Innovative prospects in 3D printed bio-scaffolds for osteochondral tissue engineering: A systematic review

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Abstract

BACKGROUND
Advancements in 3D printing technologies have significantly transformed osteochondral tissue engineering, enabling the creation of scaffolds that closely mimic the structural and biological complexities of native tissue. These scaffolds provide a 3D environment conducive to cellular adhesion, proliferation, and differentiation while maintaining critical mechanical and biodegradable properties.

AIM
To explore the feasibility of 3D printed scaffolds in osteochondral applications, highlights innovative materials and techniques, and addresses the existing knowledge gaps and challenges in clinical translation.

METHODS
This scoping review adhered to PRISMA extension for scoping reviews guidelines to systematically map innovations in 3D printed bio-scaffolds for osteochondral tissue engineering. Due to heterogeneous data, it favored a scoping over systematic or meta-analytic approaches. The review aimed to identify innovations in scaffold materials, fabrication techniques, and translational strategies. Key

questions addressed bioprinting methods, scaffold designs, and translational challenges. Studies included were in English, peer-reviewed, and focused on 3D printed scaffolds for osteochondral repair. Exclusions were non-osteochondral, non-3D fabrication studies, grey literature, editorials, and non-English papers. Literature was sourced from six databases using comprehensive keywords and Boolean operators. Backward citation tracking added relevant studies; no date limits were applied. Screening followed a four-phase selection process with dual independent reviewers. Data were charted thematically without bias assessment, focusing on methods, outcomes, and future gaps.

RESULTS
The fabrication of biomimetic scaffolds, incorporating bioactive elements such as growth factors, has shown promise in replicating the extracellular matrix and enhancing tissue regeneration. Cutting-edge techniques, including inkjet, extrusion-based, and laser-assisted bioprinting, allow precise spatial control and multi-material integration essential for osteochondral scaffolds. Innovations such as graded scaffolds and bio-inks enriched with nanoparticles have further improved scaffold functionality, mechanical stability, and biological activity. Despite these advancements, limitations persist, including material challenges in achieving the desired balance of bioactivity, biodegradability, and mechanical properties. Fabrication methods face issues of scalability, reproducibility, and resolution, while the long-term biological interactions between scaffolds and host tissues, particularly degradation products, remain underexplored. Regulatory and economic barriers also impede clinical translation, underscoring the need for collaborative research efforts. Future directions emphasize the potential of emerging technologies, such as 4D printing, smart biomaterials, and soundwave patterning, to address current challenges and unlock new opportunities.

CONCLUSION
The convergence of biomaterial science, additive manufacturing, and regenerative medicine holds immense promise for advancing personalized treatments and revolutionizing osteochondral tissue engineering.

Core Tip: Advancements in 3D printing have revolutionized osteochondral tissue engineering by enabling biomimetic scaffolds that replicate native tissue complexities. These scaffolds support cellular adhesion, proliferation, and differentiation while maintaining mechanical integrity and biodegradability. Innovative techniques, such as laser-assisted bioprinting and bio-inks enriched with nanoparticles, enhance functionality and regeneration. However, challenges persist in scalability, reproducibility, and clinical translation. Future directions, including 4D printing and smart biomaterials, offer promising solutions for personalized treatments.

INTRODUCTION

Additive manufacturing (AM) or 3D printing has revolutionized tissue engineering (TE) by enabling the development of scaffolds with greater complexity, overcoming limitations of traditional methods[1]. By utilizing precise positioning of biomaterials, 3D printing mimics the composite structure of native tissues and facilitates the production of complex human-scale architectures such as muscle, cartilage, vasculature, skin, and bone[2]. This technique integrates bioactive compounds into scaffolds, fostering tissue regeneration and high cellular viability, with osteochondral TE emerging as a prominent application[3]. Osteochondral tissues, comprising subchondral bone and articular cartilage found on joint surfaces, exemplify natural composites, inspiring TE to explore bio-composite materials that replicate the intricate composition of biological tissues while promoting regeneration[4].

