

## Commentary Paper

Strategies and Challenges in Bone Tissue Engineering:  
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**ABSTRACT**

Bone has an inherent ability to regenerate; however, this capacity is often insufficient in cases of large, critical-sized, or complex defects caused by trauma, tumor removal, infection, or degenerative diseases. Traditional methods, including autografts, allografts, and xenografts, are limited by donor site issues, immune rejection, infection risks, and poor integration with the host tissue. Bone tissue engineering (BTE) has become a promising alternative, using stem cells, scaffolds, and bioactive substances to create a biomimetic environment that promotes osteogenesis and tissue regeneration. This study provides a comprehensive review of current strategies in BTE, emphasizing cell- and growth factor-based approaches, scaffold design, and nanocomposite systems, while critically discussing the major challenges and future perspectives for advancing the development of effective, translatable therapies for bone regeneration. Scaffolds provide a temporary three-dimensional extracellular matrix, guiding cell adhesion, proliferation, and differentiation while gradually degrading as new tissue forms. A wide range of materials, including natural and synthetic polymers, bioceramics, and bioactive glasses, has been explored. The integration of nanocomposites with bioactive fillers, such as nano-hydroxyapatite and graphene oxide, further enhances mechanical strength, osteoconductivity, and cellular interactions. Despite these advances, critical challenges remain, including achieving adequate vascularization, matching native bone mechanical properties, ensuring stable host integration, and mitigating inflammatory responses associated with polymer degradation.

**Keywords:** Bone tissue engineering (BTE), Scaffolds, Stem cells, Nanocomposites, Regenerative medicine

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## Highlights

- BTE offers viable biomimetic alternatives for critical-sized bone defects.
- Stem cells and growth factors enhance osteogenic differentiation and healing.
- Polymeric and bioceramic nanocomposites improve scaffold mechanical strength.
- Incorporation of nHA and GO promotes biomineralization and cell growth.
- Vascularization and degradation matching remain critical BTE challenges.

## Plain Language Summary

Bone has a natural ability to heal itself after minor injuries such as small fractures. However, when large amounts of bone are lost due to severe accidents, cancer surgery, or serious infections, the body cannot repair the damage on its own. Currently, surgeons often take healthy bone from another part of the patient's body or use donor tissue. While these methods help, they carry risks such as pain at the donor site, tissue rejection, and infection. Bone tissue engineering (BTE) offers an innovative solution by combining laboratory-grown cells, supportive structures called scaffolds, and biological signals to help the body grow new, healthy bone. In this review, we examine the most recent advances and challenges in this field. We highlight how modern materials such as biodegradable plastics combined with microscopic ceramic particles can create artificial bone frameworks that mimic natural skeletal strength and support living cells. Despite promising progress, critical hurdles remain before these treatments can be widely used in hospitals. Ensuring that new blood vessels grow into the engineered tissue to nourish it, matching the rate at which artificial materials dissolve as real bone forms, and avoiding unwanted inflammation are the key challenges ahead. Overcoming these barriers will help bring safer, more effective bone regeneration therapies to patients worldwide.

## Introduction

**B**one, as a specialized form of connective tissue, plays a crucial role in providing mechanical support, protecting vital organs, maintaining mineral homeostasis, and supporting hematopoiesis [1]. Because of its unique cellular composition and capacity for dynamic remodeling, bone can regenerate after injury [2]. However, this regenerative potential is limited in cases of large, critical-sized, or complex defects caused by trauma, tumor resection, congenital abnormalities, infection, or degenerative diseases [3]. Under such conditions, spontaneous healing is inadequate, leading to impaired function and reduced quality of life for patients. Bone defects also impose a significant clinical and socioeconomic burden worldwide. Patients suffering from extensive bone loss often require multiple surgical procedures, prolonged hospitalization, and long-term rehabilitation [4]. Conventional clinical interventions, including bone grafting, remain the cornerstone of treatment; however, these approaches have notable drawbacks [5]. Autografts, although considered the gold standard, are limited by donor site morbidity,

limited tissue availability, and increased surgical time. Allografts and xenografts, although more accessible, carry risks such as immune rejection, disease transmission, infection, and inadequate integration with the host bone [6, 7]. These limitations highlight the urgent need for alternative therapeutic strategies that promote efficient and reliable bone regeneration [8, 9].

