DOI: https://doi.org/10.54393/pbmj.v8i1.1186

PAKISTAN BIOMEDICAL JOURNAL
https://www.pakistanbmj.com/journal/index.php/pbmj/index
ISSN (P): 2709-2798, (E): 2709-278X
Volume 8, Issue 01 (January 2025)

Review Article

OPEN ACCESS

# Emerging Trends in Bioprinting for Cartilage Regeneration: Materials, Techniques and Challenges

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## ARTICLE INFO

***Keywords:***
Cartilage Regeneration, Bioprinting, Biomaterial, Emerging Technologies

***How to Cite:***
Jeraj, A. R., & Zameer, Z. (2025). Emerging Trends in Bioprinting for Cartilage Regeneration: Materials, Techniques and Challenges: Bioprinting for Cartilage Regeneration. Pakistan BioMedical Journal, 8(1), 02-10. https://doi.org/10.54393/pbmj.v8i1.1186

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Received date: 23rd November, 2024
Revised date: 14th January, 2025
Acceptance date: 19th January, 2025
Published date: 31st January, 2025

## ABSTRACT

Cartilage repair is a major clinical problem because of the poor intrinsic healing capacity of cartilage coupled with the limitations of conventional therapies and synthetic substitutes. These challenges have been pursued by bioprinting, which is a technique that can generate scaffolds that mimic native cartilage. This review aims to discuss current and future development of bioprinting for cartilage tissue regeneration with a focus on the most common biomaterials such as alginate, gelatin, and collagen, along with the emerging materials such as smart hydrogels, nanomaterials, and bioactive molecules. The review also outlines other emerging bioprinting technologies like high resolution, 4D, hybrid, and microfluidic assisted bioprinting that are believed to improve the mechanical properties, biological integration and vascularization of the constructs produced through bioprinting. Some of the major problems which are still unresolved are those of scale up, biocompatibility and immune response that hinders the clinical application of bioprinted cartilage. The review further concludes that owing to some regulatory issues along with a lack of an ideal practice the challenges in bioprinting for cartilage regeneration still persists. Some of the future prospects that have been highlighted include the use of patient derived cells, artificial intelligence for process optimization and the development of smart and adaptive biomaterials. Mitigating these challenged and integrated these advanced technologies will enable the clinical translation of bioprinted cartilage to develop personalized, functional, and durable tissue constructs.

## INTRODUCTION

Cartilage damage, whether due to osteoarthritis, trauma, or other degenerative conditions, represents a significant clinical challenge affecting millions of people worldwide. Due to the low capacity for tissue regeneration, cartilage damage can result in progressive joint degeneration, pain, and functional impairment. Current cartilage repair approaches such as autografts, allografts and synthetic implants have been proven to have a number of shortcomings including donor site morbidity, immune response and poor integration with host tissue Galarraga *et al.*, in 2019 [1]. Bioprinting has been identified as a rapidly developing field in tissue engineering and regenerative medicine and has special potential for cartilage tissue engineering. Figure 1 showed a general outline of bioprinting technique for cartilage regeneration. In this context, currently used technique of 3D printing enables the sequential layering of cells, biomaterials and growth factors in a controlled manner, which recreates the architecture and composition of native cartilage tissue. The fact that bioprinting allows for higher resolution and repeatability when generating constructs tailored to individual patients' needs makes it a valuable approach to improving upon the current methods of cartilage repair Perera *et al.*, in 2021 [2]. Although much progress has been made in the bioprinting of cartilage tissue engineering, there are several issues that need to be addressed. Recent studies have focused on different categories of bioprinting such as extrusion bioprinting, inkjet bioprinting and laser bioprinting, and also bioinks that have naturally occurring or synthetic polymers, hydrogels and cell containing matrices. However, there are certain disadvantages such as poor mechanical properties and weak tissue integration,