Bone defects caused by trauma, fractures, tumors, infections, or genetic disorders can result in permanent abnormalities such as limb shortening and impaired function[5]. Biological treatments remain the gold standard for addressing such conditions, employing patient-derived biologics within scaffold frameworks[6]. These scaffolds, tailored to the complexity of bone structures identified through imaging techniques like computed tomography, benefit from AM coupled with computer-aided design[7]. Various 3D printing methods, including selective laser sintering, sheet lamination, and fused deposition modeling, have been employed to create bio-scaffolds[8].

Advanced TE seeks to fabricate osteochondral constructs that replicate the spatial complexity of matrix, tissue, and bioactive components[9]. Extracellular matrix (ECM) development in these engineered constructs is enhanced by synergistic interactions between growth factor administration and heterotypic tissue interplay[10]. AM facilitates the integration of biological materials during fabrication, allowing for precise spatial patterning across diverse tissue types and biologically active elements[11]. Introduced at the Massachusetts Institute of Technology, 3D printing technology utilizes inkjet-based liquid binder deposition to produce layered structures[12]. Techniques such as powder-bed fusion, vat-photopolymerization, extrusion-based processes, melt electrospinning writing, and inkjet printing underpin its versatility, offering transformative potential in regenerative medicine and TE scaffolds[13–17].

Recent advancements have demonstrated the effectiveness of 3D printing in creating intricate tissue architectures using hydrogels and bio-functional materials[16,18]. A study employed Gelatin methacrylate (GelMA) hydrogel to fabricate layers mimicking cartilage and subchondral bone[3]. Bio-inks, combining cells and structural substrates, enable the creation of 3D tissue mimics with geometrical precision[19]. Future applications include mass production of human organs—heart, kidneys, skin, and liver—using scaffold-based and scaffold-free systems, addressing critical challenges in organ transplantation[20].

3D bioprinting is extensively utilized in TE for scaffold fabrication. Recent research highlights stereolithography's potential in printing biomimetic nanocomposite scaffolds that enhance osteochondral regeneration. Human mesenchymal stem cells (MSCs) cultured on 3D printed constructs demonstrated improved adhesion, growth, and differentiation. Nano-inks, derived from advanced manufacturing processes, have been pivotal in developing innovative hydrogel scaffolds[21].

The scaffold design in TE emphasizes biological substitutes for damaged tissues and organs[22]. Strategies include direct tissue extraction for implantation, targeted delivery of bioactive molecules, cell-free scaffolds, and ECM-like scaffolds that mimic natural tissue development[23,24]. Porous scaffolds, created using methods such as freeze-drying, gas foaming, and stereolithography, support material transportation, mechanical integrity, tissue regeneration, and controlled degradation without causing toxicity or inflammation[25-28]. Hydrogels, with their adaptability and biomimetic properties, play a vital role in creating functional scaffolds for irregular defect repair[29,30]. Given the heterogeneity in experimental designs, materials used, and outcome measures, this scoping review was conducted to systematically map the state of evidence, identify knowledge gaps, and highlight translational opportunities. The methodology followed the PRISMA extension for scoping reviews (PRISMA-ScR) guidelines to ensure transparency and reproducibility.

MATERIALS AND METHODS

This scoping review was conducted following the PRISMA-ScR guidelines, to systematically map and synthesise the breadth of published research on innovations in 3D printed bio-scaffolds for osteochondral TE. This approach was selected due to the heterogeneity of study designs, models, materials, and outcomes reported in the existing literature, making it more appropriate than a traditional systematic review or meta-analysis.

Objectives and review questions

The primary objective was to explore and categorize emerging innovations in scaffold materials, fabrication technologies, and translational strategies for osteochondral TE. Specific review questions included: (1) What types of biomaterials and scaffold designs are currently employed in 3D printed osteochondral scaffolds; (2) What bioprinting techniques and structural strategies are being developed for cartilage–bone interface reconstruction; and (3) What are the reported translational challenges, limitations, and knowledge gaps?

