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Regenerative medicine in orthopedics: advances in biomaterials and cell therapies

Regenerative medicine in orthopedics: advances in biomaterials and cell therapies

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ABSTRACT

This article presents a literature review on advances in regenerative medicine applied to orthopedics, focusing on the use of biomaterials, cell therapies, and nanotechnology for bone and cartilage regeneration. Studies published between 2012 and 2022 were analyzed, highlighting the application of *scaffolds,* hydrogels, polymers, ceramics, and cell therapies such as mesenchymal and induced pluripotent stem cells. The results point to a promising future, but with challenges related to standardization, safety, and regulation.

Keywords: Regenerative medicine. Biomaterials. Cell therapies. Orthopedics. Nanotechnology.

ABSTRACT

This article presents a literature review on the advances of regenerative medicine applied to orthopedics, focusing on the use of biomaterials, cell therapies, and nanotechnology for bone and cartilage regeneration. Studies published between 2012 and 2022 were analyzed,
highlighting the application of scaffolds, hydrogels, polymers, ceramics, and cell therapies, including mesenchymal stem cells and induced pluripotent stem cells. The results indicate a promising future, but with challenges related to standardization, safety, and regulation.
Keywords: Regenerative medicine. Biomaterials. Cell therapies. Orthopedics. Nanotechnology.

1 INTRODUCTION

Regenerative medicine seeks to restore damaged tissues functionally and structurally, activating natural biological processes, unlike traditional repair approaches or replacement. This strategy is promising for musculoskeletal and joint diseases, due to its significant socioeconomic impact.

- Role of Biomaterials: Natural or synthetic materials act as scaffolds three-dimensional *(scaffolds),* mimicking the extracellular matrix (ECM) and favoring adhesion, cell proliferation and differentiation. Associated with growth factors or stem cells, modulate the inflammatory response and accelerate regeneration.

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- Challenges in Orthopedics: Bone and cartilage regeneration faces limitations. Cartilage joint is avascular and has limited regeneration capacity. Bone tissue has low regeneration capacity in critical defects or in patients with comorbidities (e.g.: diabetes, osteoporosis).
- Cellular Therapies: Mesenchymal stem cells (MSCs) are ideal candidates, obtained from bone marrow, adipose tissue, or other adult sources. They have properties immunomodulatory, anti-inflammatory and multipotent differentiation. The application of MSCs, alone or with biomaterials/bioactive factors, has promoted functional repair in injuries joints, with improved pain and mobility.

2. MATERIAL AND METHOD

This work is characterized as a narrative bibliographic review, whose objective is to analyze recent scientific production in the field of regenerative medicine applied to orthopedics, focusing on evaluating advances in biomaterials, cell therapies and nanotechnology for bone and cartilage regeneration. The methodology employed aims to provide a broad overview and updated on the topic, being fundamental for the theoretical-scientific basis of the discussion presented in Section 3.

Research and data collection were carried out in high-impact electronic databases and relevance in the biomedical and tissue engineering fields. The databases consulted were: PubMed, Scopus, Web of Science, and ScienceDirect. This selection ensures comprehensiveness. global body of published knowledge, focusing on peer-reviewed literature.

To maximize the relevance and timeliness of the findings, the search was restricted to published articles in the period between January 2012 and November 2022. This ten-year interval was chosen to delimit the most recent and consolidated innovations that have driven the field of regenerative medicine in the last decade.

The descriptors (keywords) used for searching on electronic platforms were strategically combined, covering the main pillars of the study:

- Thematic Pillars: "Regenerative Medicine", "Orthopedics", "Tissue Engineering".
- Technological Pillars: "Biomaterials", "Cell Therapy", "Nanotechnology", "Scaffolds".

The combination of these terms aimed to refine the results and focus strictly on the application orthopedic and musculoskeletal.

Strict inclusion criteria were applied to ensure the quality of the analysis:

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1. Peer-reviewed articles, available in full text and free access free (open access).
2. Accepted languages: Portuguese or English.
3. Mandatory thematic content: Focus on regenerative medicine in the system musculoskeletal (bone, cartilage, tendon or ligament), cell therapies, biomaterials or nanotechnology.

Exclusion criteria were defined to filter out non-essential or less rigorous materials scientific:

1. Duplicate articles or those that did not present the full text (abstracts of congress or editorials).
2. Opinion pieces, essays, or letters to the editor not based on original research.
3. Studies carried out exclusively on animal models, without any discussion or implication for clinical translation or translational approach in humans, except when the animal model represented a crucial technological advance for the biomaterial development.

3. RESULTS AND DISCUSSION

Advanced Biomaterials and Nanotechnology

Three-dimensional structures *(Scaffolds)* of hydrogels, porous foams, fibers and meshes have been highlighted in promoting cell adhesion, migration and differentiation, being essential for the new bone and cartilage formation. The choice of biomaterial is critical and involves the use of ceramic and polymeric materials. Ceramic materials, such as Hydroxyapatite (HA) and calcium phosphate (CaP), are highly biocompatible due to their similarity to the phase bone mineral. HA, in particular, promotes osteoblast adhesion, while ÿ-calcium triphosphate (ÿ-TCP) is notable for its controlled reabsorption by the body. However, the limited mechanical strength of these pure materials often requires the development of composites.

Biodegradable polymers also play a crucial role. Synthetic polymers, such as PLA, PGA and PLGA, allow a controlled degradation rate, essential for the new tissue has time to form. In contrast, natural polymers such as collagen, alginate and chitosan offer high biocompatibility and bioactivity, but may have weaker mechanical properties. The solution often lies in combining these

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composite materials, which provide the mechanical strength of ceramics and the flexibility and bioactivity of polymers.

