistry	Optimal cell attachment and blood absorption Stimulates activity of osteoclast and osteoblast. Mutually connected porous structure Easy to handle
RegenerOss®	Zimmer Dental	Powder	20% type-I bovine collagen, 80% carbonate apatite granules	Dentistry	Providing an osteoconductive scaffold for bone regeneration Allowing in-growth of blood vessels that provide adequate supply of nutrients, delivery of cells, and growth factors The Right Environment for Bone Regeneration
Creos™ xenogain	Nobel Biocare Services AG	Pellet	10% type-I porcine collagen, purified cancellous bovine bone mineral granules, appropriate Ca/P ratio	Dentistry	Osteoconductive properties Long-term volume stability Hydrophilic for fast rehydration Easy to handle
ZenGro™	SOUTHERN IMPLANTS	Rigid	Porcine cancellous fine/std, calcium phosphate	Dentistry	Highly porous scaffold that provides space for new bone deposition and vascularization Rough surface facilitates cell adhesion and spread for bone in-growth High volume fill per unit weight
Bio-Oss® S	Geistlich Pharma	Pellet	Remove organic matter bovine bone minerals (the main component is HA)	Dentistry	Good osteogenesis effect Improving implant survival Easy to handle
OSTEOPLANT®	BiOTECK	Pelle, Rigid powder	Equine bone tissue, bone collagen	Orthopaedic	With a fully preserved extracellular matrix Creating a favorable physiological environment for promoting bone regeneration Retaining the typical load resistance of natural bone

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Table 1 (Continued).

Trade Name	Manufacturing Company	Characteristics	Main Ingredients	Scope of Application	Advantages
Smartbone®	Industrie Biomediche Insubri	Rigid	Bovine mineral bone matrix, bioresorbable polymer, collagen fragments	Orthopaedic, Dentistry, Neurosurgery	The polymeric coating protects the graft during initial healing/ osteointegration period Bigger defects do not need autologous bone Far better stability of the augmented bone graft Easy to handle
MinerOss™ X	CAMLOG Biotechnologies	Pellet	Bovine cancellous/cortical bone granules, 5% bovine collagen	Dentistry	Easy to handle Facilitates bone formation and remodeling of the defect site Suitable for extraction sockets, alveolar ridge enhancement, and sinus augmentations
Mp3®	Tecnoss Dental	Paste	90% granulated mix (cortico-cancellous heterologous bone mix), 10% collagen gel	Dentistry	Facilitating blood clotting and the subsequent invasion of repairing and regenerative cells Facilitating new bone tissue formation in defect sites and accelerating the regeneration process Easy to handle
Hypro-Oss®	Bioimplon	Pellet	Natural, not heated bovine bone composite (30% Atelo-collagen type I and 70% HA)	Orthopaedic Dentistry	Effective haemostatic properties, with anti-hematoma effect Highest quality of new bone formation No physical or chemical changes of the native bone material Suitable for intraosseous defects, sinus lift, periimplant defects and sinus lift
AlphaGRAFT® DBM	Alphatec Spine	Extensible	Composed of 100% demineralized fiber	Orthopaedic	Demineralization process retains osteoconductive properties and enables osteoinductive potential Superior handling for use in spinal fusion procedures Ready-to-use application that is offered freeze-dried
STRATOFUSE® DBM 100	ChoiceSpine	Extensible	100% demineralized allograft bone, no extrinsic carrier	Orthopaedic	Preserving naturally occurring BMPs and growth factors Formable and irrigation resistant Osteoconductive and Osteoinductive potential

(*Continued*)

Table 1 (Continued).

Trade Name	Manufacturing Company	Characteristics	Main Ingredients	Scope of Application	Advantages
BioAdapt® DBM	RTI Surgical	Extensible	Comprised of 100% donated human musculoskeletal tissue	Orthopaedic	Expands with hydration to provide a contoured fit to the bony defect Can be rehydrated with various types of fluid Easily mixed with autograft or allograft
StaGraft™ DBM	Zimmer Biomet	Pellet	Osteoinductive demineralized bone matrix, natural lecithin carrier, Resorbable coralline, HA granules	Orthopaedic	Coming in an array of convenient delivery sizes for a range of uses Verified Osteoinductivity and good biocompatibility Maintains integrity Easy to handle
GRAFTON™ DBM	Medtronic	Pellet	Composed of demineralized bone from human donors, trace amounts of antibiotics (gentamicin) and processing solutions	Dentistry, Orthopaedic	Preserving the osteoinductive activity required for new bone formation Can be mixed with autologous bone or allogeneic bone as a bone graft augmentor Proven bone healing results and a track record of safety
DBX® DBM	DePuy Synthes	Putty	Composed of demineralized bone from human donors, sodium hyaluronate	Orthopaedic	Osteoconductive and osteoinductive potential Ready to use, with no mixing or thawing required Biocompatible – inert carrier, pH-balanced, nonhemolytic Exemplary safety

Notes: The above data were obtained from ISO 13485, or EUDAMED or FDA's HCT/Ps official database, as well as from the official introduction of each product.
Abbreviations: BMP, bone morphogenetic protein; DBM, decalcified bone matrix; HA, hydroxyapatite, ß-TCP, β-tricalcium phosphate.

Table 2 Summary of the Characteristics of Common Bone Graft

	Ideal Bone Graft	Autologous Graft	Allograft Bone	Alloplast	TBC	DBM	FDB	DFDB	BGs
Osteogenic	++	++	–	–	–	–	–	–	–
Osteoconductivity	++	++	++	++	++	++	++	++	++
Osteoinductivity	**++**	**++**	**±**	–	–	**±**	**±**	**++**	**±**
Biocompatibility	**++**	**++**	**++**	**++**	**++**	**++**	**++**	**++**	**++**
Mechanical properties	**++**	**++**	**±**	–	**++**	–	**±**	**±**	**++**
Resorption	Regular	Regular	Regular	Slow	Slow	Regular	Regular	Regular	Slow

Notes: "±", between positive and negative, representing uncertainty; part of the table is reprinted from Jensen et al. Osteology.
Abbreviations: BGs, bioactive glasses; DBM, decalcified bone matrix; DFDB, demineralized freeze-dried bone; FDB, freeze-dried bone; TBC, true bone ceramics.

