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Bone Tissue Engineering in Veterinary Medicine: From Natural Healing to Advanced Biomaterials

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Abstract

Bone tissue engineering is an advanced approach for the repair and regeneration of bone defects that are difficult to treat using conventional methods. It combines biomaterial scaffolds, osteogenic cells, and bioactive molecules to restore bone structure and function. Recent developments in synthetic and bioactive materials have improved bone healing while reducing the limitations of traditional grafts. These advances have expanded the application of bone tissue engineering in both human and veterinary medicine.

Introduction

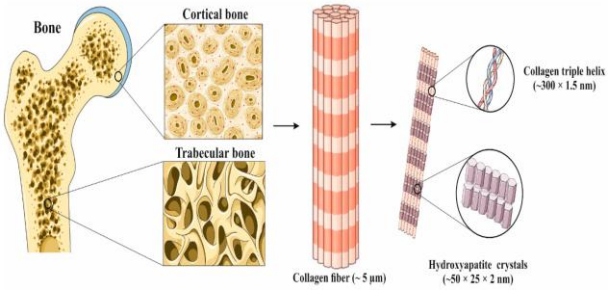
Bone is not a static structure; it is a highly dynamic and living tissue that continuously adapts to biological signals and mechanical forces. It is organised in multiple hierarchical levels, from molecular components to complex structural systems, all working together to maintain strength, flexibility, and metabolic balance. In veterinary species such as dogs, cats, horses, and other animals, bone defects commonly arise due to trauma (fractures, bone loss), infections like osteomyelitis, tumour removal, congenital abnormalities, or degenerative conditions. Although bone has an inherent ability to heal, this regenerative capacity is limited. When a defect becomes too large known as a critical-sized defect or when blood supply is insufficient, healing may be delayed or may fail completely. Conventional treatments such as autografts, allografts, metallic implants, and bone plates have been widely used, but each has important limitations. These include donor-site pain, limited availability of graft material, risk of immune reactions or infection, graft resorption, and mismatch between implant stiffness and natural bone. To overcome these challenges, bone tissue engineering has emerged as a promising multidisciplinary approach that integrates biomaterials, cells, and biological signals to repair or regenerate damaged bone.

Cellular Components of Bone

Bone tissue is maintained by the coordinated activity of three main cell types: osteoblasts, osteocytes, and osteoclasts, each playing a distinct yet interconnected role.

Osteoblasts are bone-forming cells derived from mesenchymal stem cells found in the periosteum, endosteum, and bone marrow. Their differentiation is stimulated by growth factors such as transforming growth factor-β, platelet-derived growth factor, fibroblast growth factor, and bone morphogenetic proteins. Once activated, osteoblasts secrete the organic bone matrix, known as osteoid, composed mainly of type I collagen. They also produce enzymes like alkaline phosphatase,

which initiate mineral deposition. Bone formation typically proceeds at a rate of 1–2 micrometres per day, followed by gradual mineralisation. When osteoblasts complete their active role, they either become flattened bone-lining cells or differentiate into osteocytes. **Osteocytes** are mature bone cells that reside within small spaces called lacunae. These cells form an extensive communication network through fine cytoplasmic extensions connected by gap junctions. Osteocytes act as mechanosensors, detecting mechanical stress and translating it into biological signals that regulate bone formation and resorption. In this way, they play a central role in maintaining bone architecture and strength. **Osteoclasts** are large, multinucleated cells responsible for bone resorption. Unlike osteoblasts, they originate from the hematopoietic monocyte macrophage lineage. Osteoclasts dissolve the mineral phase of bone through acid secretion and degrade the organic matrix using enzymes such as cathepsin K and matrix metalloproteinases. Their activity creates characteristic resorption pits known as Howship's lacunae and is essential for bone remodeling and mineral homeostasis.



Extracellular Matrix: The Structural Foundation of Bone

The extracellular matrix of bone provides both mechanical strength and biological signalling. It consists primarily of type I collagen fibers, which account for nearly 90% of the organic matrix, arranged in an organised, anisotropic pattern to resist mechanical loads. Along with collagen, the matrix contains proteoglycans, glycoproteins, and other important matrix proteins include alkaline phosphatase, osteocalcin, osteopontin, osteonectin, bone sialoprotein, TGF-β, thrombospondin, insulin-like growth factor-1 (IGF-1), and FGF. Many of these molecules remain stored within the matrix and are released during osteoclastic resorption, where they influence new bone formation and vascular growth. Cement lines are thin, elastic boundaries between bone layers which help to prevent the spread of microcracks and provide insight into the bone's growth history and mechanical loading patterns.