Eligibility criteria

Studies were included if they were published in peer-reviewed journals in English and focused on AM, specifically 3D bioprinting or 3D fabrication of scaffolds for osteochondral or chondral/bone interface repair. We included original research works and reviews describing scaffold materials, fabrication techniques, or biological evaluation (*in vitro*, animal, or clinical). Studies that did not specifically focus on osteochondral applications or did not involve 3D scaffold fabrication were excluded. Grey literature, reviews conference abstracts, editorials, and non-English articles were also omitted.

Information sources and search strategy

A comprehensive literature search was conducted on January 25, 2025, across six databases: PubMed, EMBASE, ScienceDirect, Springer, IEEE Xplore, and Scopus. The search included keywords and MeSH terms such as: ("3D printing" OR "additive manufacturing") AND ("osteochondral" OR "cartilage" OR "bone") AND ("scaffold" OR "bioscaffold") AND ("regeneration" OR "tissue engineering"). Boolean operators (AND/OR) were applied to refine and expand the search scope. No date restrictions were imposed. Additional articles were identified through backward citation tracking from reference lists of key publications (Supplementary material).

Study selection

All retrieved records were imported into a reference management tool for duplicate removal. The selection process followed four stages: Identification, screening, eligibility, and inclusion. Two independent reviewers screened the titles and abstracts against inclusion criteria. Discrepancies were resolved through consensus discussion. Full texts of eligible

studies were reviewed for final inclusion. A modified PRISMA-ScR flow diagram was used to summarize the study selection process.

Data charting and synthesis

Instead of extracting quantitative effect estimates, data were charted narratively to capture scaffold materials, bioprinting techniques, cell types (if applicable), and outcome domains. Findings were organized thematically across five categories: Feasibility, materials and methods, structural innovations, translational challenges, and future directions. A risk of bias assessment was not performed, in accordance with scoping review conventions; however, methodological variability and reporting limitations were noted in the discussion.

RESULTS

Study selection

The initial database search across PubMed, EMBASE, ScienceDirect, Springer, IEEE Xplore, and Scopus yielded a total of 2668 records. After removing 493 duplicate entries, 2175 unique records remained for title and abstract screening. Of these, 1785 studies were excluded for not meeting the inclusion criteria based on relevance to 3D printing, osteochondral focus, or scaffold application. The remaining 390 full-text articles were assessed for eligibility. Following detailed evaluation, 333 studies were excluded for reasons including: Lack of 3D printing involvement and insufficient data on the subject (n = 220), absence of osteochondral relevance (n = 95), or insufficient outcome reporting (n = 10) and non-English language (n = 8).

Ultimately, 57 studies met all inclusion criteria and were included in the final scoping synthesis. These studies covered a range of scaffold materials (hydrogels, ceramics, polymers, composites), fabrication technologies (inkjet, extrusion-based, laser-assisted), and application models (in vitro, preclinical, and early clinical investigations). A revised PRISMA-ScR flow diagram detailing the selection process is presented in Figure 1.

DISCUSSION

Thematic synthesis

Scaffold feasibility and design requirements: AM (3D printing) has emerged as a pivotal technology in regenerative medicine, providing unprecedented precision in creating scaffolds that closely mimic the biological, structural, and functional characteristics of native tissues[4]. Its ability to fabricate intricate three-dimensional constructs with tailored material properties and cellular arrangements positions it as a transformative approach in TE[31-33]. This section evaluates the feasibility of employing 3D printed scaffolds for tissue regeneration by exploring their critical attributes, such as biocompatibility, biomimicry, mechanical properties, biodegradation, and printability.

The advent of 3D printing, or AM, has revolutionized TE by offering unprecedented capabilities in scaffold fabrication [34,35]. This transformative technology allows for the precise spatial arrangement of biomaterials, enabling the replication of complex biological structures[36-38]. Osteochondral TE, which addresses the challenges of repairing the articular cartilage and subchondral bone interface, stands to benefit immensely from these advancements[4,39]. By leveraging the inherent advantages of 3D printing, researchers have developed innovative scaffolds designed to facilitate tissue regeneration, making significant strides in both laboratory and preclinical studies[8].