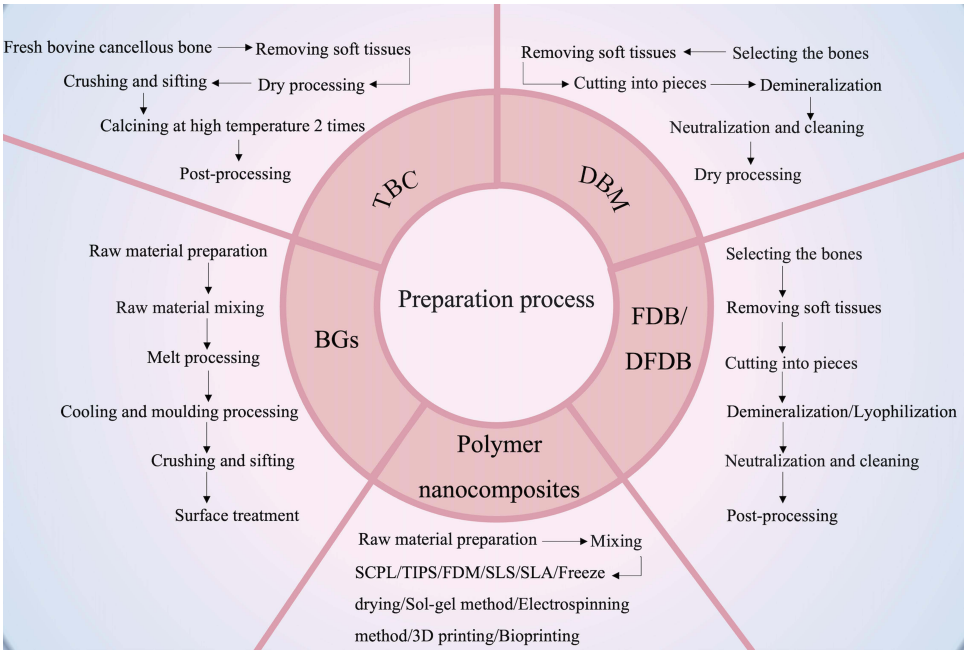

Figure 3 A brief procedure for the preparation of bone graft listed in the review.
Abbreviations: BGs, bioactive glasses; DBM, decalcified bone matrix; DFDB, demineralized freeze-dried bone; FDB, freeze-dried bone; FDM, fused deposition modeling; SCPL, solvent casting and particulate leaching; SLA, stereolithography; SLS, selective laser sintering; TBC, true bone ceramics; TIPS, thermally-induced phase separation.

porosity of decalcified bone meal are significantly greater than those of non-decalcified bone meal to enhance its capacity for bone conduction. Following decalcification,[68] BMP and vascular endothelial growth factor (VEGF) released from surrounding mineral components synergistically promote osteoinductive potential.[69] Additionally, the residual collagen in DBM imparts essential physical and biological properties to the matrix, facilitating a 3D configuration that supports the growth of host capillaries, perivascular tissues, and bone progenitor cells within the graft, thereby enabling bone formation.[70] Pan et al[71] obtained a composite bone graft with anti-inflammatory, prevascularization and endogenous stem cell homing by subcutaneous implantation of DBM, which was confirmed that it significantly promoted the regeneration of skull defects in rats. Liu et al[72] used fresh halibut bone as raw material to make fish DBM (FDBM), and the results showed that FDBM not only had a good repair effect on bone defects, but also had good physicochemical properties, biosecurity, cell adhesion and lower economic cost. Furthermore, Mahyudin et al[73] constructed a rabbit femoral defect model and implanted allogeneic lyophilized bovine cortical bone, allogeneic lyophilized New Zealand white rabbit cortical bone, xenogeneic hydroxyapatite bovine bone, and xenogeneic decalcified bone matrix bovine bone. Their results revealed that the decalcified bone matrix group exhibited the most favorable bone healing outcomes. The raw materials of DBM derived from xenogeneic sources are more abundant, which greatly improve the utilization rate of resources and provide a promising biomaterial for the treatment of bone defects.[74] A study conducted at the New York Special Surgery Hospital from 2002 to 2004 found that 10% of all used bone substitutes were allogeneic bone, while 82% were DBM products.[66] Consequently, DBM has been demonstrated as a viable alternative for bone conduction and osteoinduction. The use of DBM in bone reconstruction presents several advantages:[70] ① it is independent of the number of grafts; ② it minimizes complications associated with the acquisition of autologous bone grafts at the donor site; ③ it reduces both surgery and recovery time. DBM is extensively utilized in clinical practice, particularly for rotator cuff repair and anterior cruciate ligament reconstruction, as it promotes tendon-bone healing.[75] The efficacy of DBM in cervical and lumbar fusion procedures has been corroborated by multiple studies.[76–78] In a level I prospective multicenter randomized clinical trial, Kang et al[79] reported on the effectiveness of Grafton DBM™ compared to iliac crest autograft for single-segment posterior lumbar fusion. The final follow-up results indicated a fusion rate of 86% in the DBM™ group and 92% in the autograft group. Commercially available DBM is primarily derived from human allogeneic bone and is available in various forms, including powders, granules, gels, putty, and bars. While there have been no

Table 3 Studies Related to the Modification of TBCs by Adding Bioactive Molecules or Metal Ions

Study	Year	Add Ingredients	Formulations	In vivo Trial	In vitro Trial	Advantage	Conclusion
Minamide et al[52]	2004	BMP	BMP-TBC	Rabbit spine model	Non	All pores of grafted TBC fragments are filled gradually with new bone formation	TBC is better than common vectors
Zhang et al[53]	2012	DFO	DFO-TBC	Rabbit radial bone defect model	Non	Cavities of new bone in the scaffold are filled with bone marrow components and blood vessels	DFO-TBC is a promising bone graft substitute for the treatment of bone defects
Deng et al[54]	2012	OIC-A006	OIC-A006-TBC	Rabbit radial bone defect model	Non	Significantly promotes new bone regeneration	OIC-A006-TBC may be an approach for treatment of large segmental defects of long bones
Li et al[55]	2017	Sr	Sr-TBC	Rabbit femoral defect model	MTT assay, live/dead staining, ALP activity, qRT-PCR analysis	Significantly enhances the adhesion, proliferation and osteogenic differentiation of osteoblasts	Sr10-TBC could be a promising biomaterial for bone defect regeneration
Yang et al[56]	2018	PTHdP	PTHdP- CH/TBC	Rabbit femoral defect model	MTT assay, Live/dead staining, ALP activity, qRT-PCR analysis	High loading efficiency and controlled slow release, and enhanced bioactivity	PTHdP- CH/TBC could be an ideal delivery scaffold
Cui et al[57]	2018	P28	P28/HMSN-TBC	Rabbit radial bone defect model	Cell Adhesion Assay, MTT assay, ALP activity	Significantly promotes cell proliferation and osteogenic differentiation	P28/HMSN-TBC provide a promising approach for BTE and regenerative medicine
Sun et al[58]	2018	SIS	mSIS-TBC	Mice skull defect model	Cell proliferation, ALP activity, SEM observation, XPS investigation, qRT-PCR analysis, western-blot staining	Significantly enhances cell proliferation and osteogenic differentiation	mSIS/TBC is an excellent alternative for bone regeneration
Zhang et al[59]	2021	rhBMP-2, Sr	BMP-2/Sr-TBC	Rabbit femoral defect model	CCK-8 assay, ALP activity, SEM observation	Significantly promotes cell proliferation and good osteogenic activity	BMP-2/Sr-TBC has good biological activity and osteogenic repair effect

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Table 3 (Continued).