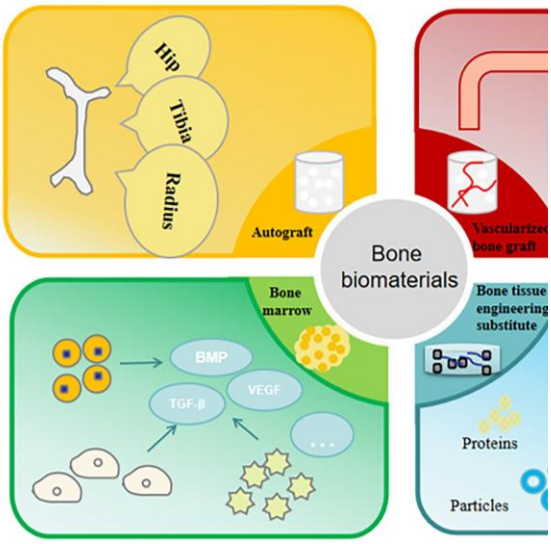
Structural Organisation of Bone Tissue

At the tissue level, bone exists in two main forms: cortical (compact) bone and trabecular (cancellous) bone. Cortical bone forms the dense outer shell of bones and provides most of the mechanical strength. It is organised into cylindrical units called osteons, each centred around a blood vessel. In rapidly growing animals, early bone is often primary bone, which later remodels into mature secondary osteons. Trabecular bone has a spongy, lattice-like structure composed of thin plates and rods. It plays a major role in mineral metabolism and is the primary site of bone remodeling. Another form, woven bone, contains randomly arranged collagen fibers and is typically seen in fetal development, fracture healing, and pathological conditions.

Core Principles of Bone Tissue Engineering

Bone tissue engineering is based on the interaction of three fundamental components: scaffolds, cells, and bioactive molecules. The scaffold provides a three-dimensional framework that supports cell attachment, tissue ingrowth, vascularisation, and mechanical stability. Osteogenic cells, such as mesenchymal stem cells or osteoblast precursors, generate new bone tissue. Bioactive molecules including growth factors and cytokines guide cell differentiation, stimulate blood vessel formation, and regulate bone remodeling. An ideal bone tissue engineering construct must be biocompatible, support new bone formation, allow bone growth through its structure (osteoconductive), induce stem cell differentiation (osteoinductive), degrade at a rate matching

new bone formation, and possess mechanical properties appropriate for the repair site. Adequate porosity and interconnectivity are also essential to ensure nutrient diffusion and vascular ingrowth.



Types of Bone Biomaterials

Biomaterials employed in bone tissue engineering may be broadly classified into naturally derived materials, synthetic materials, and semi-synthetic or hybrid systems.

Autografts: Autografts, obtained from the patient's own body, are regarded as the gold standard because they contain viable cells and possess superior osteogenic, osteoinductive, and osteoconductive properties. Despite their advantages, autografts require an additional surgical site, which may result in donor-site pain, infection, hemorrhage, or cosmetic defects, and the quantity of available graft material is often limited.

Allografts: Allografts are harvested from genetically similar individuals of the same species and are commonly processed in tissue banks to remove cellular components and reduce immunogenicity. Although advancements in tissue banking have greatly decreased the risk of disease transmission, allografts may still elicit immune reactions and carry a small risk of viral infection.

Xenografts: Xenografts are derived from different species, most commonly bovine or porcine sources. While ethical considerations and concerns regarding cross-species disease transmission restrict their application, extensively processed xenogenic materials are widely used in clinical practice. Examples include bovine-derived Geistlich Bio-Oss® and porcine-derived Synthes XCM Biologic™, both of which are commonly employed in bone repair procedures.

Natural Biomaterials: Natural biomaterials are obtained from biological sources and include collagen, demineralized bone matrix (DBM), chitosan, alginate, and silk fibroin. These materials are highly biocompatible and often exhibit inherent bioactivity, such as the presence of natural cell-binding motifs in collagen. However, their clinical use in load-bearing applications is limited by relatively poor mechanical strength and variable degradation rates.

Composite Biomaterials: Composite biomaterials combine two or more material types, such as natural polymers with synthetic polymers or ceramics, to exploit the advantages of each component. For instance, collagen–hydroxyapatite composite scaffolds offer enhanced bioactivity along with improved mechanical strength. Such hybrid systems are designed to better mimic the native bone environment and improve regenerative outcomes.

Synthetic Biomaterials and Ceramic Scaffolds: Synthetic biomaterials include biodegradable polymers such as polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), and ceramic materials such as hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), bioactive glass, and calcium phosphate cements. These materials provide greater control over mechanical properties, degradation rates, and scaffold architecture. Although they are not inherently osteoinductive, they are highly osteoconductive, allowing bone to grow along their surfaces. Bone regeneration using these materials depends on factors such as porosity,

granule size, and surface chemistry, which can be further enhanced by surface modification with proteins like laminin or fibronectin to improve cell adhesion and osteogenesis.