Recent advances in biomaterials science have significantly expanded the range of materials available for scaffold fabrication, including natural polymers, synthetic polymers, bioceramics, and bioactive glasses. Synthetic polymers such as poly (lactic acid) (PLA), polycaprolactone (PCL), and poly (lactic-co-glycolic acid) (PLGA) are widely used because of their tunable mechanical properties, controlled degradation rates, and processability with advanced fabrication techniques such as electrospinning and three-dimensional (3D) printing. However, their limited bioactivity and suboptimal cell adhesion properties remain key challenges [8, 10]. To address these limitations, nanotechnology has emerged as a transformative tool in bone tissue engineering (BTE). Incorporating nanoscale bioactive fillers, such as nano-hydroxyapatite, graphene oxide, and other nano-

**Table 1.** Comparison of scaffold materials used in BTE

| Material Class                    | Common Examples              | Key Advantages                                                                | Main Limitations                                          | Typical Applications                               |
|-----------------------------------|------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------|----------------------------------------------------|
| Natural polymers                  | Collagen, gelatin, chitosan  | High biocompatibility, excellent cell adhesion, bioactivity                   | Low mechanical strength, rapid degradation                | Small defects, soft-hard tissue interfaces         |
| Synthetic polymers                | PLA, PCL, PLGA               | Tunable mechanical properties, controlled degradation, and easy processing    | Low intrinsic bioactivity, acidic degradation by-products | Load-bearing scaffolds, custom-designed constructs |
| Bioceramics                       | Hydroxyapatite, $\beta$ -TCP | High osteoconductivity, chemical similarity to bone                           | Brittleness, poor tensile strength                        | Bone fillers, coatings, and defect repair          |
| Nanocomposites / Hybrid scaffolds | PLA/nHA, PCL/GO, PLGA/HA     | Enhanced mechanical strength, improved osteogenesis, and biomimetic structure | Complex fabrication, scalability challenges               | Critical-sized defects, advanced bone regeneration |

Abbreviations: HA: Hydroxyapatite; nHA: Nano-hydroxyapatite; GO: Graphene oxide; PLA: Poly(lactic acid); PCL: Polycaprolactone; PLGA: Poly(lactic-co-glycolic acid).

structured additives, into polymeric matrices has enabled the development of composite and nanocomposite scaffolds with enhanced osteoconductivity, mechanical performance, and biological functionality [11]. These nanostructured systems more closely resemble the hierarchical architecture of natural bone tissue and promote improved cell-material interactions, thereby enhancing osteogenic differentiation and mineralization [12].

Despite significant progress, several critical challenges continue to hinder the successful clinical translation of BTE strategies. These challenges include achieving adequate vascularization within engineered constructs, matching scaffold mechanical properties with native bone, ensuring complete and stable integration with host tissue, and managing inflammatory responses associated with scaffold degradation [13]. In particular, the acidic by-products generated during the degradation of commonly used synthetic polyesters such as PLA and PLGA can create an unfavorable local microenvironment, potentially triggering inflammatory reactions and impairing tissue regeneration [14-16]. Therefore, this study aims to provide a comprehensive overview of current BTE strategies, emphasizing cell-based therapies, growth factor delivery systems, and scaffold-based approaches (Figure 1). Additionally, the major challenges facing clinical applications are critically discussed, and future perspectives focusing on advanced composite materials, nanostructured scaffolds, and intelligent material design are highlighted. By addressing both opportunities and limitations, this review study seeks to contribute to the ongoing development of effective and translatable solutions for bone regeneration [17, 18].

