

THE REHABILITATION OF ANTHROPOLOGICAL PARAMETERS THROUGH BONE REGENERATION MATERIALS AND TECHNIQUES

Agop Forna Doriana¹, Ecaterina Ionescu^{2*}, Norin Forna¹, Vlăduț Burduloi¹, Liliana Savin¹, Lorenza Forna¹, Alina Jehac¹, Anca Gradinariu¹, Carina Balcoș¹, Elena Claudia Coculescu^{2*}, Cristian Budacu¹, Norna Forna¹

¹ University of Medicine and Pharmacy "Grigore T. Popa", Iași

² University of Medicine and Pharmacy "Carol Davila", București

Corresponding authors:

Ecaterina Ionescu: ecaterinaionescu2008@yahoo.com,

Elena Claudia Coculescu: elena-claudia.coculescu@umfcd.ro

Authors with the same contribution as first author

Abstract

Bone regeneration materials and techniques aid in restoring bone structure and function, consequently improving mobility and alleviating discomfort or disability in individuals suffering from bone defects or injuries. This restoration contributes significantly to an improved quality of life for affected individuals. Continuous research and innovation in bone regeneration materials have led to the development of more sophisticated and effective techniques. These advancements are pivotal in the evolution of medical technology and its potential to address various bone-related conditions. Traditional methods, such as autografts, are associated with limitations like donor site morbidity and limited supply. Emerging bone regeneration materials and techniques offer alternatives that mitigate these issues, potentially reducing reliance on traditional approaches. In conclusion, the utilization of bone regeneration materials and techniques holds substantial promise in rehabilitating anthropological parameters, improving patient outcomes, advancing medical technology, and contributing to a more comprehensive and ethical approach to healthcare.

Key words: bone regeneration, anthropological parameters, surgery

Introduction

The realm of medical science has witnessed remarkable advancements in the rehabilitation of anthropological parameters through the application of bone regeneration materials and techniques. This progressive field has significantly contributed to restoring skeletal integrity, mobility, and functional capabilities in individuals grappling with bone-related issues.

Bone, an ever-evolving natural composite, experiences ongoing alterations via precise bone-building and bone-breaking procedures carried out by osteoblasts and osteoclasts, correspondingly, throughout an individual's lifespan (1). Ordinarily, bone tissue possesses inherent self-repair abilities after an injury, enabling the affected area to

restore its original structure and mechanical strength. Interestingly, the mending process of a fractured bone, dependent on osteoblasts derived from mesenchymal stem cells, can occur through two distinct mechanisms: intramembranous (linked to the creation of flat bones such as those in the skull and clavicles) and endochondral (observed in long bones like the femur and tibia) bone formation (2).

The impact of these bone regeneration materials and techniques extends beyond mere physical restoration. By restoring bone structure and function, individuals regain not only their physical mobility but also a crucial aspect of their anthropological identity. This restoration enables active engagement in societal, occupational, and personal spheres, leading

to a significant improvement in their overall quality of life.

The applications of these advancements span various skeletal disorders, including fractures, degenerative bone diseases, and congenital skeletal abnormalities. The continuous evolution and refinement of these methodologies hold the promise of elevating standards of care for patients with diverse skeletal conditions.

Bone Regeneration Materials

Assessing a range of crucial factors is essential in utilizing biomaterials for bone regeneration, aiming to achieve optimal outcomes for forthcoming translational uses. Genetically modified tissues are now a viable approach in the recovery of severely affected bones due to external injuries, cancer, or the aging process. Tissue engineering shows promise in addressing the scarcity of biological organs, tissues, and bone regrowth. (3)

Osteopenia has a significant impact on millions of individuals, and projections estimate it will affect 16 million by 2030, leading to healthcare costs exceeding \$65 billion annually. Globally, approximately 3.3 million bone implant surgeries are performed each year to aid in fracture healing, filling voids, and repairing spinal abrasions. (4). While autografts remain the gold standard for treating damaged bones, their availability is limited, and concerns arise regarding donor site morbidity. Bone allografts offer a superior alternative to autografts but are associated with high costs and complications, including functional disturbances. The limitations of current therapies and their financial ramifications have generated interest in developing alternative solutions for bone treatments (3).

The cornerstone of this field lies in the development and utilization of a spectrum of materials tailored explicitly for bone regeneration. Biocompatible polymers, bioactive ceramics, and

biodegradable scaffolds have emerged as pivotal components in facilitating tissue regeneration at sites of bone injury or degradation. These materials provide structural support while encouraging the proliferation of new bone tissue, serving as crucial catalysts in the regenerative process.