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which limit the application of the designed scaffold into clinical applications Liu *et al.*, in 2023 [3]. Furthermore, there is a lack of extensive clinical studies that would prove the efficiency of cartilage constructs developed through means of bioprinting Perera *et al.*, in 2021 [2]. Thus, the field calls for enhanced materials and techniques that would not only afford the purpose and longevity, but also blend with the native tissue. However, scalability, standardization and regulations continue to be other challenges that need to be overcome in order to transfer bioprinted cartilage constructs from the lab to clinical application Wei *et al.*, in 2021 [4]. This paper will present a comprehensive literature review on bioprinting of cartilage tissue with focus on the current trends, new materials and technologies. The review is novel in that it considers the field from a materials science and bioengineering perspective, as well as its clinical relevance. Potential strategies will be identified in biomaterial design, cell sourcing, and fabrication techniques that seem to have the possibility of solving present challenges. Furthermore, new regulatory trends and standardization processes will be addressed that are necessary to bring bio-printed cartilage constructs closer to clinical manifestations. The study concludes that the findings of this critical analysis will encourage additional research and development in the field of cartilage bioprinting, which will have a positive impact on the lives of patients with cartilage-related diseases.

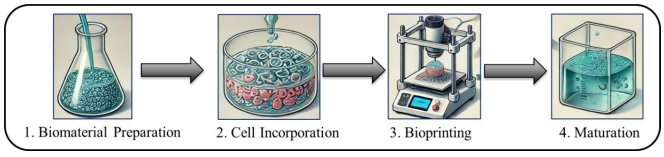


**Figure 1:** A General Overview of the Bioprinting Process for Cartilage Tissue Engineering

## Traditional Biomaterials in Cartilage Bioprinting

Traditional biomaterials have played a crucial role in cartilage bioprinting for an extended period. They are commonly used in the fabrication of scaffolds that replicate the bio-morpohological and mechanical characteristics of natural cartilage Łabowska *et al.*, in 2021 [5]. Some of the conventional biomaterials utilized in this are hydrogels which comprise alginate, collagen and gelatin. All these materials have properties and certain drawbacks Łabowska *et al.*, in 2021; Ren *et al.*, in 2022; Serafin *et al.*, in 2023 [5-7].

### Alginate

Alginate is a well-regarded polymer derived from brown seaweed that is compatible with living tissue and fully biodegradable. Consequently, it has several disadvantages in particular its weak mechanical strength, which diminishes its applicability in load-bearing situations such as cartilage. There are no specific binding sites for cells on alginate, which complicates the creation of 3D cell culture Łabowska *et al.*, in 2021 [5]. These limitations can be however overcome by incorporating alginate with other materials to enhance its mechanical properties and ability to adhere to cells Wierzbicka *et al.*, 2024 [8].

### Gelatin

Gelatin is produced from collagen and is much preferred for its outstanding biocompatibility and ability to aid cell attachment. Even though gelatins' mechanical properties are good, their mechanical strength is usually adequate for structural applications without the need for reinforcement from other materials Ren *et al.*, 2022 [6]. However, one of the additional limitations is a quick degradation rate. This requires the modification of its structure, or the combination with other polymers to achieve the intended properties Andreazza *et al.*, in 2023; Serafin *et al.*, in 2023 [7, 9].

### Collagen

Cartilage is a major structural protein found in collagen. It presents certain difficulties; as collagen hydrogels generally do not have the mechanical strength needed for effective use in cartilage engineering. This constraint requires that additional materials be integrated to improve stiffness and durability Jiao *et al.*, in 2023 [10]. Also, the cost of producing collagen is typically high relative to other biomaterials, which may restrict its broad utilization in assorted bioprinting processes Serafin *et al.*, in 2023 [7].

## Emerging Biomaterials with Enhanced Functionalities

Although traditional biomaterials such as alginate, gelatin, and collagen are essential for bioprinting cartilage, their deficiencies make it necessary to create composite hydrogels. The intent behind these composites is to exploit the strengths of each material while reducing their weaknesses,thereby accelerating the field of tissue engineering.

### Composite Hydrogels

Scientists have recently developed a novel class of composite hydrogels made of alginate, gelatin, and collagen. For example, the improvement of mechanical properties in collagen-alginate composites also provides cell-binding sites from collagen, which contributes to better cell viability and proliferation in 3D cultures Łabowska *et al.*, in 2021 [5]. Furthermore, the aldehyde derivative of alginate gel and gelatin hydrogel facilitate improved cell adhesion and better control of mechanical characteristics, which are beneficial for tissue engineering applications Łabowska *et al.*, in 2021; Serafin *et al.*, in 2023 [5, 7].