To enhance regeneration, biomaterials are often combined with growth factors. Bone Morphogenetic Proteins (BMPs), notably BMP-2 and BMP-7, are central to osteogenesis, inducing the differentiation of Mesenchymal Stem Cells into osteoblasts. Other important factors include Vascular Endothelial Growth Factor (VEGF), which is vital for angiogenesis and vascularization of new tissue, and Growth Factor Platelet-Derived Growth Factor (PDGF), which aids in proliferation and recruitment cellular. The application of these factors is optimized by controlled release systems, using microspheres, nanocapsules or functionalized *scaffolds* , which overcomes the challenges of rapid degradation and direct application.

Nanotechnology represents a significant advance, allowing the manipulation of biomaterials in nanometer scale. This scale provides greater surface area and promotes signaling more effective biochemistry with cells. Nanoparticles are used for delivery controlled use of drugs, osteoinductive factors and even antibiotics, such as nanoparticles of silver in titanium implants, which demonstrated antimicrobial effect and gene stimulation osteogenic (Zhu et al., 2019). Furthermore, nanofibers, produced by electrospinning, mimic the extracellular matrix of bone tissue more faithfully, which favors cell proliferation and differentiation. Surface engineering of metal implants and ceramics to increase nanometric roughness have also been developed to improve osseointegration.

Cell Therapies and Tissue Engineering

Cartilage regeneration remains a challenge due to its avascular nature and limited repair capacity. In this context, hydrogels have shown promise, as are capable of mimicking the extracellular matrix of hyaline cartilage. There are hydrogels natural ingredients, such as hyaluronic acid, alginate and chitosan, which offer high biocompatibility, hyaluronic acid is known to induce chondrogenic differentiation of MSCs. In In parallel, synthetic hydrogels such as PEG, PVA and PVCL are used, which allow a strict control over their mechanical properties. For joint repair, *scaffolds* three-dimensional structures must have interconnected porosity, permeability and resistance mechanics compatible with joint loads. 3D bioprinting technology is a

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important boundary, allowing the construction of *scaffolds* with zonal gradients that attempt mimic the complex architecture of natural cartilage (Levato et al., 2017).

In the field of cell therapies, Mesenchymal Stem Cells (MSCs) continue to be the most used, due to their multipotency and immunomodulatory functions. Their main mechanism of action is paracrine, secreting exosomes and trophic factors essential for the repair. Other approaches include Autologous Chondrocyte Therapy (ACI), which involves the collection and reimplantation of the patient's own chondrocytes. However, this technique often results in the formation of fibrocartilage, a tissue of inferior quality to hyaline cartilage.

An unlimited source of cells are Induced Pluripotent Stem Cells (iPSCs), which can be differentiated into functional chondrocytes (Suchorska et al., 2017), although the risk of tumor formation and high costs are significant challenges (Augustyniak et al., 2015).

In vitro tissue engineering seeks to integrate biomaterials, stem cells and bioactive factors for functional reconstruction outside the organism. This involves growing cells on *scaffolds* porous and hydrogels. Advanced systems, such as bioreactors, provide physical stimuli and continuous biochemical (compression, flow) that are crucial for functional maturation, especially in joint tissues. New biomaterials are being developed as smart *scaffolds ,* which respond to external stimuli, such as pH or temperature, to release bioactive factors in a precise and controlled manner.

Clinical Applications and Challenges

Regenerative medicine is applied in several areas of orthopedics. In bone regeneration, it is used for the treatment of critical defects, extensive fractures and consolidation failures. The use of osteoconductive and osteoinductive biomaterials is combined with stem cells and BMPs in procedures such as spinal fusion. In the treatment of osteoporosis, the combination of biomaterials with anabolic factors and MSCs aims to increase bone mineral density and prevent fractures. In cartilage repair, combined techniques of hydrogels, *scaffolds* bioactives and stem cells have shown promising results in functional reconstruction.

In sports medicine, *scaffolds,* MSCs and growth factors (PRP) are used to accelerate recovery from ligament, meniscal and tendinopathy injuries.

Despite advances, the field still faces significant challenges. Regulation by agencies such as ANVISA, FDA and EMA require rigorous proof of efficacy, safety and reproducibility. The scalability and cost of industrial production of cell therapies and biomaterials are barriers that technologies such as 3D bioprinting and bioreactors seek to overcome

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overcome. There is a growing interest in personalized medicine, in which therapies are tailored to the genetic characteristics of each patient, possibly using autologous iPSCs. The The future points to the integration of these technologies with gene and immunomodulatory therapies to increase cellular regenerative capacity and graft acceptance.

FINAL CONSIDERATIONS

Regenerative medicine is a promising field, driven by advances in biomaterials bioactives, cell therapies, and tissue engineering. Technologies such as 3D bioprinting, functionalized *scaffolds* and the use of MSCs and iPSCs have created innovative solutions for the repair of bone, cartilage, tendons, and ligaments. The development of biomaterials biomimetic and intelligent favors functional regeneration, mimicking the native ECM and acting in synergy with growth factors and biomechanical stimuli.

Despite encouraging clinical results in osteochondral lesions, spinal fusions and osteoporosis, large-scale clinical translation still faces obstacles:

- Strict regulation by ANVISA, FDA and EMA.
- Cost barriers and industrial scaling.
- Need for greater standardization and personalization of treatments.

The future involves integration with gene and immunomodulatory therapies. Collaboration interdisciplinary approach between materials engineering, cell biology and pharmacology will be crucial for consolidate these therapies as routine clinical practice and transform the paradigm of care in health.

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