The use of bioactive glass combined with biocompatible polymers for bone applications can be significant in the field of regenerative medicine and bone implants. This combination can offer numerous advantages, such as healing and regenerating properties for bone tissue, given that bioactive glass has ion-releasing properties that can promote bone growth and healing. When combined with biocompatible polymers, it can provide a supportive and stimulating environment for bone regeneration. Another quality of this combination is biological compatibility. Biocompatible polymers, such as polyurethanes or polyetheretherketones (PEEK), can be combined with bioactive glass to create materials that are well-tolerated by the body and do not provoke adverse reactions (5).

The flexibility and mechanical strength of this material combination are determined by the polymers that provide flexibility and mechanical strength to the material, which can be beneficial in bone implant applications to support bone structure and prevent fractures. This combination may allow for the control of active substance release, such as medications or growth factors, which can be integrated into the bioactive glass and polymer composite, contributing to bone healing and regeneration (6).

Therefore, the use of bioactive glass together with biocompatible polymers represents an important research area in regenerative medicine and bone implant development, with the potential to enhance bone tissue healing and regeneration processes.

Cutting-Edge Techniques

In tandem with these materials, sophisticated surgical techniques play a crucial role in augmenting bone regeneration. Autografts and allografts, along with tissue engineering methodologies, have become indispensable in addressing complex bone defects. Incorporating growth factors and osteogenic proteins has significantly accelerated the bone healing process, contributing to effective reconstruction.

Autologous bone grafts remain the clinical landmark for treating bone defects due to their osteoconductive and osteoinductive properties. Typically, autografts are primarily obtained from the iliac crest or other bone sources, but they are associated by limited availability, donor site complications, and a failure rate of up to 30% (7). So, we have the possibility to use allogeneic or xenogeneic bone sources (8).

Xenografts are mainly obtained from bovine sources and possess osteoinductive/conductive properties, but they are unsuitable due to an increased risk of infection, immunogenicity, and rejection by the host (8,9).

Allografts sourced from cadaveric donors offer the advantage of being both osteoconductive and osteoinductive. These grafts are limited in supply and carry the risk of rejection and potential transmission of infectious diseases (10). Although tissue processing and sterilization effectively eliminate the risk of disease transmission, irradiation may cause several adverse effects.

Bioactive factors including a large group of cytokines, growth factors (GFs), peptides, and hormonal signals that regulate cellular behaviors. These factors stimulate osteogenic differentiation and proliferation of cells by activating the signaling cascades related to ossification and angiogenesis. GFs and bioactive peptides are significant parts of the bone tissue engineering systems. Besides, the use of the osteogenic potential of hormonal signals has been an

attractive topic, particularly in osteoporosis-related bone defects (11).

Growth factors (GFs) represent a pivotal element within tissue regeneration strategies, creating an environment conducive to osteogenesis. These soluble proteins adhere to their designated receptors (e.g., tyrosine kinase receptors) initiating sequences of events that impact cell fate and activity. The primary receptors involved in growth factor-induced bone formation fall into two main groups: serine-threonine kinase receptors, which function as high-affinity receptors for TGF- β s and BMPs growth factors, and tyrosine kinase receptors that specifically bind to FGFs, VEGFs, PDGF, and IGF growth factors. Serine/threonine kinase receptors consist of type I and type II receptors housing a cytosolic kinase domain. TGF- β s and BMPs belong to the multifunctional transforming growth factor- β (TGF- β) superfamily, influencing cellular behavior by selectively binding to these receptors (12).

Derived from allogeneic sources, demineralized bone matrix (DBM) products used to constitute approximately 50% of the bone graft market. However, with the introduction of several FDA-approved synthetic bone grafts (as mentioned below), the DBM portion in the grafting market has decreased to around 20%. The osteogenic effectiveness of commercial DBM can vary significantly due to discrepancies in the levels of osteogenic molecules (such as BMP-2 and BMP-7), likely stemming from differences among donors, sterilization methods, and storage techniques (13).

Technological Innovations

The integration of advanced technologies, such as 3D printing, has revolutionized the customization of implants and scaffolds, aligning them with the unique anatomical requirements of individual patients. These personalized solutions mark a significant breakthrough,

ensuring enhanced compatibility and efficacy in bone regeneration processes.

Tissue engineering (TE) is a well-established domain within biotechnology that has undergone development for more than two decades. Its objective is to fabricate biological replacements to repair and sustain the normal function of damaged or diseased tissues, utilizing insights from biology, cell transplantation, materials science, and bioengineering. In this approach, extensive research is often conducted on a biodegradable three-dimensional (3D) porous scaffold combined with biological cells or molecules to facilitate tissue or organ regeneration (14).