Biocompatibility

The fundamental requirement for scaffolds in tissue regeneration is biocompatibility, ensuring that materials are well-tolerated by human tissues without inducing adverse immune responses[40-42]. Biocompatibility encompasses a broad range of characteristics, including the stability of the material and its interaction with biological systems over time[43,44]. Advances in biomaterial science have enabled the development of polymers and composites that meet these criteria, offering promising solutions for long-term tissue regeneration[45-47]. The absence of inflammatory reactions and immune responses *in vivo* remains a cornerstone for the clinical translation of 3D printed scaffolds[48].

Biomimicry

The design and fabrication of scaffolds that replicate the ECM are essential for guiding cellular behavior, enhancing tissue integration, and promoting regeneration[49-51]. Biomimetic scaffolds aim to recreate the dynamic environment of the ECM by incorporating bioactive cues, growth factors, and cytokines that regulate cell adhesion, proliferation, and differentiation[43,52,53]. The application of biomimicry in 3D printing enables the reproduction of complex tissue types, such as osteochondral tissue, where cartilage and bone components coexist[54,55]. Recent innovations have demonstrated that integrating multiple biomimicry techniques within a single construct significantly improves scaffold functionality[56].

Mechanical properties

The mechanical stability of a scaffold is another crucial factor determining its feasibility for tissue regeneration[23,57]. Scaffolds must possess sufficient strength to withstand surgical manipulation and provide structural support during the regeneration process[42,58,59]. This is particularly critical for load-bearing tissues such as bone and cartilage, where
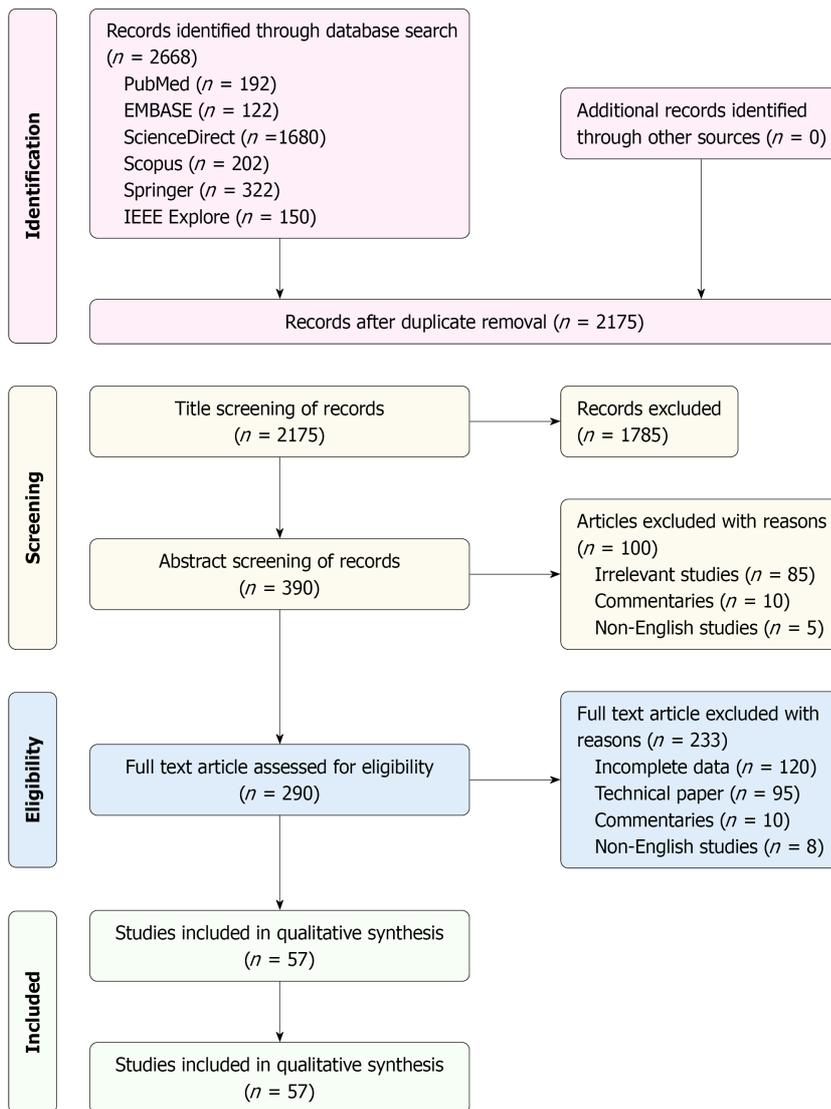
Identification