## Materials and Methods

A comprehensive literature search was conducted using PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar to identify peer-reviewed articles published through 2024. The search strategy incorporated relevant keywords and Medical Subject Headings (MeSH), including “bone tissue engineering,” “bone regeneration,” “biomimetic scaffolds,” “mesenchymal stem cells,” “osteogenic differentiation,” and “nanocomposites.” Studies addressing cell-based approaches, growth factor delivery systems, polymeric and composite scaffolds, vascularization strategies, and recent translational challenges in bone defect repair were critically evaluated, and their findings were synthesized. Non-English publications and studies lacking sufficient methodological detail were excluded.

## Results

### Bone tissue engineering strategies

#### Cell-based approaches

Mesenchymal stem cells (MSCs) are a crucial cell type for bone regeneration because of their ability to differentiate into osteogenic lineages. These cells, along with stromal cells and differentiated osteogenic cells, are used to improve bone repair. MSCs offer high proliferation, osteogenic potential, and immunomodulatory effects, aiding in the formation of new bone tissue and its integration with host structures [8-10].

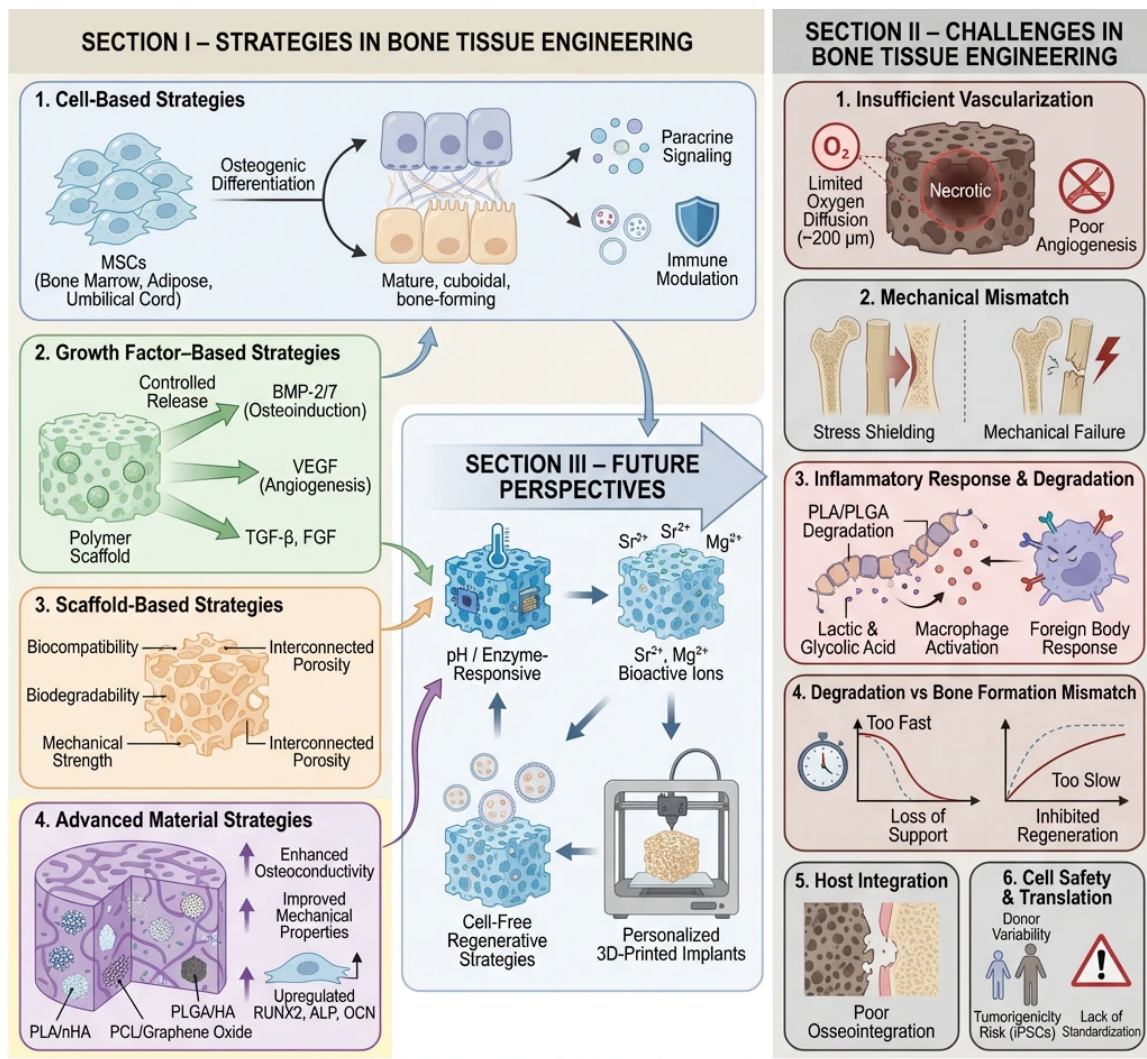


**Figure 1.** Illustration of BTE strategies and challenges

### Growth factor-based approaches

Growth factors such as bone morphogenetic proteins (BMPs), vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF- $\beta$ ), and fibroblast growth factor (FGF) guide cell growth, specialization, and the production of extracellular matrix. By using controlled delivery methods, their local biological activity and prolonged release can be optimized, which in turn improves tissue regeneration [19-21].