Tissue engineering advancements have led to the creation of constructs mimicking the extracellular matrix, guiding natural bone healing by utilizing signaling molecules to stimulate osteoinduction and angiogenesis, crucial for new bone tissue formation. While current research focuses on innovative systems delivering growth factors for bone repair, it's vital to acknowledge the intricate nature of the extracellular matrix. Exploring scaffolding and growth factors in isolation may not be comprehensive enough. Hence, approaches that integrate both concepts hold significant promise in enhancing the efficacy of bone regeneration techniques.

Biodegradable scaffolds are typically seen as essential components in the creation of living tissues, serving as temporary structures with mechanical and biological characteristics akin to the native extracellular matrix (ECM). These scaffolds enable the regulation of cell adhesion, invasion, proliferation, and differentiation before the restoration of biologically functional tissue, or the natural ECM begins. 15

Biodegradable polymer scaffolds in a three-dimensional (3D) structure, featuring pores, typically serve as temporary frameworks for the seeding, attachment, growth, and multiplication of living cells,

directing the regeneration and formation of new tissues, while the biodegradable polymer matrix undergoes degradation. Furthermore, the porous 3D architecture of the scaffold plays a role in influencing cell migration by regulating the transportation of oxygen and nutrients. Another significant use of biodegradable polymeric scaffolds lies in their function as supportive materials for various drug incorporations (16-18).

Various synthetic and natural biomaterials have undergone extensive exploration as scaffolds in tissue engineering endeavors. Within this array, aliphatic polyesters such as polylactide (PLA), polyglycolide (PGA), polycaprolactone (PCL), and their copolymers such as poly(lactide-co-glycolide) (PLGA), poly(l-lactide-co-caprolactone) (PLCL), poly-(glycolide-co-caprolactone) (PGCL), and poly(l-lactide-co-glycolide-co- ϵ -caprolactone) (PLLGC) have garnered substantial scientific attention due to their commendable biocompatibility and biodegradability. Beyond the utilization of natural/synthetic polymeric scaffolds across diverse tissue engineering sectors, a promising approach involves formulating and producing binary hybrid/composite matrices comprising biodegradable polymers and inorganic additives like hydroxyapatite (HA) and tricalcium phosphate (TCP). These matrices are particularly suited for the regeneration of bone-like tissues (14).

Numerous methodologies have been devised for fabricating porous scaffolds in tissue engineering. These include porogen leaching, emulsion freeze drying, 3D printing, gas foaming, electrospinning, thermally-induced phase separation (TIPS), and potential combinations of any two of these techniques. Among these methods, TIPS stands out as particularly efficient due to its straightforward implementation and its potential to generate scaffolds with adjustable properties (14,19).

3D porous polymeric scaffolds developed by TIPS can be used for a wide range of tissue engineering applications for regeneration of cartilage, bone, osteochondral, dermal, cardiovascular, neural tissues and so on (20).

Nanotechnology in tissue engineering

Nanotechnology amplifies the bioactivity of scaffolds due to the increased surface area conferred by nanoparticles and in association with proteins and initiators, there is the potential to functionalize them, because they can prompt the adhesion, growth, and differentiation of bone cells. Nanotechnology has been a consistent presence in the remarkable advancements witnessed in the biomedical field in recent years. As a result, nanomaterials are currently undergoing significant industrial-scale production, with certain products already available on the market. However, persistent challenges revolve around the toxicity associated with these nanomaterials (21).

Within the surgical field, nanocomposites have garnered significant

attention in bone tissue engineering. This is due to the recognition of living bone tissue as a nanocomposite, showcasing a sophisticated hierarchical makeup consisting of fibrous collagen within an organic matrix, alongside nanocrystals and a mineral medium like HA. As a result, bone cells naturally favor nanostructured materials. Polymers incorporating nanoparticles hold the capability to replicate this textured surface (22).

Conclusion

In conclusion, the rehabilitation of anthropological parameters through bone regeneration materials and techniques represents a transformative breakthrough in modern medicine. The synergy between innovative materials, advanced surgical techniques, and technological innovations has paved the way for personalized and effective treatments. This burgeoning field continues to evolve, promising a brighter future for individuals grappling with bone-related ailments, offering renewed hope and vitality to countless lives.