Records identified through database search
(*n* = 2668)
   PubMed (*n* = 192)
   EMBASE (*n* = 122)
   ScienceDirect (*n* =1680)
   Scopus (*n* = 202)
   Springer (*n* = 322)
   IEEE Explore (*n* = 150)

Additional records identified
through other sources (*n* = 0)

Records after duplicate removal (*n* = 2175)

Screening

Title screening of records
(*n* = 2175)

Records excluded
(*n* = 1785)

Abstract screening of records
(*n* = 390)

Articles excluded with reasons
(*n* = 100)
   Irrelevant studies (*n* = 85)
   Commentaries (*n* = 10)
   Non-English studies (*n* = 5)

Eligibility

Full text article assessed for eligibility
(*n* = 290)

Full text article excluded with
reasons (*n* = 233)
   Incomplete data (*n* = 120)
   Technical paper (*n* = 95)
   Commentaries (*n* = 10)
   Non-English studies (*n* = 8)

Included

Studies included in qualitative synthesis
(*n* = 57)

Studies included in qualitative synthesis
(*n* = 57)

Figure 1 PRISMA extension for scoping reviews flowchart for selection of studies.

mechanical demands are high[60]. The balance between mechanical integrity and porosity, which facilitates cell infilt-ration and vascularization, is a key challenge in scaffold design[22,61,62]. Advanced 3D printing technologies now allow precise tuning of scaffold architecture to achieve optimal mechanical performance[63].

Biodegradation

A hallmark of effective scaffolds is their ability to degrade in tandem with the formation of new tissue[64,65]. Biodegradable materials offer the advantage of being gradually replaced by native tissue, eliminating the need for secondary removal surgeries[66,67]. The degradation products must be biocompatible and easily metabolized or excreted without eliciting toxicity or inflammation[68]. Controlled degradation, aligned with tissue maturation, ensures the scaffold maintains its structural integrity until the regenerating tissue can independently support itself[69].

Printability

Printability refers to the material's capacity to be precisely processed by 3D printing technologies to form high-resolution, reproducible constructs[70,71]. Key parameters, such as rheological properties and solidification mechanisms, influence the success of scaffold fabrication[72-74]. Techniques like extrusion-based printing and inkjet printing have advanced the field by enabling the integration of bioactive materials and living cells into 3D printed constructs[2,75-77]. Furthermore, the scalability and reproducibility of the printing process are critical for clinical applications, where consistent quality is paramount[69]. Having established the fundamental design requirements for osteochondral scaffolds, we next explore the array of material and fabrication innovations shaping this evolving landscape. While feasibility defines the theoretical blueprint, the next section explores how material science and fabrication technologies have actualized these concepts into functional osteochondral scaffolds.

Innovations in materials and fabrication

The development of innovative materials and advanced 3D printing techniques has been pivotal in improving the efficacy of treatments for osteochondral TE[54,78,79]. By integrating biological functionality with precise structural control, these advancements enable the creation of scaffolds that support tissue growth, repair, and regeneration with unprecedented efficiency[80-82]. This section explores a variety of materials, fabrication methods, and cutting-edge innovations that are advancing the field as illustrated in Figure 2.

Advancements in biomaterials

Biomaterials form the foundation of osteochondral scaffolds, providing the necessary mechanical support, biological cues, and bioactivity for tissue regeneration[83-86]. A diverse range of materials, including synthetic and natural polymers, hydrogels, ceramics, and bio-composites, has been utilized to enhance scaffold functionality[27,42,87-91].

