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REVIEW

A Review on Bone Tumor Management: Cutting-Edge Strategies in Bone Grafting, Bone Graft Substitute, and Growth Factors for Defect Reconstruction

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Abstract: Bone tumors present complex challenges in orthopaedic oncology, requiring precise management strategies to restore skeletal integrity and function with minimal morbidity. Traditional autologous bone grafting has been the gold standard due to its osteogenic, osteoconductive, and osteoinductive properties. However, limitations such as donor site morbidity and graft availability have prompted the development of alternative approaches.This review evaluates contemporary approaches in bone tumor management, focusing on advancements in bone grafting techniques, bone graft substitutes (eg, ceramics, polymers, bioactive materials), and growth factor-based therapies. The efficacy and safety of these substitutes are compared with autografts, examining their potential benefits and drawbacks.Recent innovations in bone graft substitutes show promise in overcoming autograft limitations. Ceramic, polymer, and bioactive materials offer diverse properties that may enhance bone regeneration. Growth factor-based therapies, including bone morphogenetic proteins (BMPs) and vascular endothelial growth factor (VEGF), have revolutionized bone healing by stimulating osteogenesis and angiogenesis.

Plain Language Summary:

- The review compares efficacy and safety of bone graft substitutes with traditional autografts, highlighting their potential benefits and challenges, thus helping clinicians choose the most suitable option for bone tumor management.
- Autologous bone grafting remains the gold standard; its limitations—such as donor site morbidity and limited graft availability—have driven the development of alternative approaches like bone graft substitutes and growth factor-based therapies.
- Advances in materials such as ceramics, polymers, and bioactive substances offer promising solutions for bone defect reconstruction, providing enhanced properties for bone regeneration and overcoming the shortcomings of autografts.
- Growth factor therapies, including Bone Morphogenetic Proteins (BMPs) and Vascular Endothelial Growth Factor (VEGF), transform bone healing by stimulating osteogenesis and angiogenesis, improving the recovery and function of the affected bone.
- Integrating bone graft substitutes and growth factor therapies, there is significant potential to improve clinical outcomes in orthopaedic oncology, offering more effective bone defect reconstruction and enhanced quality of life for patients.

Keywords: Bone tumors, bone graft, tumor management, defect reconstruction, growth factor

Introduction

Human bone, a highly dynamic connective tissue, facilitates mobility, shields vital organs, and provides structural support. Despite its remarkable strength and regenerative abilities, critical-sized defects from trauma, tumors, or infections hinder autonomous bone regeneration.[1] Bone often becomes a target for cancer metastasis, contributing to rare primary tumor formation. Managing both primary and secondary bone tumors poses challenges due to issues like

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drug resistance and disease recurrence with conventional treatments.[1] Extensive research and development efforts aim to enhance bone cancer therapies. Primary and secondary bone tumors, notably sarcomas like osteosarcoma, chondrosarcoma, and Ewing sarcoma, comprise a significant portion, while secondary tumors arise from various advanced malignancies.[1–4] Extensive bone damage necessitates bone substitutes or grafts. Bone grafting relies on four bone-specific principles: osteointegration, in which bone tissue adheres to scaffolds or implant surfaces; Osteoconduction, which facilitates cell relocation and management on the surfaces of the scaffold; osteoinduction, which recruits and induces mesenchymal stem cells to discriminate into osteoblasts; Osteogenicity, which allows for development of newly generated osseous tissues from cells within the graft materials.[5] Bone grafting is a widely utilized surgical method within orthopaedic practices, with more than two million procedures performed worldwide each year, making it the second most common form of tissue transplantation following blood transfusion.[6,7] Autologous bone remains the gold standard due to its comprehensive properties necessary for bone regeneration.[8] However, apprehensions persist regarding restricted availability and complications associated with donor sites. Bone allografts are the second most preferred choice among orthopaedic surgeons, constituting approximately one-third of all bone grafts utilized worldwide.[9] Allografts are accessible and varied in different forms, demonstrating osteoconductive characteristics with reduced osteoinductive abilities, especially in demineralized bone matrix preparations.[10] Concerns over inferior healing and potential disease transmission persist.[11,12] With the growing demand for bone grafts amidst global aging and obesity trends, synthetic bone substitutes have emerged as promising alternatives.[13] Calcium phosphate-based biomaterials, such as hydroxyapatite, cement, and ceramics, are widely used, offer osteoconductive properties, and are utilized in reconstructing large bone defects.[14] The orthopaedic industry has shifted towards synthetic substitutes and biological factors, reflecting the evolving landscape of bone grafting procedures.[15] Tissue engineering is an alternative method for addressing bone defects and fractures by manipulating the natural bone-healing mechanism.[16] Lengthy bony defects pose a huge challenge to the repair process. Firstly, leaving the bone exposed for extended periods risks infection and necrosis without muscle or skin coverage.[17] Secondly, these defects disrupt bone physiology and can damage tendons and nerves, underscoring the importance of graft size and vascularization for regeneration and nerve function restoration. Therapeutic interventions during tissue regeneration treatments include localized delivery of functional factors to fractured sites, facilitated by advances in tissue engineering and biomaterials research.[17,18] In vivo models have identified vital growth factors (GFs) during the process of fracture healing, such as bone morphogenetic protein (BMP), transforming growth factor (TGF), insulin-like growth factor (IGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF).[19,20] While VEGF primarily modulates angiogenesis and BMPs induce osteogenesis, various GFs indirectly enhance both processes during fracture repair, commercially available rhPDGF, delivered using β-tricalcium phosphate as a carrier, has shown efficacy in treating foot, ankle, and distal radius fractures clinically.[21–25] Augmenting the natural bone-healing process through GF delivery at fracture sites is promising, yet concerns persist regarding off-label clinical applications due to dosage, adverse effects, and cost issues.[26,27] Along with the recent advancements, the function of growth factors and bone grafting materials in bone regeneration and healing (Figure 1) is thoroughly explored in this Review article.