Study	Year	Add Ingredients	Formulations	In vivo Trial	In vitro Trial	Advantage	Conclusion
Xu et al[60]	2021	(DSS)6-liposome/ CKIP-1 siRNA/	(DSS)6- liposome/CKIP-1 siRNA/calcine bone	Rat skull defect model	CCK-8 assay, qRT-PCR analysis, Alizarin red staining, Western-blot staining	Significantly promote the proliferation of osteoblasts,	(DSS)6-liposome/CKIP-1 siRNA/ calcine bone is effective in repairing bone defects
Hu et a[61]	2023	Zn–Sr	Zn–Sr/TBC	Rat skull defect model	ALP activity, Antibacterial test, Cell proliferation and viability assay, Cell adhesion assay, Alizarin Red staining, qRT-PCR analysis	Significantly upregulate the expression of osteogenic genes and promote the mineralization of ECM	$Zn_{0.25}Sr_{0.20/}$TBC has the best bone repair ability, and it is an excellent new bionic bone repair material with more prospects.
Jiang et al[62]	2024	COL1	TBC/COL1	Nude mice subcutaneous model	CCK-8 assay, SEM observation, western-blot staining, Cell adhesion and spreading, H&E and Safranin-O staining	Good biocompatibility while maintaining the cartilage phenotype	TBC/COL1 composite scaffolds are fabricated with both sufficient support and allow for cartilage regeneration.

Abbreviations: ALP, alkaline phosphatase; BMP, bone morphogenetic protein; BTE, bone tissue engineering; CCK-8, cell counting kit-8; CH/TBC, true bone ceramics incorporated with nano-hydroxyapatite coating and chitosan; CKIP-1, casein kinase 2-interacting protein-1; COL1, type I collagen; DFO, desferrioxamine; DSS6, trimethylammo-nium propane-based cationic liposomes attached to six repetitive sequences of aspartate, serine, serine; ECM, extracellular matrix; H&E, hematoxylin and eosin; HMSN, hollow mesoporous silica nanoparticle; MTT, Methylthiazolyldiphenyl-tetrazolium bromide; mSIS, mineralization submucosa; OIC-A006, osteogenic inducible compound-active 006; PTH, parathyroid hormone-derived peptide; P28, a novel bmp-2-related peptide; qRT-PCR, quantitative real-time polymerase chain reaction; rhBMP-2, recombinant human bone morphogenetic protein-2; Sr, strontium; SEM, scanning electron microscope; TBC, true bone ceramics; XPS, x-ray photoelectron spectroscopy.

documented cases of infectious disease transmission associated with commercial DBM products, the processing methods can not eliminate the risk of prion contamination.[66] Furthermore, the osteoinductive properties of DBM are influenced by exposure time and HCl concentration, with significant variability in osteoinductive potential observed across different donor characteristics.[80–82] Despite the development of various DBM products, limitations remain:[70,83] ① no DBM product currently satisfies all the ideal conditions for bone grafting materials; ② there are inconsistencies in the osteogenic activity of DBM products processed under different materials, methods, and reagents, even when produced under identical conditions; ③ the required mechanical properties to withstand tension and load continue to pose challenges. In light of these issues, BTE seeks to leverage the characteristics of DBM and enhance its osteogenic activity (Table 4). [84–102]

Freeze-Dried Bone and Demineralized Freeze-Dried Bone

Freeze-dried bone (FDB) is derived from various sources, predominantly of human origin. The processing of FDB encompasses several steps, beginning with donor screening, followed by soft tissue stripping, size reduction, decontamination, antimicrobial treatment, freeze-drying, dehydration, secondary size reduction, and final sterilization (Figure 3).[103] This meticulous process primarily aims to significantly reduce the water content in the graft to less than 5%, enabling a storage duration of up to five years at room temperature. Additionally, the removal of water serves to disrupt the lipid envelope, thereby inactivating envelope viruses and further decreasing the risk of disease transmission.[104,105] Although the treatment of FDB preserves the structural characteristics of the natural donor bone tissue and minimizes the impacts on osteoconductivity and biocompatibility, it can result in the destruction of osteoblasts and a reduction in the expression of major histocompatibility complex class I antigens in these cells.[106,107] Meanwhile, FDB is recognized as an inert, rapidly fixable, and degradable bone graft.[108] Its low failure rate for bulk grafts and high implant survival rate, particularly in complex defects with significant bone loss, address the limitations of granular bone grafts, with the solid form of FDB compensating for this shortcoming.[109] FDB is extensively utilized in clinical practices such as spine surgery, trauma orthopedics, dentistry, and maxillofacial surgery, yielding promising clinical outcomes.[110–113] A comprehensive 10-year review of augmentation rhinoplasty indicated that FDB grafts represented a safe and equivalent alternative.[114] The osteoplasticity of FDB was believed to be comparable to that of autologous bone grafts.[115–117] Kreuz et al[118] demonstrated that FDB and autologous bone integrated similarly in canine models, as evidenced by the qualitative similarity in the extent of new bone formation and subsequent bone incorporation. Novell et al[105] reconstructed the atrophied maxilla using FDB and conducted a follow-up over five years, finding that the outcomes were comparable to those achieved with autologous bone. Notably, the degree of FDB resorption was lower than that observed with autologous bone. Iasella et al[119] assessed osteogenesis in FDB and reported approximately 65% bone presence after six months, which included 28% vital bone and 37% non-significant graft remnants. Furthermore, clinical evaluations of FDB indicated predictable outcomes comparable to those of autologous bone when guided bone regeneration surgery was performed.[120] There was no significant difference in the effects of bone regeneration effect with or without the application of a layer of autologous bone for augmentation, suggesting that FDB can effectively stimulate bone regeneration and may serve as a viable alternative to autologous bone.[121] FDB demonstrates superiority over allogeneic materials regarding dimensional stability, new bone formation, and cost-efficiency.[122,123] Additionally, specific bone remodeling genes can be upregulated during two-stage maxillary sinus augmentation with FDB, with gene expression results aligned with osteopontin (OPN) immunoreactivity findings. The expression patterns of FDB are similar to those of natural bone, and bone formation-related genes are more highly expressed, indicating its potential clinical superiority over deproteinized bovine bone (DBB).[124] Concurrently, in vitro studies have demonstrated that FDB particles possess greater potential than HA/β-tricalcium phosphate (β-TCP) particles in supporting the attachment and proliferation of human dental pulp stem cells (DPSCs), as well as in inducing their alkaline phosphatase (ALP) activity.[125] Compared to fresh frozen bone, FDB is easier to maintain and has lower isoimmunogenicity, as well as a reduced risk of infection. However, it is important to note that freeze-drying significantly decreases the Young's modulus of FDB by 15%, leading to a reduction in its mechanical properties.[126] Te Stroet et al[127] reported 10-year survival rates for any cause and aseptic loosening of acetabular prostheses at 87% and 97%, respectively, when fresh frozen allografts were used. In contrast, Villatte et al[128] reported clinical and radiographic 10-year survival rates of 96.2% and 84.5% for acetabular components