Hydrogels have garnered significant attention due to their ability to mimic the ECM, providing a hydrated, biocompatible environment conducive to cell proliferation and differentiation[43,92-95]. Recent innovations have focused on integrating bioactive compounds, such as growth factors and nanoparticles, into hydrogels to promote osteochondral regeneration[96-99]. For example, a multi-layered scaffold utilizing GelMA and nano-hydroxyapatite demonstrated superior mechanical properties and biological activity, making it suitable for cartilage and subchondral bone repair[100-104].

Polymeric materials, both synthetic (*e.g.*, polycaprolactone) and natural (*e.g.*, collagen), have been widely employed for their biocompatibility, biodegradability, and tunable properties[105,106]. Composite materials combining polymers with ceramics, such as calcium phosphate or bio-glass, have further improved the mechanical stability and osteoconductivity of scaffolds[69,100,107-109]. These hybrid scaffolds facilitate seamless integration with host tissue while supporting bone and cartilage regeneration[110]. Building on these advances, the next frontier lies in integrating multifunctionality and dynamic behavior through cutting-edge approaches that push beyond static design constraints.

Disruptive fabrication strategies

Advancements in AM techniques have revolutionized the production of osteochondral scaffolds by enabling precise control over scaffold architecture and material composition[106,111-113]. Among these techniques, inkjet printing, extrusion-based printing, and laser-assisted bioprinting have emerged as key players[114].

Inkjet printing: Known for its high resolution and precision, inkjet printing is extensively used to fabricate complex osteochondral scaffolds[16,115,116]. This non-contact technique employs thermal or piezoelectric methods to deposit bio-inks containing cells and growth factors onto a substrate[43]. The ability to print multiple materials with accuracy allows for the creation of biomimetic structures that replicate the native osteochondral interface[117].

Extrusion-based printing: This method involves the layer-by-layer deposition of materials, such as hydrogels or thermoplastics, using a mechanical nozzle[77,118,119]. Its versatility makes it suitable for fabricating scaffolds with a wide range of materials, from soft hydrogels to stiff polymer composites[120-122]. Extrusion printing has been optimized to ensure cell viability during the printing process, particularly through the use of low-temperature and low-pressure conditions[69]. While extrusion and inkjet-based bioprinting have been widely adopted, recent adaptations—including shear-thinning bioinks and dual-phase deposition heads—have enhanced cell viability and stratified scaffold design critical for osteochondral repair.

Laser-assisted bioprinting: By using focused laser energy, this technique achieves high-resolution patterning of cells and biomaterials[123]. The ability to deposit cells with precision enables the fabrication of scaffolds with intricate spatial arrangements, essential for tissue regeneration[124]. Laser-assisted bioprinting also supports the integration of bioactive compounds within the scaffold, enhancing its therapeutic efficacy[125]. Beyond conventional methods, several disruptive strategies are poised to redefine scaffold functionality and integration.

Emerging innovations

Recent innovations in 3D bioprinting have introduced novel approaches to scaffold fabrication, including multi-material printing, graded scaffolds, and soundwave patterning technology[126,127]. Multi-material printing enables the creation of scaffolds with distinct layers for cartilage and subchondral bone, mimicking the natural osteochondral interface[128]. Graded scaffolds, which transition seamlessly from one material to another, support the regeneration of complex tissues while maintaining mechanical and biological functionality[129] as shown in Figure 3. These innovations are aimed at overcoming current limitations in scaffold integration, mechanical compatibility, and biological function. Soundwave patterning technology offers a significant advancement over traditional 3D printing methods by eliminating shear stress during the deposition of cells and biomaterials[130]. This innovation enhances cell viability and localization, improving the scaffold's therapeutic potential[129].