### Scaffold-based approaches

Scaffolds provide a 3D framework that facilitates cell attachment, proliferation, and growth, effectively functioning as an artificially engineered extracellular matrix (ECM) [21-23]. Cells naturally secrete macromolecules that assemble into the ECM, which offers a structural and biochemical environment essential for cellular growth

and proliferation [24, 25]. In this context, a scaffold acts as a temporary, supportive architecture that promotes cell adhesion, migration, and differentiation, thereby regulating tissue development. As tissue regeneration progresses, scaffolds are designed to degrade gradually, providing initial mechanical stability while also serving as a template to guide new tissue formation [26, 27].

According to recent studies, an optimal scaffold must exhibit several key properties:

**Biocompatibility:** This property ensures that the scaffold supports normal cellular activities, facilitates host cell infiltration, and promotes seamless tissue integration without inducing toxic effects or adverse inflammatory responses [27-29].

**Biodegradability:** This refers to the scaffold's capacity to undergo controlled and gradual degradation, thereby permitting progressive tissue replacement and cellular colonization over time [30]. Many commonly used synthetic polymerbased biomaterials primarily degrade through hydrolytic processes. Two principal degradation mechanisms have been identified: (a) surface erosion, in which the scaffold gradually diminishes in size while preserving its overall geometry, and (b) bulk erosion, where the scaffold maintains its external dimensions but undergoes nonlinear internal degradation. Careful selection of the polymer is therefore essential, as the degradation rate must be synchronized with the bone regeneration process [30]. In the case of largescale bone defects, scaffolds function as temporary microenvironments that support cell migration and facilitate callus formation.

**Architecture and bioactivity:** An ideal scaffold should exhibit high porosity, adequate mechanical strength, and appropriate bioactivity to effectively support tissue regeneration.