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Table 4 Studies of Composite Materials for Repair of Bone Defects Based on DBM

Study	Year	Add Ingredients	Formulations	In vivo Trial	In vitro Trial	Advantage	Conclusion
Kirk et al[83]	2013	Bioactive glass	NanoFUSE® DBM	Mouse thigh muscle model	MTT assay, ALP activity, Cytotoxicity assay, Alizarin red staining	Significantly promotes the adhesion and proliferation of osteoblasts	NanoFUSE® DBM could be an effective bone graft substitute
Chen et al[84]	2014	Fibrin gel	DBM/fibrin gels	Rabbit radial bone defect model	ALP activity, HE staining, OPN immunofluorescence, Serum proteomics analysis	Significantly promotes the regeneration of new bone	DBM/fibrin gel scaffolds have feasibility and efficacy in repairing large bone defects
Wang et al[85]	2015	BMSCs	BMSCs/DBM	Rabbit radial bone defect model	TRAP staining, Alizarin red staining, FDA/PI staining, SEM observation, von Kossa staining	Significantly promotes the regeneration of new bone	BMSCs/DBMs have good capabilities in the treatment of critical bone defects in osteoporotic animals
Horváthy et al[86]	2016	Serum albumin	Serum albumin/DBM	Rat skull defect model	MTT assay, Cell adhesion rate assay	Significantly promotes cell adhesion and repairs animal bone defects	Serum albumin/DBM provides a convenient environment for stem cell, reducing the healing time of defects
Man et al[87]	2016	CS	CS/DBM	Rabbit cartilage defect model	Live/Dead assay, qRT-PCR analysis, Biochemical analyses	Significantly improves cell distribution and adhesion	CS/DBM is found to be an ideal biomaterial for cartilage tissue engineering
Supronowicz et al[88]	2016	MAPCs	MAPCs/DBM	Rat ectopic pouch model	ALP activity, Cell attachment assay, Cell proliferation assay, Western-blot staining,	Significantly enhances cell adhesion, proliferation, and the ability of osteoinduction	MAPCs/DBMs can provide a viable alternative for bone repair, healing, and regeneration
Xie et al[89]	2017	EV	EV/DBM	Subcutaneous bone formation model in nude mice	Scratch wound healing assays, CCK-8 assay, SEM observation	Significantly promotes vascularization in grafts and enhances bone regeneration	EV/DBM offers a promising approach to promote vascularization, which is essential for BTE
Wu et a[90]	2018	Fetal-BMSCs	Fetal-BMSCs /DBM	Goat skull defect model	CCK-8 assay, FDA/PI staining, SEM observation, Alizarin red staining, Cell proliferation assay	Significant repairs of goat skull defect models, especially in young individuals	Fetal-BMSCs/DBM promotes the repair of bone defects, especially in young goats
Chang et al[91]	2021	MSCs	fTEB	Non	CCK-8 assay, Cell migration assay, qRT-PCR analysis, Western-blot staining, Cell proliferation assay, Alizarin red staining	Significantly promotes cell proliferation, differentiation, and osteogenesis, accelerate the production of ECM	fTEB were shown to be a promising alternative to TEB
Leng et al[92]	2021	RNA	RNA/DBM	Rat critical-sized cranium defect model	ALP activity, Cell viability assay, Alizarin red staining, qRT-PCR analysis	Significantly enhances ECM secretion and the formation of new collagen	mRNA/DBM may provide a powerful tool for bone defect repair in BTE

Chen et al[93]	2022	Fg	Fg /SDBM	Rabbit cartilage defect model	ALP Staining, Cell Viability Assay, Alcian Blue Staining, HE/Masson Staining,	Significantly promotes the cartilage differentiation and the formation of high-hardness layer blood vessels	Fg/SDBM is a feasible strategy for the regeneration of osteochondral with knee defects
Chen et al[94]	2022	OECs	OECs/DBM	Mice dorsal skinfold window-chamber model	Non	Significantly increases the number of microvessels around the implantation area	OECs/DBMs can better fuse with receptor vessels to obtain blood perfusion in the receptor region
Hao et al[95]	2022	BRUS	BRUS/DBM	Rabbit femoral defect model	Cell viability Assay, Cell spreading Assay, Cell proliferation Assay, VEGF release study	Significantly promotes MSCs adhesion, proliferation and osteogenic differentiation	BRUS/DBM provides a new strategy for bone regeneration and large-area bone defect repair
He et al[96]	2022	ECM	sDCB-ECM	Non	CCK-8 assay, Live/dead staining, Fluorescent staining, Transwell migration assay, PCR analysis, Western-blot staining	Significantly promotes cell proliferation, allowing MSCs to differentiate into osteogenesis and cartilage	sDCB-ECM might be a potential bioscaffold to enhance the tendon-bone interface regeneration
Ye et al[97]	2023	BMP-2	BMP-2/DBM	Rat calvarial defect model	CCK-8 assay, Live/dead staining, ALP activity, Alizarin Red Staining, qRT-PCR analysis	Significantly promotes cell proliferation and osteogenic differentiation	BMP-2/DBM can be used as an effective bone repair material for clinical bone defect repair
Yu et al[98]	2023	GT	HDBM-GT	Nude mice/goat model	Cell adhesion rate assay, Live/dead staining, Cell proliferation, SEM observation	HDBM-0.6% GT is more suitable for seeding chondrocytes	HDBM-0.6%GT is a promising strategy for regenerated mature cartilage tissues
Liu et al[99]	2023	ECG	ECG-DBM	Nude mice subcutaneous model	SEM observation, Histological analyses, Immunohistochemical analyses, Quantitative biochemical analysis	Significantly increases DNA, total collagen and GAG content in cartilage tissue	ECG-DBM provides the possibility and guidance for the application of DBM in cartilage tissue engineering
Wang et al[100]	2024	BMSCs	BMSC/DBM	Diabetic rat femoral defect / subcutaneous pouches model	HE staining, Van Gieson staining	Significantly promotes mineralised tissue production	BMSC/DBM is a promising strategy to induce and improve bone regeneration in diabetic patients
Chen t al[101]	2024	SNS	SNS@DBM	Rat cranium defect model, Nude mice tumor-bearing model	SEM observation, HE/Masson Staining, ALP and alizarin red staining, Western-blot staining	Upregulatesosteogenic genes, promotes macrophages M2 polarization, and intensify angiogenesis of H-type vessels	SNS@DBM is a promising strategy for the treatment of neoplastic bone defects