Polymeric Scaffolds: Polymeric scaffolds are biodegradable and biocompatible structures that provide temporary mechanical support while guiding new bone formation. Their physical and chemical properties can be tailored to regulate degradation rate, pore size, and mechanical strength. In addition, polymeric scaffolds serve as effective carriers for cells, growth factors, and bioactive molecules, supporting bone regeneration and remodeling. Natural polymers such as type I collagen are widely used due to their excellent biological compatibility; however, their mechanical weakness limits their application in high-load areas. Consequently, synthetic polymers including PLGA, PLA, PGA, and PCL are often preferred because of their adjustable strength and degradation characteristics.

Biodegradable Poly (α-hydroxy acids): Polymers derived from α-hydroxy acids, such as PLA, PGA, and their copolymer PLGA, are among the most extensively studied materials in bone tissue engineering. PGA exhibits high tensile strength and crystallinity, while PLA degrades more slowly and provides better mechanical stability, making it suitable for load-bearing applications. PLGA offers flexible degradation rates by modifying the lactic-to-glycolic acid ratio and is widely used in bone regeneration as well as controlled drug delivery systems.

Demineralized Bone Matrix (DBM): Demineralized bone matrix is a widely used osteoinductive material containing collagen and growth factors that promote bone healing through mitogenic, angiogenic, and differentiation pathways. Commercial DBM products such as Grafton Allogeneic Bone Matrix are available in various formulations, including gel, putty, and flexible sheets, and are often used alone or in combination with autografts to augment internal fixation. However, DBM lacks sufficient mechanical strength for weight-bearing applications. The osteoinductive potential of DBM is highly dependent on processing methods, and variability among bone banks necessitates experimental validation of its biological activity.

Hydrogels: Hydrogels are highly hydrated polymer networks capable of encapsulating living cells and growth factors. Their hydrophilic nature makes them excellent delivery systems for biological molecules. However, due to their limited mechanical strength, hydrogels are generally restricted to non-load-bearing bone defects. Common natural hydrogels include alginate, chitosan, agarose, collagen, fibrin, and hyaluronic acid. These materials function as space fillers, promote cell attachment and proliferation, and facilitate localized delivery of growth factors to enhance bone healing.

Current Advances in Biomaterials for Bone Regeneration

Recent advances in bone tissue engineering have increasingly focused on the development of multifunctional biomaterials that combine structural scaffolds with bioactive molecules to enhance and accelerate bone regeneration. Rather than serving only as passive fillers, modern biomaterials are designed to actively participate in the healing process by modulating cellular behaviour, angiogenesis, and remodeling. Several FDA-approved products exemplify this approach, including Medtronic's Infuse®, which consists of a bovine type I collagen sponge loaded with recombinant human bone morphogenetic protein-2 (rhBMP-2), and Gem 21S®, a β-tricalcium phosphate scaffold combined with recombinant human platelet-derived growth factor-BB (rhPDGF-BB). These products have demonstrated excellent clinical outcomes by stimulating osteogenesis and vascular ingrowth. However, they typically deliver supraphysiological doses of growth factors, which may increase cost and raise safety concerns. Consequently, current research aims to develop delivery systems capable of releasing smaller, more physiologically

relevant doses in a controlled and sustained manner.

Nanotechnology and Nanodelivery Systems

Nanotechnology has emerged as a transformative tool in bone tissue engineering, offering innovative strategies to improve scaffold performance and biological response. Nanoparticles and nanofibrous scaffolds closely mimic the nanoscale architecture of natural bone extracellular matrix, thereby enhancing cell adhesion, proliferation, and differentiation. Nanostructured materials also improve mechanical properties and enable precise control over the spatial and temporal release of osteogenic signals. Current research explores the incorporation of growth factors, siRNA, and DNA plasmids into nanoparticles ranging from 6 to 50 nm, which can be embedded within scaffolds. These systems allow the sequential release of signaling molecules in harmony with the natural phases of bone healing. In addition, osteogenic gene transfer techniques that stimulate osteoblast differentiation are being investigated as cost-effective alternatives to recombinant proteins such as rhBMP-2 and rhBMP-7.

Strontium-Modified Biomaterials

Strontium (Sr) is a biologically active trace element known for its dual effect of promoting bone formation while simultaneously inhibiting bone resorption. Although oral strontium ranelate has demonstrated beneficial effects on bone architecture and strength, concerns regarding cardiovascular safety particularly an increased risk of non-fatal myocardial infarction have limited its systemic use. To overcome these limitations, recent strategies have focused on incorporating strontium directly into bone substitute materials. Localized delivery through strontium-doped ceramics and scaffolds enables high concentrations at the defect site while minimizing systemic exposure. Preclinical studies in normal and osteoporotic animal models have shown that such materials significantly enhance bone formation, improve microarchitecture, and increase mechanical strength, supporting their potential for safer clinical application.