Biological Structure of Bone

The bone is a vital structural component that supports and protects organs while facilitating mobility.[28] This multi-functionality stems from its intricate hierarchical architecture, comprising collagen protein and apatite mineral.[29] Despite macroscopic variations across bone types and species, the assembly of mineralized fibrils by collagen molecules and apatite crystals remains a fundamental building block (Figure 1).[30–32] The stiffness of bone tissue, crucial for its functionality, is determined by the mineral content in the collagen/mineral composite.[28] Dynamic maintenance of bone occurs through two processes: modeling and remodeling, which are essential for growth, adaptation, and recovery from fractures.[33] Bone remodeling, a lifelong process, ensures continuous renewal, with a significant portion of bone replaced annually.[34]

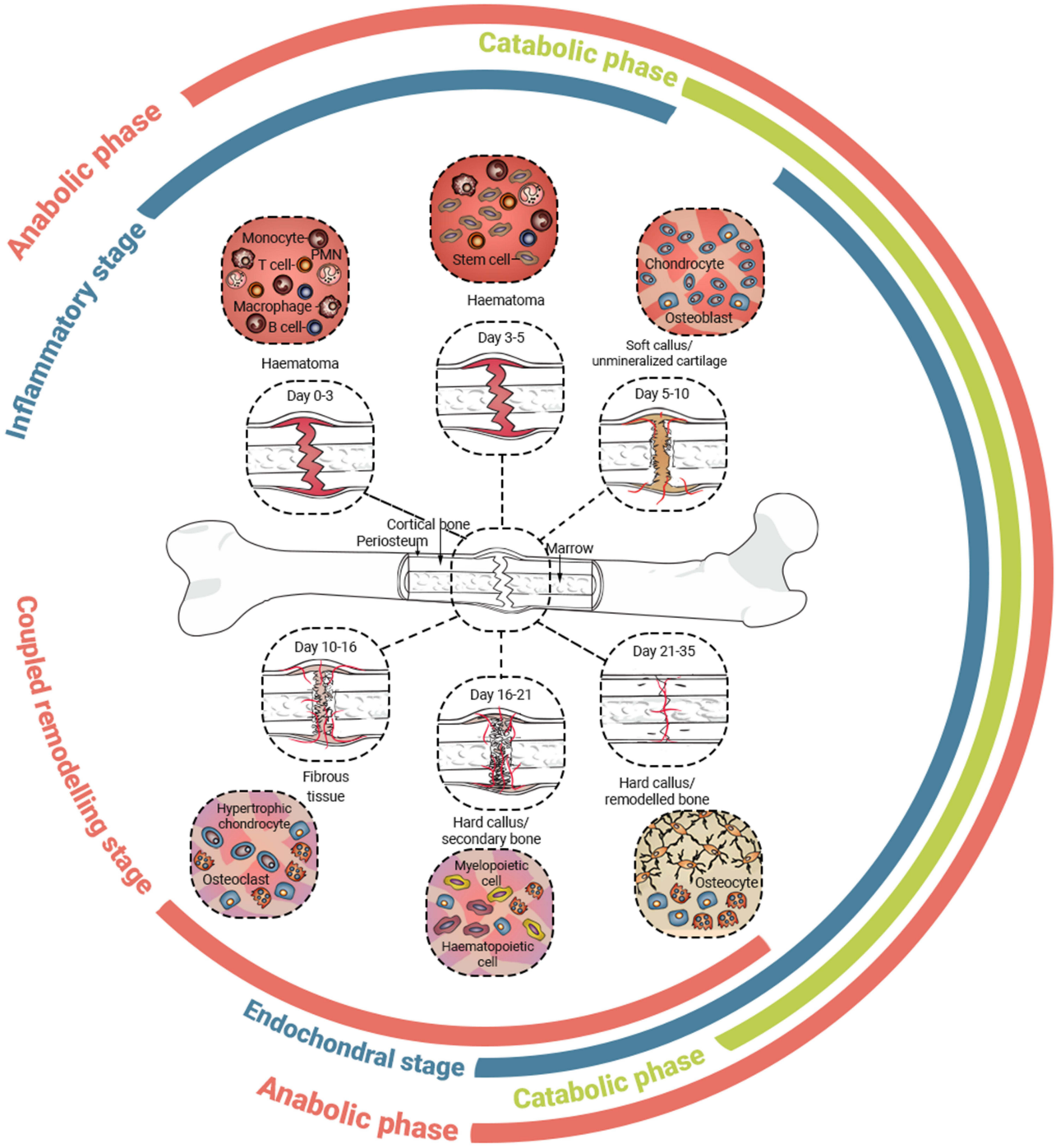

Figure 1 Schematic illustration demonstrating a distinctive bone fracture healing mechanism, key biological proceedings, and cellular paths at various stages.

Bone Tumor

Bone tumors can be categorized into primary (sarcomas) and secondary (metastases). Sarcomas originate from mesenchymal cells, emerging amidst diverse cell types like mesenchymal stem cells, fibroblasts, and immune cells. Osteosarcomas, chondrosarcomas, and Ewing sarcomas dominate primary bone tumors.[35] In contrast, secondary tumors result from advanced cancers, predominantly breast and prostate, posing grim prognoses due to skeletal invasion.[36] Although incurable, treatments aim to mitigate pain and retard progression. Metastatic cells, residing in a dormant state within the bone microenvironment, eventually stimulate osteoclasts, inciting a damaging "vicious cycle".[37,38] This

interplay underscores shared microenvironmental niches between sarcomas and metastases, highlighting complexities in bone tumor pathology and treatment strategies.[35]