Abbreviations: ALP, alkaline phosphatase; BMP-2, bone morphogenetic protein-2; BMSCs, bone marrow mesenchymal stem cells; BTE, bone tissue engineering; BRUs, bone regeneration units; CCK-8, cell counting kit-8; CS, chitosan hydrogel; DBM, decalcified bone matrix; ECG, engineered cartilage gel; ECM, extracellular matrix; EV, extracellular vesicles; FDA/PI staining, fluorescein diacetate/propidium iodide staining; Fg, fibrinogen; fTEB, functional tissue-engineered bones; GAG, glycosaminoglycan; GT, gelatin; H&E staining, hematoxylin and eosin staining; HDBM, human decalcified bone matrix; MAPCs, multipotent adult progenitor cells; MSCs, mesenchymal stem cells; MTT, methylthiazolyldiphenyl-tetrazolium bromide; OECs, outgrowth endothelial progenitor cells; OPN, osteopontin; PCR, polymerase chain reaction; qRT-PCR, quantitative real-time polymerase chain reaction; RNA, ribonucleic acid; sDCB, segmentally demineralized cortical bone; SEM, scanning electron microscope; SNS, silicene nanosheet; TRAP staining, tartrate-resistant acid phosphatase; VEGF, vascular endothelial growth factor.

using irradiated FDB allografts. Unlike FDB, DFDB is processed with varying concentrations of hydrochloric acid for different durations. Although Heiple et al[129] compared the osteogenic properties of various types of bone grafts in dogs, they found that histologically, FDB ranked second only to autologous implants and was superior to frozen, decalcified, frozen irradiated, and fresh deproteinized allografts. The demineralization process of DFDB enhances the proximity and release of various growth factors, including BMP-2, 4 and 7, which facilitate rapid revascularization and hard tissue growth at bone defects.[130,131] Consequently, this promotes regeneration, making DFDB more osteoinducible than FDB. However, due to the demineralization process, DFDB is not visible on X-rays, and the ultimate strength of the bone is significantly reduced (by 93%),[126] which complicates its application in high-stress limb bone defects.[132] FDB can be utilized in specific cases of early bone formation, including immediate implantation and maxillary sinus lift surgery, to achieve functional rehabilitation.[131] Consequently, there are notable differences between FDB and DFDB (Table 5). Histological analysis by Wood et al[133] demonstrated that, following the implantation of DFDB in humans, after 19 weeks, there was significantly greater bone formation and reduced graft material compared to FDB. In vitro studies examining the osteoinductiveness of both FDB and DFDB revealed that both possessed osteoinducibility and could promote the osteogenic differentiation of osteoblast-like cells (Saos-2 and MG-63), with the DFDB group exhibiting a superior capacity for osteogenic differentiation, characterized by a calcium/phosphorus ratio approaching that of native bone (1.67).[134] However, certain studies comparing treatments for chronic periodontitis noted that, through the evaluation of clinical and imaging parameters preoperatively, as well as at three and six months postoperatively, DFDB could not demonstrate any improvement in the clinical and imaging parameters of intraosseous defects relative to FDB.[135] A study investigating surgical and clinical complications following maxillary sinus floor lift and dental implant survival, comparing DFDB to bovine-derived xenografts, concluded that extensive rehabilitation of the atrophic maxilla using DFDB was a reliable treatment option, with a success rate comparable to that of xenografts for maxillary sinus augmentation.[136] The rate of bone formation in DFDB varies significantly based on factors such as the age of the donor, medical condition, preparation protocol and sterilization procedure.[137,138] It is also important to recognize that the amount of growth factor released by DFDB is just one of several factors influencing the success of the graft, alongside the accuracy of the procedure, cleanliness and the condition of the recipient.[139]

Others

Bioactive Glasses

Bioactive glasses (BGs) are a category of synthetic, silicate-based ceramics originally composed of various inorganic compounds. These compounds were subsequently modified to form more stable materials through the incorporation of potassium oxide (K_2O), magnesium oxide (MgO), and boron oxide (B_2O_3), with silicate constituting 45–52% of the total weight (Figure 3).[140] BGs are preferred for bone regeneration due to their effective bone conduction and osteoinduction

Table 5 Differences Between DFDB and FDB

	FDB	DFDB
Structural differences	Mineralized	Demineralized
Osteoconductive	Regular	Regular
Osteoinductivity	Weak or none	Relatively obvious
X-ray fluoroscopy	Visible on x-rays	Relatively invisible on X-ray
Resorption rate	Rapid	Regular
Mechanical strength	Young's modulus decreased by 15% compared to fresh frozen bone	Young's modulus decreased by 90% compared to fresh frozen bone
Clinical application	Maxillofacial reconstruction, periodontal bone defects, fracture healing, bone tumors, spinal fusion	Immediate implants, maxillary sinus lift surgery, periodontal regeneration

Abbreviations: DFDB, demineralized freeze-dried bone; FDB, freeze-dried bone.

properties.[141,142] They rapidly form a HA layer via ion dissolution, facilitating the binding of proteins, collagen, fibrin and growth factors. This layer is crucial for promoting the migration and adhesion of bone-forming cells, thereby aiding the bone remodeling process.[143] Over time, during long-term implantation, this HA layer is partially replaced by bone through the creep replacement process.[144] Additionally, the release of ions from BGs interacts with surrounding cells, enhancing their affinity for bone,[145] and contributing to the expression of bone markers such as ALP, collagen type 1, and osteocalcin. These makers increase osteoinductive properties and promote bone healing.[146] The biological activity and absorptive capacity of BGs vary according to their chemical composition, and in vivo studies indicate that they promote new bone growth on their surfaces, demonstrating a balance between intramedullary bone formation and material resorption, thus exhibiting effective bone conduction.[147] BGs exhibit remarkable biocompatibility, demonstrating minimal inflammatory response, foreign body reaction, or fibrous encapsulation[148] when implanted in human or animal models. Moreover, BGs have been shown to upregulate essential genes for new bone formation, such as insulin-like growth factor (IGF-II) and VEGF, which facilitate osteoblast proliferation.[149] However, similar to other ceramics, BGs possess brittle ness, slow absorption rates, a theoretical risk of fracture, and limited clinical data regarding their application in trauma orthopedics.[150] Additionally, local pH changes may induce cytotoxicity in vitro, although no significant clinical reports have documented this concern.[151] When combined with growth factors (GF), BGs can be utilized for the reconstruction of facial defects and can also serve as carriers for drugs and biologics.[152,153] To address various clinical needs, BGs have been developed with antibacterial properties against microorganisms.[154] Additionally, they promote osteogenesis and angiogenesis by incorporating various of functional elements such as strontium and zinc.[155] In a prospective comparative study of periodontal defects treated with autografts and BGs, Sumer et al [156] concluded that both grafts led to significant improvements in clinical and radiographic parameters at six months post-surgery, although these outcomes could be influenced by the morphology or location of the bone defects. Katuri et al [157] compared BGs with DFDB as treatments for periodontal defects and found significant differences after twelve months. Specifically, sites treated with DFDB exhibited greater reductions in periodontal probing depth (PPD), increased clinical attachment levels and a higher percentage of bone filling compared to those treated with BGs. Given their osteoconductive and osteoinductive properties, as well as promising in vitro and in vivo results, BGs continue to be a focal point of research as composite materials for bone substitutes.[158]