### Novel Hybrid Biomaterials

New bio-hybrids including PEG-collagen hydrogels for bioprinting cartilage tissues and tissue engineering are being developed since they possess improved mechanical characteristics and biological activity. The hybrids enhance the properties of the combination material that is mechanical, thermal, electrical, optical, and biological in

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nature. Among the reported examples are PEG-collagen hydrogels for both corneal and cardiac tissue engineering, double network hydrogels that demonstrate enhanced mechanical properties, and collagen-chitosan composites for corneal tissue engineering. The use of collagen-mimetic peptide-PEG hybrids is to mimic collagen bioactivity in synthetic scaffolds. These hybrid materials have been noted to show improved mechanical properties, such as strength, elasticity, and cell responses essential for tissue engineering endeavors Rafat *et al.*, in 2008; Grover *et al.*, in 2013 [11, 12].

**Smart Hydrogels**

Advanced biomaterials known as smart hydrogels change according to their environmental conditions, such as pH, temperature, and light. Such characteristics makes smart hydrogels highly suitable for cartilage bioprinting and tissue engineering El-Husseiny *et al.*, in 2022 [13]. Temperature sensitive hydrogels like PNIPAA can encapsulate cells and deliver growth factors while pH sensitive hydrogels adjust the rates of swelling in response to changes in pH, which is useful in drug delivery. Photodegradable hydrogels provide spatial and temporal control over tissue development. These hydrogels enable the sustained delivery of growth factors, the modulation of mechanical properties, and the activation of scaffolds for tissue repair. In bioprinting, they offer a means to control the viscosity for enhanced shape accuracy and alterability of properties. However, the challenge that arises in the case of cartilage regeneration applications is to obtain the right balance of all these properties, namely responsiveness, biocompatibility, and mechanical strength Bordbar-Khiabani and Gasik *et al.*, in 2022 in 2022 [14].

**Nanomaterials**

Graphene and Carbon Nanotubes (CNTs) are two promising nanomaterials widely incorporated into cartilage bioprinting to enhance both mechanical properties and biological activity. Graphene based nanocomposites improve mechanical strength, electrical conductivity, cell adhesion and proliferation. CNTs can give support as well as enhance the mechanical characteristics and act as a vehicle for controlled drug delivery Di Marzio *et al.*, in 2020 [15]. Nanoparticles added to bioinks improve the printability of the material, replicate native cartilage conditions, and provide additional properties, including mechanical strength and conductivity. Some examples include graphene oxide/scaffold composites and CNT/collagen composites which demonstrate enhanced mechanical properties and cell growth. Some pertinent issues include the uniform distribution of nanoparticles, the compatibility of mechanical and biological properties, and toxicity of certain nanomaterials Theus *et al.*, in 2021 [16]. Further work on nanomaterials will be important in the development of functional and biomimetic cartilage constructs.

**Bioactive Molecules**

Bioactive molecules including growth factors like TGF-β and BMPs are essential for chondrogenesis during cartilage bioprinting Thielen *et al.*, in 2019 [17]. TGF-β is involved in cartilage formation through the regulation of MSC chondrogenic differentiation as well as synthesis of Extracellular Matrix (ECM). BMP-2 and BMP-7 are also reported to promote chondrogenesis, increase chondrocyte proliferation and ECM production (Wu *et al.*, in 2024) [18]. However, some BMPs can induce hypertrophy, which is not favorable for articular cartilage tissue. TGF-β and BMPs have been found to acts synergistically when used together, and thus can enhance chondrogenic differentiation. The incorporation of biomaterials included direct addition, encapsulation, surface modification and gene delivery. Important factors include dose, timing, stability and compatibility with scaffold materials to enhance effective controlled tissue regeneration Keller *et al.*, in 2011; Liu *et al.*, in 2023 [19, 3].

**Enhancing Material Performance in Cartilage Bioprinting**

Identifying research gaps in the material aspect of cartilage bioprinting reveals several issues. The current hydrogels do not possess sufficient mechanical properties for cartilage applications; stiffer composite materials including graphene or carbon nanotubes are yet to be investigated Crawford *et al.*, in 2021 [20]. There are two major challenges with respect to material selection that remains to be addressed: controlling degradation rates on par with tissue formation and designing stimuli responsive hydrogels Theus *et al.*, in 2021 [16]. The chronic biocompatibility, immunogenicity and stability of new materials-especially of nanomaterials-requires further research. Yet another challenge is the surface modification of the biomaterials for growth factor delivery and chondrogenesis, without causing hypertrophy. Moreover, enhanced technology translation for clinical application, developing smart biomaterials, enhancing angiogenesis, and addressing immune responses are still challenging and significant research topics for future studies involving materials used in bioprinting Crawford *et al.*, in 2021; Theus *et al.*, in 2021 [16, 20].