Biology of Bone Regeneration

Fractures can be prevented by the dynamic equilibrium of bones unless they are subjected to extreme or cumulative damage from cyclic loading.[39,40] Bone healing reflects embryonic skeletal development and fully restoring damaged organs. Factors such as tissue loss delineate bone repair into primary and secondary healing processes. Primary healing is characterized by fracture gaps less than 0.1 mm and rigidly stabilized, involving direct ossification without cartilage or connective tissue.[41,42] Secondary healing, more commonly, involves multiple events like clotting, inflammation, and remodeling.[41,43] Anabolic processes initially increase bone volume, followed by catabolic activities. Large, critical-sized bone defects hinder revascularization and tissue differentiation, potentially leading to non-union.[44] Defining a critical-sized defect varies but typically refers to one not healing spontaneously during an animal's lifetime or showing <10% bony regeneration.[45,46] The size of the defects exceeding 2 to 2.5 times the bone diameter is often considered critical.[41,47,48] Non-union from such defects poses significant challenges, impacting patients' lives and healthcare costs.[49]

Bone Graft Substituents for Bone Defect Treatments

Bone replacements fulfil dual roles of mechanical stiffness and osteoregeneration, involving vital biological properties such as osteoconduction, osteoinduction, osteogenesis, etc.[50,51] Osteoconduction supports osteoblast attachment and cell migration within the graft's architecture.[51] Osteoinduction prompts undifferentiated cells to become bone-forming cells, inducing osteogenesis.[51,52] This process involves osteo-differentiation and the generation of new bone from the donor cells. Osteointegration, crucial for bone healing evaluation, refers to implant anchoring with bony tissue formation at the bone-implant interface.[53]