Hybrid bio-inks enabling ECM responsiveness

The development of bio-inks has been instrumental in advancing 3D bioprinting for osteochondral TE[131]. These materials combine cells, growth factors, and structural substrates to form a cohesive bio-functional printing medium[132]. Nano-inks, which incorporate nanoparticles into bio-inks, have shown remarkable potential in enhancing scaffold properties[133]. For instance, nanocomposite hydrogels demonstrate improved mechanical strength, bioactivity, and degradation rates, making them ideal for osteochondral applications[21]. While bio-inks and composites offer enhanced biological activity, their long-term behavior *in vivo* remains a source of concern—an issue explored further in the
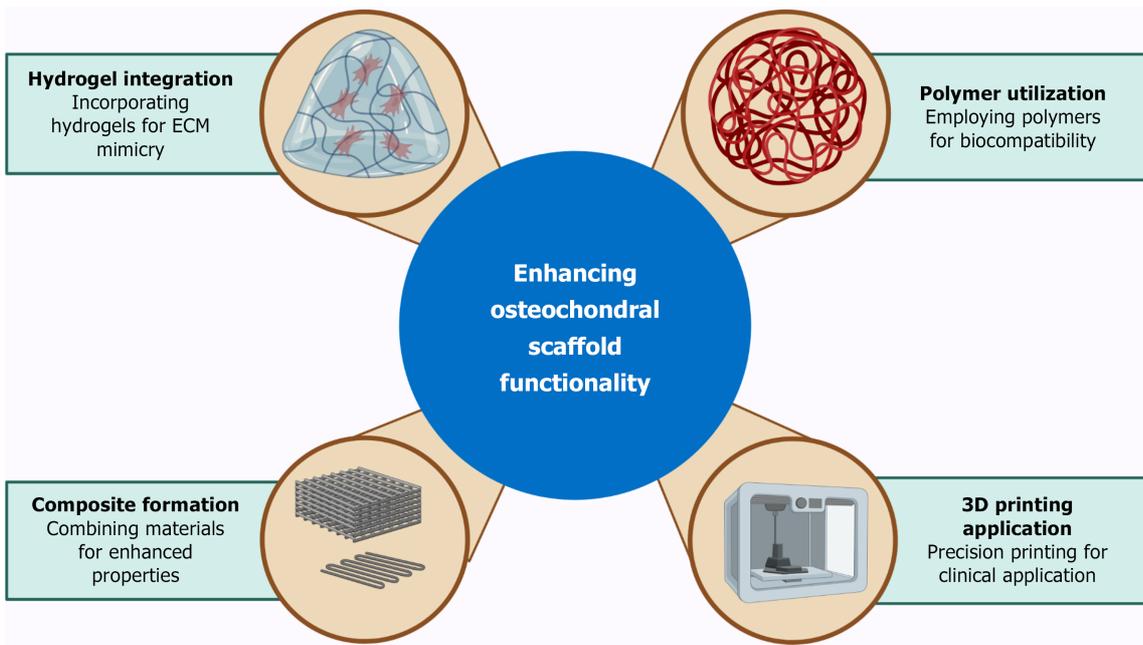
Figure 2 Schematic overview of strategies employed to enhance osteochondral scaffold functionality, including material composition (hydrogels, composites), printing technologies (inkjet, laser-assisted, extrusion-based), and biological cues (growth factors, cytokines). ECM: Extracellular matrix.
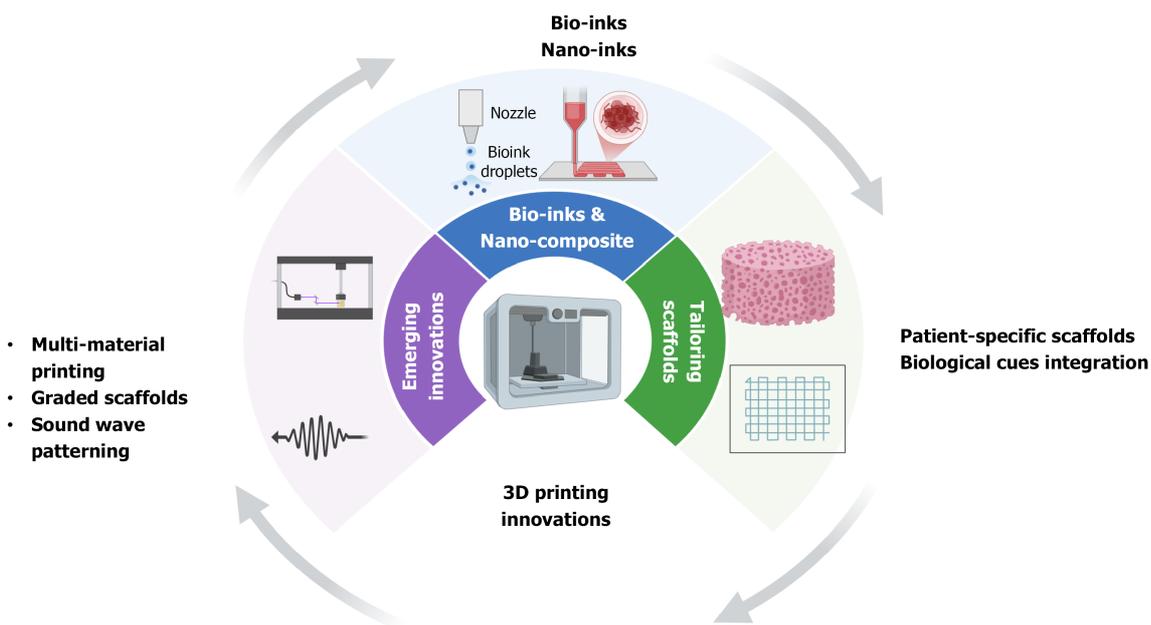