Bone Marrow Aspirate Concentrate

Bone marrow aspirate concentrate (BMAC) is a cellular graft characterized by its osteogenic and osteoinductive properties. It is composed of pluripotent stem cells, including mesenchymal stem cells, hematopoietic stem cells, and endothelial progenitor cells, as well as heterogeneous aggregates of various monocyte types, such as macrophages, lymphocytes, mast cells, and other cells. Additionally, BMAC contains cytokines and GFs,[159–161] with $CD11b^+$ macrophages constituting approximately 70% of the total number of cell population, T cells accounting for 15%, and it also includes 2–5 colony-forming units (CFUs)/10^6 cells.[162] BMAC is primarily harvested from the posterior region of the iliac bone, with a maximum volume of up to 150 mL obtainable.[163] Muschler et al[164] noted that 85% of the pluripotent stem cells are found in the initial 4 mL of BMAC; however, significant variability exists in the stem cell counts among different patients. This diverse cell mixture from BMAC contributes to the establishment of a stable microenvironment conducive to osteogenesis, with each cell type potentially playing a distinct role in tissue regeneration. Some studies indicated that a mixed population of bone marrow-derived cells could demonstrate superior potential for bone regeneration compared to populations enriched with specific cell types.[165] BMAC serves as a rich source of GFs, including TGF-β, platelet-derived growth factor (PDGF), BMP-2, BMP-7, and fibroblast growth factor-2 (FGF-2), which are believed to exhibit anti-inflammatory, angiogenic, trophic, and immunomodulatory properties,[166,167] potentially facilitating tissue repair through paracrine and autocrine mechanisms.[168] Clusters of monocytes derived from fresh bone marrow are equipped with angiogenic factors supplied by $CD34^+$ endothelial precursor cells and $CD34^-$ cells, which may assist not only in revascularization but also in the differentiation of osteoblasts and endothelial progenitor cells into bone and endothelial cells, ultimately promoting angiogenesis and supporting bone regeneration.[169] Du et al[170] compared the efficacy of concentrated fresh bone marrow mononuclear cells and cultured bone marrow mesenchymal stem cells (BMSCs) in Beagle dogs. They found that the fresh group promoted bone regeneration more effectively than the cultured

group. Specifically, the grafts in the fresh group exhibited superior mineralization and demonstrated collagen arrangement and biomechanical properties akin to those of the natural tibia. This suggests that concentrated fresh bone marrow mononuclear cells may be more effective than in vitro-expanded stem cells in repairing segmental bone defects. In a comparative study of BMAC versus platelet-rich fibrin (PRF), Koyanagi et al[171] reported that BMAC clots were uniformly distributed and contained a higher density of hematoxylin-stained cells, including leukocytes, adipocytes, and bone marrow-derived stem cells, indicating greater bone regeneration potential. BMAC was found to release higher GF than PRF (whether arterial or venous-derived) and exhibited enhanced capabilities for cell migration, angiogenesis, collagen synthesis, and osteoblast differentiation compared to the control PRF group. This positions BMAC as a promising option for promoting wound healing and bone regeneration. Lim et al[172] utilized BMAC alongside an autologous bone graft to address a 14 mm segmental defect in a rabbit ulna model. They concluded that both treatment strategies yielded comparable results, suggesting that BMAC could serve as an alternative to autologous bone therapy for long bone healing. The potential advantages of BMAC include its straightforward harvesting technique, the absence of risk for allogeneic disease transmission,[173] and its applicability in treating cartilage lesions, bone defects, tendon injuries, and maxillofacial diseases.[174–177] However, its poor mechanical properties limit its suitability for load-bearing applications. The combination of BMAC with osteoconductive biomaterials to create composite grafts possessing osteoinductive, osteoconductive, and osteogenic properties can stimulate bone formation, thereby introducing new biological functionalities.[178] Consequently, the efficacy of BMAC is significantly enhanced when utilized in conjunction with autologous bone graft, PRF and other scaffolding materials.[176] Kanakaraj et al[179] demonstrated adequate bone formation was found in the mandible using a combination of BMAC and autogenous cortical cancellous bone for treating odontogenic keratocysts. Furthermore, Saad et al[180] developed a rabbit model featuring a 10×15 mm bone defect in the mandibular region, filled the defect site with bone marrow-derived undifferentiated mesenchymal stem cells (BM-MSCs)/β-TCP, as well as BM-MSCs without scaffolds. Their findings indicated that the combination of BM-MSCs with the β-TCP scaffold exhibited superior and accelerated bone regeneration potential. Overall, the integration of BMAC with graft materials can possess bone conduction properties and maximize its benefits demonstrating significant promise for bone regeneration.

Polymer Nanocomposites

Inadequate integration with host tissues, inflammatory responses, and infections may limit the performance of bone implants. The surface characteristics of these bone biomaterials significantly influence the biological activity of immune cells and osteoblasts.[181] With the rapid development of BTE and modern nanotechnology, nanocomposites have gradually gained prominence. These materials combine polymer and biodegradable biomatrix structures with biologically active and easily absorbable nanofillers (Figure 3).[182] The objective is to endow biomaterials with critical physical and chemical properties, such as increased surface area, enhanced mechanical strength and stability, and improved cell adhesion, proliferation, and differentiation (Table 6).[183–194] Furthermore, various characterization tests (eg, electron microscopy, spectroscopy and mechanical stress testing) evaluate osteoblast adhesion, viability, and mineralization, thereby creating nanostructured surfaces that can influence osteogenesis and immune cell activity while adjusting physicochemical properties.[195,196] Polymers are favored for their capacity to rapidly absorb and stimulate autologous bone repair in vivo; Thus, composites combined with nanofillers may facilitate bone tissue repair.[197,198] The application of bone tissue regeneration necessitates specific modifications to the polymer structure to fabricate composites that are flexible, rigid, and bioactive.[199,200] Common polymers utilized in BTE include polycaprolactone (PCL), polylactic acid (PLA), and poly (lactic-co-glycolic) acid (PLGA). PCL is an aliphatic and semi-crystalline polymer known for its excellent toughness, adjustable mechanical properties, high crystallinity, non-toxicity, and adequate biocompatibility.[201] However, it is limited by its slow degradation rate.[202] Karimipour-Fard et al[203] prepared PCL/Nano-HA (nHA) /Chitin-Nano-Whisker (CNW) nanocomposites using PCL/nHA and PCL/CNW as raw materials. They found that the inclusion of nHA and CNW nanofillers enhanced the biodegradation rate of PCL, and resulting nanocomposites significantly improved the biological and mechanical properties of 3D printed bone tissue scaffold. PLA, derived from the polyesterification of lactic acid, exhibits essential properties for bone regeneration, including non-toxicity, biocompatibility, thermal stability, and biodegradability. However, it lacks the mechanical strength required for effective bone tissue regeneration systems,[204] which can be addressed through the incorporation of various nanofillers create nanocomposite