**Traditional 3d Bioprinting Approaches**

Traditional 3D bioprinting approaches, including extrusion bioprinting, inkjet bioprinting, and laser direct bioprinting, each have their own advantages and disadvantages, as noted by Di Marzio *et al.*, in 2020 [15]. Extrusion based bioprinting is cheap and has high adaptability; but has low resolution and affects cells with shear force. Inkjet bioprinting is fast but has low cell viability. It is suitable for low viscosity bioinks, and can be blocked as well. Laser assisted bioprinting works with high resolution and cell compatible fabrication but has high cost, low rate of production and less flexibility Vijayavenkataraman *et al.*, in

DOI: https://doi.org/10.54393/pbmj.v8i1.1186

2023 [21]. These traditional methods of 3D bioprinting are associated with a number of general disadvantages. Low resolution, ranging from hundred to two hundred micrometers, prevents the recreation of the intricate microstructure of tissues. Lower printing rates, particularly in laser assisted approaches, result in long fabrication durations which might affect cell survival. As the size of the constructs increases, issues such as cell survival and construct stability become more difficult to address Wu *et al.*, in 2023 [18]. Viscoelastic properties like viscosity of bioink impose limitations on the nature of biomaterials that may be employed. In addition, the post-printing maturation, insufficient vascularization, mechanical durability issues, and the inability to consistently replicate the procedure from one batch to the next make the process difficult. These limitations have been a subject of worry and are being investigated with the aim of increasing resolution, rate, and scale. This research will help to preserve biological functionality for superior tissue engineering and bioprinting applications Di Marzio *et al.*, in 2020; Vijayavenkataraman *et al.*, in 2023; Wu *et al.*, in 2023 [15, 18, 21].

**High-Resolution Bioprinting**

Two-photon polymerization is a bioprinting method that utilizes a high resolution and is applicable for the assembly of cartilage tissue. It makes it possible to create sophisticated 3D structures with a spatial resolution of around tens of nanometers, suitable for the production of scaffolds that have a topography similar to the natural ECM of cartilage Jing *et al.*, in 2022 [22]. The benefits of TPP include resolution around 100 nm, precise control over scaffold architecture and possibility to fabricate complex structures. It may also contain bioactive molecules and help cell proliferation by controlling pore size and connectivity. However, TPP has drawbacks including slow fabrication rates, small build volumes, and a limited choice of materials Valente *et al.*, in 2022 [23]. Current research focuses are directed on the increase of speed, widening of materials, and optimization of scaffolds to promote cartilage regeneration. Although primarily a research application, TPP holds great potential for the development of new generation cartilage tissue engineering scaffolds Jing *et al.*, in 2022; Valente *et al.*, in 2022 [22, 23].

**4d Bioprinting**

4D bioprinting is a new development of the 3D bioprinting technique that involves the use of smart or stimuli responsive materials where the scaffold structures can change shape or function in response to stimuli. In cartilage tissue engineering, 4D bioprinting can be a powerful tool for designing dynamic scaffolds that can produce an optimal mechanical and biological environment during the tissue formation process Yazdanpanah *et al.*, in 2022 [23, 24]. The benefits include the potential for replicating native chondrogenesis, modulating properties in response to mechanical stimuli, and altering geometry to match defect spaces. This technique generally employs smart materials sensitive to temperature, pH, mechanical loading and biochemical signals. Some issues are still present in the creation of bioinks with suitable rheological properties and bio-properties, and in the ability to maintain scaffold configurations over time and to control change. Still, 4D bioprinting is a promising approach towards designing cartilage scaffolds that are more adaptive and biomimetic Di Marzio *et al.*, in 2020; Yazdanpanah *et al.*, in 2022 [15, 24].