A diverse range of materials has been employed for scaffold fabrication, including natural polymers, synthetic polymers, bioceramics, and bioactive glasses, which are primarily selected based on their osteoconductive properties and capacity to support cellular function (Table 1). Among synthetic polymers, materials such as PLA, PCL, and PLGA are widely used due to their structural versatility and tunable degradation behavior. Nevertheless, the intrinsic biological inertness and limited bioactivity of these polymers often necessitate their modification through the development of composite and nanocomposite scaffolds. The incorporation of bioactive nanoparticles, including nanohydroxyapatite (nHA), graphene oxide (GO), and carbon nanotubes, has been shown to significantly enhance mechanical performance, bioactivity, and osteogenic differentiation [31, 32]. For example, PLA/GO nanocomposites fabricated using 3D printing techniques demonstrated superior cell proliferation and mineralization compared to pure PLA scaffolds [33]. Similarly, electrospun PCL/nHA fibers exhibited improved cytocompatibility and osteogenic potential, as evidenced by the upregulation of key bone-related markers [34]. In addition, freeze-dried PLGA/HA scaffolds provided a more favorable microenvironment for osteoblast differentiation than their electrospun counterparts, underscoring the critical influence of fabrication methods on scaffold performance [35]. Furthermore, innovative hybrid scaffolds that combine synthetic polymers such as PCL with natural polymers including gelatin and chitosan have been developed to integrate the mechanical robustness of synthetic materials with the enhanced bioactivity of natural polymers, thereby creating a more biomimetic and regenerative extracellular environment [36].

## Bone tissue engineering challenges and future perspectives

Despite advances, key challenges remain in BTE, which include establishing stable vascular networks, achieving mechanical properties comparable to native bone, ensuring complete host integration, optimizing cell sources and safety, and achieving controlled delivery of bioactive factors [37]. A specific and significant challenge with widely used synthetic polyesters such as PLA and PLGA is the release of acidic by-products (e.g. lactic and glycolic acid) during degradation. The accumulation of these by-products can create a localized acidic microenvironment, potentially leading to an inflammatory foreign body response and adversely affecting the survival and function of neighboring cells. Furthermore, achieving a degradation rate that perfectly matches the pace of new bone formation remains a complex endeavor [7].

Future research should focus on advanced biomaterials, the use of bioreactors, pre-vascularized constructs, and personalized strategies to improve clinical outcomes and scalability for widespread application [38]. A key future research domain is the rational design of advanced nanocomposite and hybrid scaffolds. Recent studies have argued that no single material meets all tissue replacement parameters. A composite scaffold combining synthetic and natural polymers can offer a tissue substitute that meets all therapeutic standards. Future scaffold design should involve creating “smart” composites that not only provide structural support but also actively orchestrate regeneration through controlled release of ions (e.g.  $\text{Sr}^{2+}$ ,  $\text{Mg}^{2+}$ ), drugs, and growth factors, while mitigating adverse immune responses [6, 39].

## Conclusion

BTE presents a promising alternative to conventional grafting methods, integrating stem cells, scaffolds, and growth factors to repair complex bone defects. The versatility of synthetic polymers, especially when enhanced as nanocomposites with bioactive fillers, provides a powerful platform for creating tailored scaffolds. However, overcoming challenges related to the inflammatory potential of degradation products, achieving optimal vascularization, and ensuring perfect mechanical and functional integration with the host bone remains critical for successful clinical translation. Future research focusing on these areas, particularly on the development of intelligent, multi-functional composite systems, are essential to advance the field from the bench to the bedside.

## Ethical Considerations

### Compliance with ethical guidelines

This article is a review study and does not involve any human participants, patient data, or animal experimentation.

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### Authors' contributions

Conceptualization: Negar Karimi Hajishoreh and Reza Heidari; Investigation: Negar Karimi Hajishoreh; Writing the original draft: Reza Heidari, Parisa Abedi Elkhichi, and Razieh Moosavi; Review, editing, and final approval: All authors.

### Conflict of interest

The authors declared no conflict of interest.