Natural Bone Grafts

Autologous Bone Grafts

Autologous bone grafting involves transferring bone from one site to another within the same individual.[54] With osteoconductive, osteoinductive, and osteogenic attributes, autologous grafts swiftly and comprehensively assimilate into host bone, establishing a benchmark for managing bone defects and evaluating alternative grafting methods.[54] However, drawbacks such as donor site complications, pain, increased blood loss, longer operative times, infection risks, and limited material are well-documented.[55,56] Reamer-irrigator-aspirator (RIA) scheme, pioneered by F.M. Kovar et al, provides an alternative to traditional methods, yielding lower complication rates (6% with respect to 19.37% with iliac crest bone) and increased bone size (15–20 mL to more than 40 mL).[57,58] RIA-grafted bone exhibits higher gene expression levels related to vascular, skeletal, and hematopoietic tissues and a greater abundance of stem cells and growth factors.[59] Nonetheless, complications like iatrogenic fracture, cortical damage, exsanguination, and heterotopic ossification have been noted by M.V. Belthur et al and C. Mauffrey et al.[60,61]

Cancellous autografts, the predominant form, retain abundant mesenchymal stem cells despite low osteoblast and osteocyte numbers, enhancing osteogenic potential.[62] Their extensive surface area facilitates superior revascularization and graft incorporation.[50] The preserved graft-derived proteins contribute to osteoinduction when properly handling autografts.[50] Early transplantation involves rapid hematoma and inflammation formation, followed by gradual necrotic tissue elimination, neovascularization, and osteoid seam production by osteoblasts.[50] Complete graft resorption and replacement occur within 6–12 months.[63]

Cortical autografts, though structurally sound, feature fewer osteoprogenitor cells.[53] Unlike cancellous grafts, their incorporation involves predominantly osteoclast-mediated creeping substitution due to dense architecture hindering revascularization and remodeling.[54]

Depending on the size and location of the graft, this phenomenon, which is characterized by the formation of bone layers surrounding a necrotic core, may last for several years.[54,64]

Allogeneic Bone Grafts

Allogeneic grafting of bone entails transplanting bone tissue from one genetically distinct individual to another of the identical species.[53,54] Because of limitations associated with autologous grafts, allografts are the prime alternative, predominantly for patients with diminished healing capacity, non-union, or extensive fracture comminution.[54] Allografts are available in diverse forms, including cortical and cancellous varieties, and highly processed variations, such as demineralized bone matrix, which offer flexibility for machining and customization.[53] However, compared to autografts, allografts pose higher immunogenicity and failure risks attributed to major histocompatibility complex (MHC) antigen activation.[65] This immune response can disrupt the initial osteoinduction phase, leading to necrosis of osteoprogenitor cells.[65] Strategies like reducing immunogenicity and improving tissue bank practices have been proposed to mitigate these risks.[54]

Cancellous allografts, often supplied as cuboid blocks, find application in spinal fusion augmentation and filling cavitary defects, albeit with slower incorporation than autografts.[53,54] Host inflammatory responses may delay osteointegration, forming fibrous tissue around the graft.[66]

Cortical allografts, prized for their mechanical strength, are utilized in scenarios requiring immediate load-bearing resistance, typically in spinal augmentation.[53] To minimize immune reactions, marrow and blood-free frozen or freeze-dried products are preferred.[54] As with autogenous grafts, cortical allograft integration begins with osteoclast resorption and progresses to intermittent bone formation through apposition.[53,54]

Demineralized bone matrix (DBM), an extremely processed allograft, retains growth factors crucial for osteoinduction post-demineralization.[67] Its structural integrity limitations make it suitable for defect filling, with incorporation mechanisms akin to autogenous grafts triggering an endochondral ossification cascade and subsequent bone generation.[68]

Synthetic Bone Graft

The shortage of natural bone grafting and the challenge of meeting the demands of the aged community have spurred the expansion of the bone grafts and substitutes (BGS) marketplace. Currently, the most commonly utilized synthetic alternates of bone comprise calcium sulfate, calcium phosphate (CaP) ceramic and cement, bioactive glass, or various combinations thereof.[69]

Calcium sulfate, an osteoconductive and decomposable ceramic comprised of CaSO4 that has been utilized for void defect filling since 1892.[70] Despite lacking macroporosity, and having weak internal strength, it resorbs rapidly and suits minor bone defects with rigid fixation. Niu et al described how the resorption rate often outpaces bone deposition, limiting optimal fusion in spinal arthrodesis.[71] Steinhausen et al reported loading antibiotics onto calcium sulfate treats chronic osteomyelitis.[72] Nan Jing et al showed that modifying the masquelet technique with calcium sulfate for massive bone defect treatment simplifies surgery and fosters membrane formation for successful reconstruction.[73]