**Hybrid Bioprinting Techniques**

The use of multiple techniques in a single process is called 'hybrid bioprinting', widely employed to address the drawbacks of singular methods in tissue engineering, hence improving both the mechanical and biological aspects. There is no universal answer to tissue engineering needs regarding scale. Therefore, synergistic methods incorporate the benefits of extrusion and laser bioprinting or multiple heads in a single bioprinter Wu *et al.*, in 2023 [18]. This makes it possible to fabricate scaffolds with multiple materials, gradients, high resolution, high accuracy and improved mechanical properties. Hybrid techniques also allow the incorporation of one or more cell types and biomolecules which offers better control over the scaffold architecture and the cell distribution. Some of the uses are tissue engineered constructs, vascularized models and functional scaffolds. However, issues like complexity, cost and cell damage resulting from multiple processing steps persist with this method. Future directions include better integration, expansion, and robotization for the improved and biomimetic tissue assembly Wu *et al.*, in 2023 [18].

**Microfluidic-Assisted Bioprinting**

Bioprinting for cartilage tissue engineering using microfluidic techniques offers high fidelity in the fabrication of 3D tissue scaffolds with optimal resolution and customizable cell organization. This enables precise control over flow, mixing, and deposition of cells and bioinks in microchannels. Thus, minimizing shear stress and providing a better physiological environment for native cartilage formation Serex *et al.*, in 2021 [25]. This technique enables fabrication of scaffolds with multiple materials and gradients, and tubular and vascularized structures, which are essential for nutrition and interfaces between cartilage and bone Lee *et al.*, in 2022 [26]. Some applications include creation of zonal cartilage constructs, delivery of bio active molecules and formation of hydrogel fibers. Some of the issues facing bioinks are composition of bioinks, their stability and scalability for tissues of large size. Future developments for optimal use if this technique requires integrating the hybrid modal techniques, utilizing stimuli sensitive material, and optimizing artificial intelligence inspired automation technology for clinical use Davoodi *et*

DOI: https://doi.org/10.54393/pbmj.v8i1.1186

*al.*, in 2020; Serex *et al.*, in 2021; Lee *et al.*, in 2022 [26-28].

**Improving Bioprinting Methods for Enhanced Precision**

Several issues remain in the scalability and standardization of bioprinting, with a notable focus on the transition from laboratory scale to clinical scale [29-31]. Existing methods are still limited by the scaffold size, speed, resolution and cell integrity when moving from micro to macroscale (Table 1).

**Table 1:** Bioprinting Techniques and Their Key Advantages and Limitations

| Technique Type | Resolution | Speed | Material Compatibility | Scalability | Strengths | Weaknesses | Sources |
|---|---|---|---|---|---|---|---|
| Hybrid Bioprinting | Varies based on combined techniques | Moderate | Varied based on techniques | High | Combines strengths of multiple techniques | Complexity and cost,potential cell damage | [3] |
| Microfluidic-assisted Bioprinting | 10-100 Î¼m | High | High compatibility with various bioinks | High | Precise control over material deposition | Bioink stability, difficult to scale for large tissues | [26] |
| Extrusion-based Bioprinting | 100-300 Î¼m | Medium | High (hydrogels, polymers) | High | Adaptable, supports multiple materials, cost-effective | Low resolution, potential cell damage due to shear force | [27, 28] |
| Inkjet Bioprinting | 50-100 Î¼m | High | Low viscosity materials only | Medium | High speed, good for low viscosity bioinks | Low cell viability, risk of nozzle clogging | [29] |
| Laser-assisted Bioprinting | 10-50 Î¼m | Low | Limited to specific bioinks | Low | High precision, cell-friendly process | High cost, low throughput, limited materials | [30] |
| Two-photon Polymerization (TPP) | 100 nm | Very Low | Limited to photo-sensitive materials | Low | Ultra-high resolution, suitable for complex structures | Very slow, small build volumes | [31] |
| 4D Bioprinting | Depends on the material used | Depends on the material responsiveness | Depends on smart materials used | Medium | Dynamic scaffolds, can adjust over time | Still experimental, challenging material control | [32 ,33] |

Furthermore, the field also lacks standard operating procedures which cause variability in outcomes between them. Bioink repositories, quality assessment protocols, and approaches for the evaluation of bioinks and constructs are critical to the process Liang *et al.*, in 2023 [34, 35]. Feedback during the process of bioprinting is not continuous, leading to the need for multifunctional sensor systems in bioprinting. Others include regulatory issues, problems associated with multimaterial capability, and the requirement for bioinks that are both easy to print and biologically active. Other processes that require improvement post-printing processes, such as tissue maturation. Some of the important areas that will enable bioprinting to progress to clinical use are automation. Similarly, there is the challenge of the competence that needs to be addressed to overcome these gaps. It is clear that addressing these gaps will require interdisciplinary work and innovative technologies Liang *et al.*, in 2023 [35].