References

1. Berendsen, A.D.; Olsen, B.R. Bone development. *Bone* 2015, 80, 14–18
2. Blumer, M.J.F. Bone tissue and histological and molecular events during development of the long bones. *Ann. Anat.* 2021, 235
3. Janhavi Sonatkar, Balasubramanian Kandasubramanian. Bioactive glass with biocompatible polymers for bone applications. Volume 160, 5 November 2021, 110801
4. Tümay Sözen,¹ Lale Özışık,² and Nursel Çalık Başaran. An overview and management of osteoporosis. *Eur J Rheumatol.* 2017 Mar; 4(1): 46–56
5. Samit Nandi, Biswanath Kundu, Someswar Datta. Development and Applications of Varieties of Bioactive Glass Compositions in Dental Surgery Third Generation Tissue Eng., Orthopaedic Surgery Drug Delivery Syst. 2011, 10.5772/24942
6. Yelick PC, Sharpe PT. Tooth bioengineering and regenerative dentistry. *J Dent Res.* 2019;98(11):1173–82.
7. Schoelles, K., Snyder, D., Kaczmarek, J., Kuserk, E., Erinoff, E., Turkelson, C., et al.. *The Role of Bone Growth Stimulating Devices and Orthobiologics in Healing Nonunion Fractures.* Rockville, MD: Agency for Healthcare Research and Quality (US),2005.

8. Trice, M. E. (2009). *Xenograft Risks: What You and Your Patients Need to Know*, AAOS Now. Rosemont, IL: American Academy of Orthopaedic Surgeons.
9. Mehta M., Schmidt-Bleek K., Duda G. N., and Mooney, D. J. Biomaterial delivery of morphogens to mimic the natural healing cascade in bone. *Adv. Drug Deliv. Rev.* 64, 2012, 1257–1276.
10. Grover V., Kapoor A., Malhotra R., and Sachdeva S. Bone allografts: a review of safety and efficacy. *Indian J. Dent. Res.* 2011, 22, 496.
11. Banafsheh Safari, Soodabeh Davaran, Ayuob Aghanejad. Osteogenic potential of the growth factors and bioactive molecules in bone regeneration. *Int J Biol Macromol.*, 2021 Apr 1:175:544-557.
12. Q. Wei, T.L. Pohl, A. Seckinger, J.P. Spatz, E.A. Cavalcanti-Adam. Regulation of integrin and growth factor signaling in biomaterials for osteodifferentiation *Beilstein J. Org. Chem.*, 11 (1) (2015), pp. 773-783
13. Kowalczewski CJ and Saul JM. Biomaterials for the Delivery of Growth Factors and Other Therapeutic Agents in Tissue Engineering Approaches to Bone Regeneration. *Front. Pharmacol.* 2018, 9:513.
14. Reza Zeinali, Luis J. del Valle, Joan Torras, and Jordi Puiggalí. Recent Progress on Biodegradable Tissue Engineering Scaffolds Prepared by Thermally-Induced Phase Separation (TIPS) *Int J Mol Sci.* 2021 Apr; 22(7): 3504.
15. V. Guarino, M.G. Raucci, A. Ronca, V. Cirillo, L. Ambrosio Multifunctional scaffolds for bone regeneration. *Bone Substitute Biomaterials*, Woodhead Publishing Series in Biomaterials, 2014, Pages 95-117
16. Pellis A, Silvestrini L, Scaini D, Coburn JM, Gardossi L, Kaplan DL, Herrero Acero E., Guebitz G.M. Enzyme-catalyzed functionalization of poly(L-lactic acid) for drug delivery applications. *Process. Biochem.* 2017;59:77–83.
17. Dorati R., DeTrizio A., Modena T., Conti B., Benazzo F., Gastaldi G., Genta I. Biodegradable Scaffolds for Bone Regeneration Combined with Drug-Delivery Systems in Osteomyelitis Therapy. *Pharmaceuticals.* 2017;10:96.
18. Biomaterials: Silk gland mimic spins strong fibres. *Nature.* 2017;541:137.
19. Carfi Pavia F, Palumbo FS, La Carrubba V, Bongiovì F, Brucato V, Pitarresi G, Giammona G. Modulation of physical and biological properties of a composite PLLA and polyaspartamide derivative obtained via thermally induced phase separation (TIPS) technique. *Mater. Sci. Eng. C.* 2016;67:561–569.
20. Zhang C, Dong P, Bai Y, Quan D. Nanofibrous polyester-polypeptide block copolymer scaffolds with high porosity and controlled degradation promote cell adhesion, proliferation and differentiation. *Eur. Polym. J.* 2020;130:109647.
21. Idumah CI. Progress in polymer nanocomposites for bone regeneration and engineering. *Polymers and Polymer Composites.* 2021;29(5):509-527. doi:10.1177/0967391120913658
22. Hing KA, Best SM, Tanner KE, et al. Mediation of bone ingrowth in porous hydroxyapatite bone graft substitutes. *J Biomed Mater Res A* 2004; 68: 187–200.