Synthetic Bone Graft Substitutes in Veterinary Practice

In veterinary orthopaedics, the use of synthetic bone graft substitutes has gained increasing attention as an alternative or adjunct to autologous cancellous bone grafts, which remain the clinical gold standard. Synthetic materials offer several advantages, including unlimited availability, absence of donor-site morbidity, reduced surgical time, and consistent material quality. Among these, β-tricalcium phosphate (β-TCP)-based substitutes have shown particular promise. A notable example is Bonelike®, a synthetic bone graft substitute Veterinary clinical series describing the use of Bonelike® have demonstrated its effectiveness in filling bone voids and defects associated with non-union, delayed union, malunion, bone cysts, tumors, and arthrodesis. In cases of maxillary and mandibular bone defects, Bonelike® granules have shown excellent integration with host bone, promoting stable bonding and gradual replacement by newly formed bone tissue. The material's osteoconductive properties, appropriate resorption rate, and favorable handling characteristics make it particularly suitable for veterinary clinical use. Although autologous cancellous grafts continue to be preferred for their osteogenic potential, the increasing success of synthetic substitutes such as Bonelike® highlights a shift toward biomaterials that can reliably support bone regeneration while reducing surgical morbidity

In addition to Bonelike®, several other synthetic bone graft substitutes are increasingly used in veterinary orthopaedics, dentistry, and maxillofacial surgery. These materials are primarily based on calcium phosphate ceramics and bioactive composites and are valued for their osteoconductive properties, availability, and predictable behavior.

β-Tricalcium Phosphate (β-TCP)–based materials are among the most widely used synthetic grafts in veterinary medicine. Products such as ChronOS®, Vitoss®, and Cerasorb® have been applied in dogs, cats, and horses for the management of bone defects, delayed unions, and arthrodesis procedures. β-TCP is resorbable and gradually replaced by newly formed bone, making it suitable for non-load-bearing and moderately load-bearing defects when combined with internal fixation.

Hydroxyapatite (HA) ceramics, including dense and porous forms, are also commonly used. Veterinary-specific HA products and HA granules are frequently applied in dental and maxillofacial surgeries, fracture gap filling, and corrective osteotomies. HA degrades more slowly than β-TCP and provides long-term structural support, although its slow resorption may limit complete replacement by native bone.

Biphasic calcium phosphate (BCP) materials, which combine HA and β-TCP in varying ratios, are increasingly favored because they balance mechanical stability with controlled resorption. Products such as Maxresorb® and BioGraft® have been reported in veterinary literature for use in orthopedic defects, periodontal reconstruction, and spinal fusion models. The HA component maintains scaffold integrity, while the β-TCP fraction enhances remodeling.

Calcium phosphate cements (CPCs) are injectable synthetic grafts that harden in situ, conforming precisely to irregular bone defects. CPCs are particularly useful in minimally invasive procedures, fracture void filling, and subchondral bone defects. Their main limitation is brittleness and lower tensile strength, restricting their use in high-load regions without additional fixation.

Bioactive glass-based substitutes, such as 45S5 bioactive glass, have also shown promise in veterinary bone repair. These materials bond directly with bone and stimulate osteogenic activity through ionic dissolution products. Their use has been reported in periodontal and craniofacial applications, although wider orthopedic adoption is still evolving.

Clinical Relevance in Veterinary Medicine

While autologous cancellous bone grafts remain the gold standard due to their osteogenic and osteoinductive properties, synthetic bone graft substitutes are increasingly used either alone or in combination with autografts. Their consistent quality, ease of use, and absence of donor-site complications make them particularly valuable in geriatric animals, polytrauma cases, large defects, and repeat surgeries. As biomaterial technology advances, synthetic substitutes are expected to play an even greater role in veterinary orthopaedic and reconstructive surgery.

Conclusion

Synthetic bone graft substitutes are increasingly used in veterinary practice as effective alternatives or adjuncts to autologous bone grafts. Materials such as β-tricalcium phosphate, hydroxyapatite, biphasic calcium phosphate, calcium phosphate cements, and bioactive glass provide reliable osteoconductive scaffolds, are readily available, and eliminate donor-site morbidity. While autografts remain the gold standard due to their osteogenic and osteoinductive properties, synthetic substitutes offer consistent quality, reduced surgical time, and predictable resorption. Their growing clinical success highlights their important role in modern veterinary orthopaedic and reconstructive surgery.