Calcium phosphate (CaP) ceramics, consist of calcium hydroxyapatites, resembling the mineral phase in calcified tissues. It has gained attention since Albee's discovery of tricalcium phosphate (TCP) in 1920. β-Tricalcium phosphate (β-TCP, $Ca_3(PO_4)_2$) has a lower Ca/P ratio compared to hydroxyapatite (1.5), enhancing its absorption and degradation processes.[62,74] Biphasic calcium phosphate (BCP) blends hydroxyapatite and tricalcium phosphate in various ratios to integrate the benefits of both calcium salts.[75] A report confirms that the formulation adjustment enables control over dissolution rate and mechanical properties, suitable for bulk use or implant coatings.[76]

Calcium phosphate cements (CPCs), typically consists of two compounds, one being an aqueous therapeutic agent invented by Chow and Brown in 1980.[77,78] They aimed to enhance the versatility and moldability of CaP, making it a more ideal bone substitute. Approved by the US FDA in 1996, these substances can be readily administered via injection to address defects of diverse shapes, solidifying through an isothermic reaction upon blending with an aqueous phase.[69] Self-hardened CPCs exhibit high microporosity, cytocompatibility, and mechanical support, albeit with poor bending strength.[79]

Bioactive glass, initially developed in the 1970s, consists of silicon oxide (SiO_2), sodium oxide (Na_2O), calcium oxide (CaO), and phosphorus pentoxide (P_2O_5), later modified with potassium oxide (K_2O), magnesium oxide (MgO), and boric oxide (B_2O).[80] It forms a firm bond with host bone due to leaching silicon ions, promoting hydroxyapatite

formation, attracting osteo-progenitor cells, and supporting neo-vascular ingrowth. Resorption occurs gradually without significant inflammation. Bioglass 45S5 and S53P4 are prominent commercially available bone graft substitutes from NovaBone Products LLC and BonAlive Biomaterials.[81–83] Bioglass 13–93, an exception, resists crystallization but shows delayed hydroxyapatite formation in simulated body fluid.[84] Clinical trials demonstrate good host bone contact with bioglass 45S5 and S53P4, with the latter showing reduced resorption due to higher silica content.[85] A study by Wheeler et al demonstrated the contrast between bone regeneration and in vivo degradation of melt-derived bioglass 45S5 against sol-gel. Bone regeneration and in vivo dissipation of melt-derived bioglass 45S5 with sol-gel-derived bioglasses 77S and 58S on rabbits with critical-sized defects at the femoral condyle.[86] Sol-gel-derived bioglass having nanoporosity and increased surface area degraded faster than bioglass 45S5.

Poly (methyl methacrylate) (PMMA) bone cement, non-biodegradable and non-resorbable, resembling grout rather than cement, is extensively utilized in clinics, though not as a bone substitute material.[87–89] Its widespread use in total joint replacement and percutaneous vertebroplasty is attributed to its high mechanical rigidity and ease of handling. Antibiotic-containing PMMA serves as antimicrobial prophylaxis in primary arthroplasty.[88] However, PMMA cement's drawbacks include exothermic polymerization potentially damaging adjacent tissues, aseptic loosening resulting from monomer-induced bone injury, mechanical disparities, and its intrinsic inertness, which may contribute to arthroplasty failure over time.[90–92]

Growth Factors for Bone Regeneration

Inflammatory Factors

Platelet-secreted inflammatory mediators, recruited to clotting sites, utilize various pro-inflammatory signaling molecules was reported by Newman et al.[93] These mediators, including IL-1, IL-6, IL-12, FGF-2, TNF, prostaglandins (PGs), interferon-γ (IFN-γ), and MCSF, collectively endorse the invasion of osteoclasts, macrophages, plasma cells, and lymphocytes to injured areas.[94] Neutrophils, eosinophils, macrophages, and lymphocytes constitute the diverse cell types present in this inflammatory phase.[95] Neutrophils, as the initial responders, involve macrophages and monocytes through the secretion of monocyte chemotactic protein-1 (MCP-1) and IL-6. Macrophages and monocytes clear debris and damaged cells and recruit osteoprogenitor cells, mesenchymal stem cells (MSCs), and fibroblasts by secreting IL-17, IL-11, IL-6, IL-1, TNF-α, and IL-1β. Interleukins (1, 6, 11, and 17), along with TNF-α, predominantly promote bone resorption and the differentiation of osteoclasts, whereas interleukins (10, 13) exert inhibitory effects on bone regeneration.[96] Furthermore, TNF-α demonstrates dual effects on osteogenesis, influenced by concentration, specific cell targets, and duration of exposure.[97] IL-6 assumes a pivotal role in the initial stages of bone healing by facilitating the differentiation of monocytes into osteoclasts and modulating MSC differentiation towards pre-osteoblasts.[98] Deficiency or absence of IL-6 affects callus remodeling and mineralization at fracture sites.[99] TNF-α and its associated biofactors can induce either apoptosis or cell proliferation depending on their interaction with cell surface receptors.[99] Kon et al demonstrated an elevated expression level of TNF-α and its receptors (TNFR1 and TNFR2) during the initial 24-hour period of fracture repair, followed by a return to baseline levels within 72 hours, indicating a biphasic pattern.[96] However, TNF-α expression rises again during endochondral bone formation, mainly contributed by osteoblasts and mesenchymal cells, including hypertrophic chondrocytes.[100] The absence of TNF-α halts bone repairing in mice models, delaying endochondral bone synthesis for weeks.[101] The dual role of TNF-α in bone regeneration depends on its release profile.[101,102]