**Mechanical and Biological Integration**

One of the major limitations is the inability to achieve native cartilage mechanical properties in bioprinted scaffolds. However, hydrogels, which are widely utilized in bioprinting, generally do not possess the mechanical characteristics necessary for joint function. As a result, there is interest in the establishment of multi-material printing methods and the use of thermoplastic materials in combination with hydrogels for improved mechanical characteristics Fan *et al.*, in 2022 [9]. Thermoplastics can act as a supportive skeleton, and hybrid scaffolds exhibit mechanical properties similar to those of pure thermoplastic scaffolds. Additionally, modulating the crosslinking density and bioink concentration of alginate or PEG based hydrogels enhances the mechanical characteristic of the scaffold Zhou *et al.*, in 2023 [36].

Biological integration is also crucial while using bioactive molecules such as TGF-β1 or components of the ECM to enhance chondrocyte differentiation and cell adhesion. The structure of the osteochondral junction is mimicked by scaffolds with multiple phases, particularly hybrid structures that have varying mechanical features, which are advantageous for cartilage tissue engineering Liang *et al.*, in 2022 [29]. Nanocomposites with graphene and silk fibroin-based components are being invented for 3D bioprinting, which unite printability, mechanical characteristics, and biocompatibility [9]. In an attempt to generate bioprinted cartilage constructs that have enhanced mechanical and biological characteristics for better long term results, other post-processing methods such as mechanical stimulation are applied to advance tissue formation in the maturation phase Di Marzio *et al.*, in

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2020; Liang *et al.*, in 2022; Zhou *et al.*, in 2023 [15, 35, 36].

**Vascularization and Nutrient Supply**

The absence of vascularization in native articular cartilage, which depends on diffusion from the synovial fluid for nutrients, creates a major obstacle for the engineering of large cartilage constructs. In the absence of vascularization, oxygen and nutrient supply to deep cells within the tissue is constricted, causing cell death and necrosis in the core of engineered scaffolds. This outcome is a necrotic center accompanied by viable cells, which lessens the overall functionality and size of the cartilage Gonçalves *et al.*, in 2021 [13]. New approaches to this problem include the application of vascularization promoting factors such as VEGF and bFGF, which can stimulate blood vessel infiltration, however, this leads to the potential change in cartilage formation. The bioprinting techniques that employ gradients such as growth factor or oxygen gradients can control cell behavior and zonal differentiation. Another strategy is the pre-vascularization of scaffolds by preparing vessel like channels or culturing chondrocytes with endothelial cells. These strategies are intended to improve nutrient delivery while preserving the avascular characteristic of cartilage, which is imperative for tissue engineering applications Gonçalves *et al.*, in 2021; Shineh *et al.*, in 2023 [37, 38].

**Immune Response and Biocompatibility**

The major challenges of cartilage tissue engineering today include immune rejection and inflammatory responses in the sense that the implanted biomaterials elicit foreign body responses. This can result in acute and chronic inflammation or fibrotic encapsulation, and therefore hinder integration and functionality of cartilage constructs manufactured through bioprinting Tripathi *et al.*, in 2023 [38, 39]. These challenges are rooted in both inherent and acquired immunity and affected by the properties of scaffolds such as material, size and shape and tissue type Salthouse *et al.*, in 2023 [40]. To improve immunomodulation, bioactive scaffolds are under development to direct immune responses by linking immunomodulatory molecules such as TGF-β1 to create anti-inflammatory conditions Wei *et al.*, in 2019 [51]. Collagen and hyaluronic acid incorporated materials that are immune compatible and resemble the extracellular matrix avoid foreign body reactions. Surfaces coatings are also examined using anti-inflammation molecules and stimuli-responsive material to control immune response. Furthermore, approaches that seek to modulate macrophages and regulatory T-cells also seek to modify the immune response for a more regenerative phenotype to foster tissue integration and chronic regeneration Wei *et al.*, in 2021; Salthouse *et al.*, in 2023; Tripathi *et al.*, in 2023 [4, 39, 40].