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## References

- [1] Šromová V, D Sobola, P Kaspar, A brief review of bone cell function and importance. *Cells*. 2023. 12(21). [DOI:10.3390/cells12212576] [PMID] [PMCID]
- [2] Dimitriou R, Jones E, McGonagle D, Giannoudis PV. Bone regeneration: Current concepts and future directions. *BMC Med*. 2011; 9:66. [DOI:10.1186/1741-7015-9-66] [PMID]
- [3] Santoro A, Voto A, Fortino L, Guida R, Laudisio C, Cillo M, D'Ursi AM. Bone defect treatment in regenerative medicine: exploring natural and synthetic bone substitutes. *International Journal of Molecular Sciences*. 2025; 26(7):3085. [DOI:10.3390/ijms26073085] [PMID] [PMCID]
- [4] Ruggiero C, Baroni M, Xenos D, Parretti L, Macchione IG, Bubba V, et al. Dementia, osteoporosis and fragility fractures: Intricate epidemiological relationships, plausible biological connections, and twisted clinical practices. *Ageing Research Reviews*. 2024; 93:102130. [DOI:10.1016/j.arr.2023.102130] [PMID]
- [5] Shahrezaee, M, Heidari R. Cartilage repair in 2025: Hope, hype, or horizon?. *Archives of Bone and Joint Surgery*. 2025; 13(9):532. [Link]
- [6] Verrier S, Alini M, Alsberg E, Buchman SR, Kelly D, Laschke MW, et al. Tissue engineering and regenerative approaches to improving the healing of large bone defects. *European Orthopaedic Research Society*. 2016; 32:87-110. [DOI:10.22203/eCM.v032a06] [PMID]
- [7] Hajishoreh NK, Mellatyar H, Kaamyabi S, Abasalizadeh F, Akbarzadeh A. Preparation and evaluation of polyurethane-based nanofibers for controlled release of simvastatin for the treatment of cardiac disorders. *BioNanoScience*. 2024; 14(2):1687-95. [DOI:10.1007/s12668-024-01380-6]
- [8] Javid-Naderi MJ, Behravan J, Karimi-Hajishohreh N, Toosi S. Synthetic polymers as bone engineering scaffold. *Polymers for Advanced Technologies*. 2023; 34(7):2083-96. [DOI:10.1002/polym.6046]
- [9] Subash A, Basanth A, Kandasubramanian B. Biodegradable polyphosphazene-hydroxyapatite composites for bone tissue engineering. *International Journal of Polymeric Materials and Polymeric Biomaterials*. 2023; 72(14):1093-111. [DOI:10.1080/00914037.2022.2082426]
- [10] Rostami N, Faridghiasi F, Ghebleh A, Noei H, Samadzadeh M, Gomari MM, et al. Design, synthesis, and comparison of PLA-PEG-PLA and PEG-PLA-PEG copolymers for curcumin delivery to cancer cells. *Polymers (Basel)*. 2023; 15(14):3133. [DOI:10.3390/polym15143133] [PMID] [PMCID]
- [11] Turnbull G, Clarke J, Picard F, Riches P, Jia L, Han F, et al. 3D bioactive composite scaffolds for bone tissue engineering. *Bioactive Materials*. 2017; 3(3):278-314. [DOI:10.1016/j.bioact-mat.2017.10.001] [PMID] [PMCID]
- [12] Karimi Hajishoreh N, Dadashpour M, Akbarzadeh A. Preparation and in vitro evaluation of biological agents based on Zinc-laponite- curcumin incorporated in alginate hydrogel. *Journal of Biological Engineering*. 2023. 17(1):73. [DOI:10.1186/s13036-023-00391-3] [PMID] [PMCID]
- [13] Lee SS, Du X, Kim I. Scaffolds for bone-tissue engineering. *Matter*. 2022; 5(9):2722-2759. [DOI:10.1016/j.matt.2022.06.003]
- [14] Miller SC, de Saint-Georges L, Bowman BM, Jee WS. Bone lining cells: structure and function. *Scanning Microscopy*. 1989; 3(3):27. [PMID]
- [15] Bonewald LF. The amazing osteocyte. *Journal of Bone and Mineral Research*. 2011; 26(2):229-38. [DOI:10.1002/jbmr.320] [PMID] [PMCID]
- [16] Rostami N, Gomari MM, Abdouss M, Moeinzadeh A, Choupani E, Davarnejad R, et al. Synthesis and characterization of folic acid-functionalized DPLA-co-PEG nanomicelles for the targeted delivery of letrozole. *ACS Applied Bio Materials*. 2023; 6(5):1806-15. [DOI:10.1021/acsabm.3c00041] [PMID] [PMCID]
- [17] Capulli M, Paone R, Rucci N. Osteoblast and osteocyte: games without frontiers. *Archives of Biochemistry and Biophysics*. 2014; 561:3-12. [DOI:10.1016/j.abb.2014.05.003] [PMID]