Angiogenic Factors

Sahoo et al described the critical role of vascularization and ischemic status in the bone regeneration process.[103] Macrovascular networks not only provide oxygenation to tissues and aid in waste clearance but also promote the recruitment of osteoblasts to fracture sites, thereby significantly influencing cell differentiation and the process of endochondral ossification.[104] Angiogenesis is developing new blood vessels alongside existing ones in regenerating tissues, which is crucial for bone regeneration, as vascular networks provide nutrients and cells for tissue remodelling. Lienemann et al described the key pro-angiogenic growth factors, including TGF-β, FGFs, BMPs, and PDGF.[94] FGFs,

particularly FGF2, regulate angiogenesis and support endothelial and osteoblast cell proliferation.[103,105] However, Benoit et al explained the necessitates of the short half-life of basic FGFs (~90 s in vivo) for the development of nanocarriers to prolong their action and protect them from degradation.[93]

Osteogenic Factors

Yang et al mentioned that BMPs, released by stem cells, exert both autocrine and paracrine influences, regulating the stepwise differentiation of stem cells into cartilage and bone cell lineages.[106] The BMP family comprises over 30 members, with BMP-2 and BMP-7 extensively studied by Cecchi et al.[107] However, Haubruck et al showed recombinant human BMP-2 (rhBMP-2) and rhBMP-7, which received FDA approval for clinical use, did not surpass bone graft efficacy.[108] Helm and coworkers showed that combined BMP-2 and BMP-7 administration worked more effectively than individual protein use.[109] BMP-2, BMP-4, and BMP-6 effects on bone marrow-derived stromal cell differentiation varied by cell type. BMP-6 emerged as the most consistent and potent osteoblast regulator among tested BMPs, with exclusive BMP-6 gene expression detected before human stromal cell osteoblast differentiation.[110] Comparative studies by Kang et al highlighted BMP-6 and BMP-9 as the most efficient osteogenic proteins.[111] Clinical use of BMP-2 and BMP-7 for bone fracture repair lacks conclusive efficacy and proves costly, limiting off-label applications in musculoskeletal conditions.[112,113]

Vascular Endothelial Factor (VEGF)

A fracture site surrounded by local vascularization emerges as a critical determinant in bone regeneration. VEGF plays a central role in the dominant hormonal pathways regulating angiogenesis, namely the VEGF and angiopoietin pathways, and it has demonstrated osteogenic properties.[114–116] VEGF is secreted from hematoma upon bone fracture, stimulating endothelial cell proliferation and vascular invasion in a hypoxic environment.[117] Subsequently, during endochondral ossification, hypertrophic chondrocytes within the epiphyseal growth plate secrete VEGF, facilitating blood vessel infiltration into the cartilage and forming new bone.[116,118] Animal research highlights the effectiveness of external VEGF administration in enhancing bone fracture healing. Kaigler et al demonstrated augmented vascularization and improved bone characteristics in rodents with critical cranial bone defects when treated with VEGF-infused bioglass.[119,120] In a rabbit model, VEGF and autograft therapies significantly increased new bone generation and improved mechanical characteristics compared to carriers-alone treatments, emphasizing angiogenesis and osteoinductive elements in bone generation.[121] However, VEGF's inherent instability and short-lived nature in vivo necessitate gene delivery vehicles for its administration.[122] Concerns regarding the risk of haemangiomas or tumor reappearance further restrict VEGF's clinical application, particularly in patients with a history of radiotherapy or tumor excision.