**Clinical Translation and Regulatory Challenges**

Although there are many progresses in bioprinting, the application of the research into clinical use is still difficult. The use of biologically functional materials and the ability to incorporate printed tissues with physiological vasculature and multiple cell types are still a challenging task. These factors impede the clinical translation of bioprinted cartilage implants Ruiz-Cantu *et al.*, in 2020 [41]. The regulatory FDA/EMA guidelines for bioprinted implants are still challenging to follow since it remains a new technology. Patient care safety is relatively well defined with a focus on preclinical testing and chronic studies without standard reporting formats and quality assurance. Testing methods and bioprinting reproducibility are some of the preclinical requirements and advances that need to be standardized Ruiz-Cantu *et al.*, in 2020 [41]. More long-term in vivo studies and improved in vitro models are required in order to make predictions. In terms of the growth of the research focal areas, biomimicry, scalable solutions and collaborations with academic institutions, industry and regulatory agencies will be helpful to streamline the process Liu *et al.*, in 2023 [3]. To increase the functionality and integration of the printed tissue constructs, it will be necessary to improve the post-printing maturation and support the rapid formation of new blood vessels Davoodi *et al.*, in 2020; Ruiz-Cantu *et al.*, in 2020; Liu *et al.*, in 2023; Wei *et al.*, in 2021 [3, 4, 28, 41].

**Emerging Frontiers in Bioprinting**

New trend in the bioprinting has been focused on developing patient specific solutions using Patient Derived Cells, induced pluripotent stem cells or personalised scaffold. The presence of individual growth factors and biomolecules also enhances the formation of the tissues, following the multiple experimental designs. Some of the applications of Artificial Intelligence (AI) is assisting to optimize bioprinting parameters, predicting tissue characteristics, and developing AI integrated tools for intricate scaffold structures Liu *et al.*, in 2023 [3]. The current focus of scaffold design is on mechanical loading for the purpose of replicating the physiological environment for the dynamic culture of bioprinted constructs. These systems are usually linked to bioprinters for the ongoing maturation of tissue. Additionally, using bioprinting in combination with organ-on-a-chip technology allows for the manufacture of functional constructs of cartilage for drug screening and multi-tissue applications. This is necessary to elucidate the mechanical and biological characteristics of printed cartilage constructs and their integration and remodeling over time. The integration of biocompatible sensors with bioprinted constructs might facilitate the assessment of tissue functionality following implantation, including its mechanical and metabolic characteristics for the development of smart implants [40, 41]. Developing new biomaterials includes the design of stimuli responsive bioinks as well as the production of gradient materials to

DOI: https://doi.org/10.54393/pbmj.v8i1.1186

mirror native cartilage. The focus of vascularization techniques is to deliver nutrients to the tissue construct; enhancements to scalability and automation are necessary for tissue constructs that are applicable for clinical use Davoodi *et al.*, in 2020 [28]. The direct printing of these in situ fabrication techniques into the site of the defect during surgery is being considered. Another important area where immunomodulatory factors are being added to constructs is to facilitate tissue integration. The innovations are aimed at remedying current problems and moving cartilage bioprinting nearer to clinical use Liu *et al.*, in 2023; Shopova *et al.*, in 2023 [3, 42].

## CONCLUSIONS

Recent advancements in cartilage tissue bioprinting are mainly based on new biomaterials such as composite hydrogels, smart hydrogels, and nanomaterials that have better mechanical and biological performance. Techniques like 4D bioprinting, high resolution bioprinting and hybrid bioprinting are allowing for the development of improved and functional tissue scaffolds. However, issues such as low mechanical strength, poor incorporation of vessels, immunological reactions, and regulatory challenges are still a limiting factor. The shortcomings, such as scalability, biocompatibility, and protocol standardization, need to be addressed to advance toward clinical application. In the future, the prospects of combining artificial intelligence-based processes and smart materials are expected to define the new era of cartilage regeneration, providing the development of personalized, long lasting and functional tissue scaffolds.

## Authors Contribution

Conceptualization: ARJ
Methodology: ARJ, ZZ
Formal analysis: ARJ, ZZ
Writing, review and editing: ARJ, ZZ

All authors have read and agreed to the published version of the manuscript.

## Conflicts of Interest

All the authors declare no conflict of interest.

## Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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