- [18] Florencio-Silva R, Sasso GR, Sasso-Cerri E, Simões MJ, Cerri PS. Biology of bone tissue: structure, function, and factors that influence bone cells. *Journal of biomedicine and biotechnology*. 2015; 2015:421746. [DOI:10.1155/2015/421746] [PMID] [PMCID]
- [19] Meirelles Lda S, Fontes AM, Covas DT, Caplan AI. Mechanisms involved in the therapeutic properties of mesenchymal stem cells. *Cytokine and Growth Factor Reviews*. 2009; 20(5-6):419-27. [DOI:10.1016/j.cytogfr.2009.10.002] [PMID]
- [20] Chen JY, Mou XZ, Du XC, Xiang C. Comparative analysis of biological characteristics of adult mesenchymal stem cells with different tissue origins. *Asian Pacific Journal of Tropical Medicine*. 2015; 8(9):739-46. [DOI:10.1016/j.apjtm.2015.07.022] [PMID]
- [21] Quarto R, Mastrogiacomo M, Cancedda R, Kutepov SM, Mukhachev V, Lavroukov A, et al. Repair of large bone defects with the use of autologous bone marrow stromal cells. *New England Journal of Medicine*. 2001. 344(5): 385-6. [DOI:10.1056/NEJM200102013440516] [PMID]
- [22] Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy Position Statement. *Cytotherapy*. 2006; 8(4):315-7. [DOI:10.1080/14653240600855905] [PMID]
- [23] Colnot C. Skeletal cell fate decisions within periosteum and bone marrow during bone regeneration. *Journal of Bone and Mineral Research*. 2009. 24(2):274-82. [DOI:10.1359/jbmr.081003] [PMID]
- [24] Almubarak S, Nethercott H, Freeberg M, Beaudon C, Jha A, Jackson W, et al. Tissue engineering strategies for promoting vascularized bone regeneration. *Bone*. 2016; 83:197-209. [DOI:10.1016/j.bone.2015.11.011] [PMID] [PMCID]
- [25] Fischer KM, Morgan KY, Hearon K, Sklaviadis D, Tochka ZL, Fenton OS, et al. Poly(limonene thioether) scaffold for tissue engineering. *Advanced Healthcare Materials*. 2016. 5(7):813-21. [DOI:10.1002/adhm.201500892] [PMID] [PMCID]
- [26] Velasco MA, Narváez-Tovar CA, Garzón-Alvarado DA. Design, materials, and mechanobiology of biodegradable scaffolds for bone tissue engineering. *BioMed Research International*. 2015; 2015:729076. [DOI:10.1155/2015/729076] [PMID] [PMCID]
- [27] Das A, Botchwey E. Evaluation of angiogenesis and osteogenesis. *Tissue engineering. Part B, Reviews*. 2011; 17(6):403-14. [DOI:10.1089/ten.teb.2011.0190] [PMID]
- [28] Uselli FG, Grassi M, Maccario C, Viganò M, Lanfranchi L, Alfieri Montrasio U, et al. Intratendinous adipose-derived stromal vascular fraction (SVF) injection provides a safe, efficacious treatment for Achilles tendinopathy: Results of a randomized controlled clinical trial at a 6-month follow-up. *Knee surgery, Sports Traumatology, Arthroscopy: Official Journal of the ESSKA*. 2018; 26(7):2000-10. [DOI:10.1007/s00167-017-4479-9] [PMID]
- [29] Mizuno H, Tobita M, Ogawa R, Orbay H, Fujimura J, Ono S, et al. Adipose-derived stem cells in regenerative medicine, in principles of gender-specific medicine. In: Marianne J. Legato, editor. *Principles of gender-specific medicine*. Amsterdam: Elsevier. 2017. [DOI:10.1016/B978-0-12-803506-1.00050-4]
