Integrating cellular therapies, biomaterials, and mechanical cues in cartilage tissue engineering: A systematic review

Amira Raudhah Abdullah[1], Nurul Atiqah Zulazmi[2], Nur Nabilah Abu Bakar[1], Nadia Mohd Effendy[3], Hazim Arief[1]

[1]Department of Medical Science 1, Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia, 71800 Bandar Baru Nilai, Negeri Sembilan, Malaysia, [2]Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, 47500 Subang Jaya, Selangor, Malaysia, [3]Department of Medical Science II, Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia, 71800 Bandar Baru Nilai, Negeri Sembilan, Malaysia

ABSTRACT

Introduction: Articular cartilage injury poses a major clinical challenge due to its limited intrinsic healing capacity. Recent advances in tissue engineering have introduced various regenerative strategies aimed at restoring cartilage function. This systematic review synthesizes findings from studies employing a combination of cellular therapies, biomaterial scaffolds, biochemical stimuli, mechanical conditioning, and translational applications to enhance cartilage repair outcomes. **Materials and Methods:** This systematic review adhered to the PRISMA guidelines. A comprehensive literature search was carried out across PubMed, Scopus, and Web of Science, targeting peer-reviewed publications from 2014 to 2024. Eligible studies included original research focused on cartilage tissue engineering strategies involving therapeutic cells, biomaterials, biochemical or mechanical cues, and preclinical or clinical applications. Data extraction and classification were independently conducted by multiple reviewers. The selected studies were then organized into five primary categories: therapeutic cell sources, biomaterial and scaffold systems, growth factors and biochemical stimuli, biophysical and mechanical conditioning, and clinical/preclinical translation. **Results:** Among the cellular strategies, epiphyseal chondroprogenitor cells (ECPs), mesenchymal stromal cells (MSCs) and human mesenchymal stem cells (hMSCs) have been the most widely explored. ECPs exhibit strong chondrogenic differentiation potential. MSCs derived from bone marrow, adipose tissue, and synovium promote regeneration through both differentiation and paracrine effects. hMSCs are notable for their accessibility and ability to form hyaline-like cartilage. However, limited cell retention and inconsistent integration remain key challenges. Biomaterial scaffolds provide structural support and mimic the native extracellular matrix (ECM) environment. Hydrogels, 3D-printed scaffolds, and ECM-derived matrices have been used to facilitate chondrogenesis and enhance mechanical properties. Innovations in material design have improved biocompatibility, bioactivity, and degradation profiles. Growth factors such as TGF-β, IGF-I, and novel peptides like TP8 have shown efficacy in enhancing chondrocyte activity and ECM synthesis. Delivery systems such as growth factor-loaded scaffolds or controlled-release platforms are being developed to optimize spatial and temporal bioavailability. Mechanical and biophysical stimulation including dynamic loading and hydrostatic pressure has demonstrated the ability to promote chondrogenic gene expression and improve tissue functionality in vitro. These approaches replicate native joint mechanics and support matrix maturation. Translational studies, including animal models and early-phase clinical trials, report encouraging outcomes for combinations of cell-based therapies and scaffold-guided regeneration. Cartilage tissue engineering has evolved into a multimodal field where the integration of cellular therapies, advanced biomaterials, biochemical cues, and mechanical stimuli is essential for achieving functional regeneration. **Conclusion:** The findings of this review underscore the potential of combining these strategies to overcome current limitations and move closer to clinically viable, patient-specific treatments for cartilage repair.

Keywords: Cartilage regeneration, tissue engineering, mesenchymal stem cells (MSCs), biomaterial scaffolds, Chondrogenesis