Table 6 Summary of Representative Studies, Advantages and Limitations of Different Types of Nanocomposites for Bone Regeneration

Types of Nanocomposites	Study	Year	Formulations	In vivo Trial	Cells Used	Advantage	Conclusion	Nanocomposites Type Characteristics	Nanocomposites Type Limitations
Scaffolds	Tavakoli et al[182]	2024	FD-Sim	Rat calvarial defect model	MG-63	Significantly promote cellular accretion, adhesion and spreading for new bone formation	FD-Sim scaffold can be a perfect candidate for calvarial defect repair.	Unique carriers for cell and drug transport, which act as biological mediators to promote cell proliferation and differentiation	Complex design, special manufacturing processes, lack of functional groups necessary for protein binding or cell adhesion
	Salehi et al[183]	2024	PLA/PEG	Rat calvarial defect model	MG-63	Enhance cell viability and adhesion, and confirm osteogenic differentiation of rat-BMSCs	PLA/PEG/B30 composite scaffold is proposed as an optimal scaffold to repair bone defects.		
	Kanniyappan et al[184]	2024	IPN	Rat tibial defect model	NIH/3T3 MG-63	Good cytocompatibility, significantly upregulate osteogenic genes, and promote angiogenesis	IPN scaffolds with excellent physicochemical and biological properties are ideal for the treatment of bone defects.		
	Chen et al[185]	2024	BP@(Zn+Ag)/ EPLA	Rat calvarial defect model	MC3T3-E1	Excellent antibacterial activity, enhance cell viability and osteogenic activity	BP@(Zn+Ag)/EPLA nanofiber scaffolds have great potential for BTE applications.		

(*Continued*)

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Table 6 (Continued).

Types of Nanocomposites	Study	Year	Formulations	In vivo Trial	Cells Used	Advantage	Conclusion	Nanocomposites Type Characteristics	Nanocomposites Type Limitations
Ceramics	Trzaskowska et al[186]	2023	nanoHA/ chitosan/ agarose granules/ curdlan granules	None	MC3T3-E1	Good biocompatibility and high porosity	Mesoporous polymer-ceramic nanocomposites are promising implantable biomaterials that can be used to fill small bone defects in maxillofacial surgery.	Higher mechanical strength, biocompatibility and bone conductivity	Complexity of the process, possibility of contamination in the grinding of the required powder, need to explore the optimal solvent ratio
	Vidane et al[187]	2023	Al_2O_3/ZrO_2	None	RADMSC	Good biocompatibility, enhance cell proliferation and cell adhesion	Al_2O_3/ZrO_2 has demonstrated significant implications in BTE and is valuable biomaterials for bone replacement.		
	Tavakoli et al[188]	2024	PCL/G/35% MMT/15%BG	None	MG-63	Significantly increase cell proliferation, adhesion, and cell viability	PCL/G/35%MMT/15% BG composite nanomaterials has promising strategies for bone repair applications.		
	Avinashi et al[189]	2025	THC8/12	None	MG-63	Excellent compressive strength, high Young's modulus and fracture toughness	THC8/12 are suitable for bone regeneration at the concentration of 20 µg/mL and will also protect against bacterial infections.		

Hydrogels	Fu et al[190]	2023	Alg/Go/Ser/nHAP	Rat calvarial defect model	Rat-BMSCs /peritoneal macrophages	Good mechanical strength, stability, porosity and biocompatibility, and provide an active bone immunity for the environment	Alg/GO/Ser/nHAP provides a new concept for the design of immunomodulatory properties and osteogenesis capabilities in BTE implants.	Excellent biocompatibility and drug carrying capacity, regulated physical and chemical properties, controllable release ability, good formability and processability	Complexity of preparation, potential long-term stability, limited mechanical strength, and influenced by the acting environment
	Zhou et al[191]	2024	KBTO/OCS/Gel	Rat calvarial defects model	Rat-BMSCs	Enhance adhesion strength of the graft surface, upregulate osteogenesis-related genes, promote differentiation of BMSCs into osteoblasts	KBTO/OCS/Gel is a wireless ultrasound-driven bone-adhesive nanocomposite hydrogel that broadens the treatment range for irregular bone defects.		
	Zha et al[192]	2024	4-OI@Cu@Ge	Mouse femoral fracture model	Rat-BMSCs, RAW264.7, HuEVCs	Effectively alleviate oxidative stress, regulate the metabolic microenvironment, and improve cellular functions involved in fracture healing	4-OI@Cu@Ge as a metabolic modulator is a novel strategy for the treatment of fractures and bone defects.		
	Guo et al[193]	2025	PBM hydrogels	Rat/minipig mandible defect model	MMSCs, BMSCs, EA. hy926	Significantly enhances bone maturation, vascularization, neuronal differentiation, and skeletal muscle tissue regeneration	PBM hydrogels are an injectable and innovative bone substitute that promotes the healing of mandibular defects by tackling multiple detrimental pathologies.		

Abbreviations: Alg/Go/Ser/nHAP, alginate/graphene oxide/sericin/nanohydroxyapatite; Al2O3/ZrO2, alumina-zirconia; BMSCs, bone marrow mesenchymal stem cells; BP@(Zn+Ag)/EPLA, nanosilver/zinc-coated black phosphorus/aminated poly-L-lactic acid; BTE, bone tissue engineering; FD-Sim, freeze-dried simvastatin; HuEVCs, human umbilical vein endothelial cells; IPN, interpenetrating polymer network; Kbto/Ocs/Gel, amino-functionalized barium titanate/oxidized chondroitin sulfate/gelatin; MMSCs, mandible-derived mesenchymal stem cells; 4-OI@Cu@Ge, 4-octylitaconate@Cu@gelatin; PBM hydrogels, PEG-BSA/a-RGD@MgO NPs hydrogels; PCL/G/35%MMT/15%BG, polycaprolactone/gelatin/35%montmorillonite/15%bioglass; PLA/PEG, polylactic acid/polyethylene glycol; RADMSC, rabbit adipose-derived mesenchymal stem cells; THC8, 82tcp-10h3b03-8cu.