Fibroblast Growth Factors

Fibroblast growth factors (FGFs) play a vital role in bone development and healing, as evidenced by patients with mutations in FGF genes displaying skeletal aberrations. Maddaluno et al reported that during endochondral bone development, FGFs and their receptors (FGFRs) are notably upregulated, highlighting their significance in bone healing.[123] Recent studies underscore the direct association between FGFs and calvarium defect healing.[124] In another report, Behr et al described the delivery of FGF9 and FGF18 via collagen scaffolds in mice models having calvarium defects, leading to bone regeneration.[125] Heterozygous FGF9 knockout mice displayed impaired angiogenesis and deficient lengthy bone repair. Similarly, diminished healing responses were observed by Behr et al in heterozygous FGF18 knockout mice within a tibial defect, indicating that reductions of up to 50% in FGF levels impede bone development and healing.[125] FGFs' role in bone repair is intertwined with DJ-1 (Park7) protein, promoting bone repair by enhancing osteogenesis and angiogenesis, an effect reversed by FGFR kinase inhibition.[126] Hurley et al demonstrated the therapeutic potential of administering 18 kDa isoforms of FGF2-enhanced healing in closed tibial fractures in transgenic mice.[32] FGF2 exhibited enhanced bone healing across various preclinical models.[127]

Clinical Application of Bone Substitutes

Choosing the appropriate bone substitute for defect filling in clinical practice involves evaluating the defect's size, location, load-bearing requirements, and the patient's overall health. The most suitable material to replace bone tissue should be physically similar to bone, biocompatible, bioresorbable, osteoconductive, osteoinductive, porous, mechanically resistant, easy to use, safe, and economical, among other exacting requirements.[128] Recent literature provides valuable insights into this decision-making process:

A. Patient Related Factors

Bioactive glass and other alternatives that improve vascularization may be helpful for patients with systemic disorders like osteoporosis. In cases of infected deformities, bone substitutes that are impregnated with antibiotics are preferred.[129]

B. Defect in Size and Location

Because of their osteoconductive qualities, synthetic alternatives such as calcium phosphate or hydroxyapatite work well for minor, non-load-bearing deformities. Autologous or allogeneic grafts are more appropriate for larger lesions that need structural support, particularly in load-bearing locations. Cortical defects may require stronger materials, such as structural grafts, whereas metaphyseal defects benefit from bioactive glass alternatives, which stimulate vascularization and slow resorption.[130]

C. Growth Factor Integration

Growth factor-enhanced substitutes accelerate healing but require caution in oncological cases due to potential tumor stimulation.

By integrating cutting-edge materials and innovative techniques, emerging technologies in bone defect management are revolutionizing clinical outcomes. For example, 3D printing has made it possible to create patient-specific scaffolds that mimic natural bone structure, improving osteoconductivity and mechanical support.[131] The field of nanotechnology is gearing up for developing biomaterials with nanoscale attributes, boosting cell attachment, proliferation, and controlled release of growth factors.[129] Use of bioactive coatings on implants and scaffolds are being used to promote cell differentiation and lower the risk of infection.[130] Stem cell integration with scaffolds is showing promise in complex defect repair by enhancing osteogenesis and vascularization.[132] Smart biomaterials are becoming more and more instrumental for better therapeutic results and regulated medication delivery since they react to environmental stimuli like pH and temperature. These developments, which are backed by ongoing research, are opening the door to individualized and successful bone regeneration techniques, tackling issues in orthopaedic and maxillofacial applications. Table 1 summarizes the indication as well as contraindications of various bone substitutes that are routinely employed in clinics for better patient care.

Table 1 Indication as Well as Contraindications of Various Bone Substitutes

Bone Substitute	Indication	Advantages	Limitation	Contraindication	References
Autologous bone graft	Ideal for large defects requiring osteogenic, osteoinductive, and osteoconductive properties. Commonly used in trauma, tumor resection, and spinal fusion surgeries.	Ideal for bone regeneration, ensuring high compatibility and integration.	Limited donor availability, potential for donor site morbidity, and increased surgical time.	Patients with systemic conditions like osteoporosis or infection at the donor site.	[133,134]
Allogenic bone grafts	Suitable for defects where autografts are not feasible. Often used in revision surgeries or when structural support is needed.	Readily available and avoids donor site complications	Risk of immune rejection and disease transmission	Patients with immune disorders or a history of graft rejection.	[135]

(*Continued*)

Table 1 (Continued).