- [30] Fan H, Zeng X, Wang X, Zhu R, Pei G. Efficacy of prevascularization for segmental bone defect repair using  $\beta$ -tricalcium phosphate scaffold in rhesus monkey. *Biomaterials*. 2014; 35(26):7407-15. [DOI:10.1016/j.biomaterials.2014.05.035] [PMID]
- [31] Tang D, Tare RS, Yang LY, Williams DF, Ou KL, Oreffo RO. Biofabrication of bone tissue: Approaches, challenges and translation for bone regeneration. *Biomaterials*. 2016; 83:363-82. [DOI:10.1016/j.biomaterials.2016.01.024] [PMID]
- [32] Lyons F, Partap S, O'Brien FJ. Part 1: scaffolds and surfaces. *Technology and health Care*. 2008; 16(4):305-17. [DOI:10.3233/THC-2008-16409] [PMID]
- [33] Mondal S, Nguyen TP, Hoang G, Manivasagan P, Kim MH, Nam SY, et al. Hydroxyapatite nano bioceramics optimized 3D printed poly lactic acid scaffold for bone tissue engineering application. *Ceramics International*. 2020; 46(3):3443-55. [DOI:10.1016/j.ceramint.2019.10.057]
- [34] Chen X, Gao C, Jiang J, Wu Y, Zhu P, Chen G. 3D printed porous PLA/nHA composite scaffolds with enhanced osteogenesis and osteoconductivity in vivo for bone regeneration. *Biomedical Materials*. 2019; 14(6):065003. [DOI:10.1088/1748-605X/ab388d] [PMID]
- [35] Alam F, Varadarajan KM, Kumar S. 3D printed polylactic acid nanocomposite scaffolds for tissue engineering applications. *Polymer Testing*. 2020; 81:106203. [DOI:10.1016/j.polymertesting.2019.106203]
- [36] Pušnik Črešnar K, Aulova A, Bikiaris DN, Lambropoulou D, Kuzmič K, Fras Zemljic L. Incorporation of metal-based nanoadditives into the PLA matrix: Effect of surface properties on antibacterial activity and mechanical performance of PLA nanoadditive films. *Molecules*. 2021; 26(14):4161. [DOI:10.3390/molecules26144161] [PMID] [PMCID]
- [37] Guo W, Xu L, Feng P, Gu Y, Shuai C. In-situ growth of silica nano-protrusions on halloysite nanotubes for interfacial reinforcement in polymer/halloysite scaffolds. *Applied Surface Science*. 2020; 513:145772. [DOI:10.1016/j.apsusc.2020.145772]
- [38] Gao X, Song J, Ji P, Zhang X, Li X, Xu X, et al. Polydopamine-templated hydroxyapatite reinforced polycaprolactone composite nanofibers with enhanced cytocompatibility and osteogenesis for bone tissue engineering. *ACS Applied Materials & Interfaces*. 2016; 8(5):3499-515. [DOI:10.1021/acsami.5b12413] [PMID]
- [39] Cândido Lima Verde TF, Viana MR, Furtado ASA, de Castro Brito G, de Sousa Cunha MH, Filgueiras LA, et al. Three-dimensional printed hybrid scaffolds with layered polycaprolactone/nanosized smectic clay nanocomposite and chitosan/collagen/demineralized bone powder hydrogels targeting osteochondral tissue engineering. *Journal of functional biomaterials*. 2025; 16(12):441. [DOI:10.3390/jfb16120441] [PMID] [PMCID]