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fibers.[205,206] Canales et al[207] developed a PLA-based composite nanomaterial utilizing bioglass (n-BG) and zinc oxide (n-ZnO) as fillers, demonstrating that this material possesses bioactive and bactericidal properties suitable for BTE applications. PLGA is a linear copolymer composed of PLA and Poly (Glycolic Acid) (PGA), characterized by its biocompatibility,[208] biodegradability, controllable degradation rate, and ease of processing. However, PLGA is constrained by its inadequate mechanical properties, limited osteoinduction, and poor cell adhesion. Li et al[209] prepared MgO_2/PLGA nanocomposite scaffolds with good mechanical properties and activity by low-temperature 3D printing, and the results showed that this material was proved to promote bone repair by enhancing the differentiation of BMSCs to osteoblasts and the formation of a pro-osteoporotic immune microenvironment through macrophage M2. The unique effects arising from the interaction between polymers and organic or inorganic nanomaterials suggest that the functionalization of polymer nanocomposites presents a significant advantage,[210] with substantial potential in applications such as bone tissue engineering, drug delivery, biosensors wound healing, and magnetic hyperthermia. This advancement could significantly transform the landscape of nanomedicine, particularly for individuals suffering from bone diseases today.[211,212]

Challenges and Prospects

The scale of xenograft bone research has steadily increased over the decade from 2013 to 2023.[213] While the desirable properties of bone graft have been extensively documented for decades, no biomaterials currently available on the market encompass all of these properties. Presently, there appears to be a trend towards simulating the natural bone structure as closely as possible, often incorporating one or two active ingredients that promote bone repair and regeneration. This approach has led to the development of new materials for bone defect repair. Although it is encouraging to see the emergence of numerous reparative materials in tissue engineering, it is crucial to remember the ultimate goal of these new bone repair materials, namely the application in clinical practice to effectively address patients' bone defects. The apparent disconnect between research teams and clinical practitioners seems to contribute to this issue. Strengthening communication and collaboration among researchers from various disciplines is a fundamental and essential step towards improving the ideal bone graft. From the perspective of tissue engineering researchers, the ideal bone graft should not only focus on the aforementioned characteristics but also emphasize extending the retention period, enhancing vascularization, and eliminating size limitations, while paying closer attention to the intricate details of the graft material itself. Conversely, clinicians prioritize the effectiveness of bone defect repair and economic viability, ensuring safety as a prerequisite. Only by integrating the perspectives of both researchers and clinicians can we advance more effectively and consistently towards the development of ideal bone graft. As advancements in characterization methods continue to reveal new insights into the structural arrangement and crystalline phases of bone, an additional challenge arises from the potential overemphasis on the surface microstructure of active tissues like bone. Currently, regardless of the source of bone tissue repair materials, most approaches have exhausted various methods to enhance synthesis, primarily aiming to better replicate the microstructure of natural bone. This includes aspects such as mechanical properties, interconnected voids, surface structure, and pore morphology. However, these efforts often overlook the critical role of the bone microenvironment as a metabolic tissue essential for survival, as well as the integration with surrounding tissues and vascular nerves. Fortunately, an increasing number of researchers are now focusing on promoting bone repair and regeneration within the extracellular matrix, highlighting the significance of the bone microenvironment. The application of 3D printing rapid prototyping technology to create complex scaffold materials that mimic the properties of natural bone, along with utilizing these scaffolds as carriers for load various cytokines and active substances with osteogenic potential, may offer promising solutions to overcome the limitations in treating bone-related diseases in the future. Another challenge lies in the fact that current in vivo experiments on bone graft are predominantly conducted in small animal models, with a notable lack of high-quality animal studies and randomized controlled trials to validate the feasibility of the target materials. While xenografts still face certain limitations, including immune rejection, biocompatibility issues, risk of infectious diseases, poor functional recovery, and uncertainty regarding long-term effects, they nonetheless present a viable treatment option for patients and an avenue for clinical practice. Thanks to the rapid advancements in tissue engineering technology, the future xenotransplantation may increasingly emphasize immunomodulatory techniques, biomaterials engineering, stem cell and gene therapy, personalized therapy, bioprinting technology and regenerative medicine, thereby enhancing the development of xenotransplantation in a safer, more effective, and personalized manner.

Conclusion

A brief procedure for the preparation of bone grafts is summarized (Figure 3). The selection of bone graft is crucial for effective bone repair and regeneration, as each option presents distinct advantages and disadvantages (Table 7).[43,52,66,70,105,107,110–112,126,131,145,150,152,159,178,182,214–217] In summary, the decision regarding bone graft is influenced by specific clinical requirements, including the specific characteristics of the bone defect, the patient's overall

Table 7 Advantages, Disadvantages and Potential Clinical Applications of the Materials Described in the Review

Bone Graft Type	Advantages	Disadvantages	Potential Clinical Value
TBC	Good biocompatibility and osteoconductivity, providing a scaffold for inward bone growth Excellent mechanical properties and stability.[43]	Limited ability to promote osteoinduction compared to living tissue. Potential brittleness and difficulty in achieving desired shapes during surgery.[52]	Suitable for reconstructive surgery where load bearing is required.[214]
DBM	Osteoinductive properties with some degree of stimulation of new bone formation Easy to handle and mold to various shapes.[66,70]	Probably variability in composition and properties due to processing Potential risk of immune response.[66]	Suitable for spinal fusion and joint reconstruction, especially when osteoinduction is essential for healing.[217]
FDB	Maintains natural bone structure while being easy to store and transport Good biocompatibility and osteoconductive provide scaffolds and some biological activities for bone growth[105]	Limited osteoinductive capability and potential donor site complications when harvested Potential risk of immune response.[107]	Suitable for dental, plastic and orthopaedic procedures to increase bone mass, fill cavities and repair fractures[110–112]
DFDB	Enhances osteoinductive properties compared to FDB due to demineralization Retains important protein and growth factors that assist in bone healing.[126]	Potential variability in osteoinductive potential based on processing methods Lower mechanical strength compared to FDB.[126]	Suitable for specific cases of early bone formation that require strong osteoinduction.[131]
BGs	Highly bioactive, promotes binding to surrounding bone and induces favorable biological response that enhances osteogenesis.[145]	Limited mechanical strength compared to conventional ceramics Degradation can occur in vivo, necessitating long-term studies.[150]	Suitable for non-load bearing applications and can be used as a coating for implants to enhance osteogenesis.[152]
BMAC	Rich in mesenchymal stem cells and growth factors, providing a significant biological advantage for bone healing; minimally invasive collection process.[159]	Variability in cellular content and growth factors can be patient-dependent Limited supply and no mechanical strength.[178]	Suitable for orthopaedic diseases with poor healing ability such as articular cartilage and intervertebral disc.[215,216]
Polymer nanocomposites	Versatile and can be engineered for specific mechanical and biological properties.[182]	Potential risk regarding biocompatibility and the long-term behavior of the degradation products May require complex manufacturing processes.[182]	With customizable properties, promising for innovative applications in bone repair and regeneration.[182]

Abbreviations: BGs, bioactive glasses; BMAC, bone marrow aspirate concentrate; DBM, decalcified bone matrix; DFDB, demineralized freeze-dried bone; FDB, freeze-dried bone; TBC, true bone ceramics.

health, and the expected treatment outcome. A thorough evaluation of the advantages and disadvantages of each material is essential to optimize patient outcomes. A comprehensive understanding of these factors can enhance the efficacy of surgical interventions related to bone repair and regeneration.

Data Sharing Statement

The data are available from the corresponding author Gang Xu on reasonable request.

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