Bone Substitute	Indication	Advantages	Limitation	Contraindication	References
Synthetic bone substitutes	Best for small to medium-sized defects, especially in non-load-bearing areas. Used in trauma, benign bone cysts, or iatrogenic defects.	Customizable, biocompatible, and avoids donor-related complications	Limited osteoinductive properties and slower integration	Large, load-bearing defects requiring structural support	[136,137]
Bioactive glass and calcium phosphate substitutes	Suitable for defects requiring enhanced osteoconductivity and gradual resorption.	Promotes bone ingrowth and vascularization	May not provide immediate structural stability	Defects requiring rapid bone regeneration or high mechanical strength.	[138]
Growth factor enhanced substitutes	Used in cases where accelerated healing is desired, such as in non-union fractures or post-tumor resection.	Enhances bone regeneration and healing.	Potential risk of stimulating residual tumor cells in oncological cases.	Malignant or aggressive bone tumors without thorough evaluation.	[139]

Multidisciplinary Treatment Approaches

Multidisciplinary approaches are essential for managing bone tumors. Standard treatment involves surgical resection and adjuvants like liquid nitrogen, ethanol, or phenol.[140] The combination of high-speed burr and adjuvant treatment has shown efficacy.[141] Bone tumor predominantly affects extremities like the distal femur, proximal tibia, distal radius, and distal tibia.[141] Campanacci et al classified the bone tumor into three grades, guiding treatment decisions.[142] Preservation of joints is crucial, with curettage recommended for both stage 1 and stage 2 tumors. Post-resection, bone voids are filled with bone allografts, hydroxyapatite powder, or polymethylmethacrylate bone cement.[143,144] Denosumab, approved in 2013, is recommended for bone tumors not suitable for surgery or causing impairment post-resection.[145,146] Despite an increased recurrence risk, it reduces the need for invasive surgery. Tissue substitutes mimicking native tissue's physiological functions and mechanical properties, including hardened scaffolds and hydrogels, are supplemented with modified biomolecular formulations to regulate cell activity.[147,148] Both bulk material analysis and consideration of the in vitro native extracellular matrix, with its micro- and nanoscale domains, are crucial in tissue engineering models for bone tumors.

Conclusions

This review has comprehensively examined modern approaches to bone tumor management, with an emphasis on bone grafting and the role of growth factors in defect reconstruction. Drawing from recent literature and clinical insights, it highlights key findings. Firstly, it delves into the intricate biology of bone and the complexities of bone tumors, shedding light on the mechanisms driving bone regeneration. This understanding is pivotal for advancing diagnostic techniques, enabling early intervention and personalized treatments. Secondly, it outlines the array of bone grafting options—autologous, allogeneic, and synthetic—which provide clinicians with flexible solutions for defect repair, each with unique benefits and limitations. Additionally, the use of growth factors emerges as a promising strategy to enhance bone regeneration and support healing after tumor resection. Numerous significant advancements have been made in the field of tissue engineering research, including the employment of various bone substitutes made of ceramic and polymers that have been modified with living osteogenic progenitor cells or integrated with growth hormones. Advancements in our knowledge of these materials and growth factors will enable greater precision in controlling and altering their structure, understanding surface characteristics, and optimizing their interactions with other materials or the physiological

environment. These developments may pave the way for designing and creating more efficient solutions for reconstructing bone defects. The future of effective bone grafting procedures depends on the concepts of customized medicine because there is not a single grafting material or method that is observed superior in all aspects when compared with other alternatives. The size and location of the defect, the patient's general health, and the options that are readily available in each situation all influence the transplant choice. Therefore, it is reasonable to assume that customized strategies will enhance the results for each patient requiring bone grafting.

However, further research is warranted to refine their therapeutic efficacy and safety profiles. Overall, this review underscores the importance of staying abreast of advancements in bone tumor management to optimize patient outcomes and enhance the quality of care in orthopedic oncology.

Future Perspectives

Future research in bone tumor management holds immense promise, but there are still a number of issues and unresolved questions that need to be addressed. These include the establishment of standardized protocols for graft selection and optimization, the discovery of dependable biomarkers for prognostic stratification, and the investigation of novel therapeutic targets to reduce tumor recurrence and metastasis. Additionally, the best possible integration of multidisciplinary approaches is still a crucial area for future study, with a particular emphasis on shared decision-making frameworks and patient-centered care models. Innovative approaches to improving bone regeneration, reducing treatment-related complications, and improving patient outcomes will be made possible by ongoing developments in tissue engineering and regenerative medicine. Additionally, integrating emerging technologies like nanotechnology, 3D printing, artificial intelligence and machine learning holds promise for enhancing therapeutic monitoring, treatment planning, and diagnostic accuracy in the management of bone tumors.

Disclosure

The authors report no conflicts of interest in this work.

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