Figure 3 Schematic overview of emerging innovations in osteochondral tissue engineering. This figure illustrates advanced fabrication strategies such as graded scaffolds for layer-specific regeneration, multi-material 3D bioprinting for replicating the complex cartilage-bone interface, and soundwave-based patterning technology for high cell viability and spatial accuracy.

following section.

Tailoring scaffolds for specific applications

The adaptability of 3D printing technologies allows for the customization of scaffolds to meet specific clinical needs[134]. Patient-specific scaffolds, designed based on medical imaging data, ensure precise anatomical fit and enhanced therapeutic outcomes[135]. Such personalization is critical for complex osteochondral defects, where the scaffold must support both cartilage and bone regeneration[136]. Additionally, the integration of biological cues, such as growth factors and cytokines, within scaffolds has advanced their functionality[137]. Controlled release systems embedded in scaffolds allow for the sustained delivery of bioactive molecules, promoting tissue regeneration while minimizing side effects[43, 69]. Despite these promising trajectories, the field remains constrained by several persistent limitations that hinder clinical

scalability and standardization, as discussed below.

Translational bottlenecks and scalable innovations
The transition from laboratory research to clinical application is fraught with regulatory, economic, and logistical hurdles. Regulatory agencies, such as the United States Food and Drug Administration, require extensive testing to evaluate scaffold safety, efficacy, and bioactivity. The lack of standardized criteria for assessing 3D printed scaffolds prolongs the approval process and delays clinical implementation[138-142]. Furthermore, scaffolds requiring complex surgical techniques often face resistance due to the associated costs and risks, which may limit their adoption[142].

Economic factors, including the high costs of materials, equipment, and intellectual property rights, present additional barriers to commercialization. While patient-specific scaffolds offer personalised solutions, their production remains expensive and time-intensive, posing challenges for widespread accessibility[69]. While the aforementioned advances are promising, persistent gaps remain in both experimental rigour and translational feasibility.

Identified knowledge gaps
Despite significant progress, the precise mechanisms underlying osteochondral tissue regeneration are not yet fully understood. Current models fail to account for the heterogeneity of osteochondral defects, which vary widely in size, shape, and severity. Moreover, the long-term performance of printed scaffolds *in vivo* remains poorly characterized, with limited studies investigating their efficacy over extended time periods[43,60].

The interaction between scaffolds and MSCs also requires further exploration. While MSCs play a critical role in tissue regeneration, their differentiation pathways and behavior within 3D printed constructs are not yet fully elucidated[69]. Research into optimizing scaffold design to enhance MSC migration, attachment, and differentiation is essential for improving therapeutic outcomes.

While advancements in 3D printing and osteochondral TE hold significant promise, several unresolved challenges and knowledge gaps continue to hinder the full realization of their potential. Addressing these limitations is essential for improving scaffold design, enhancing material properties, and advancing clinical translation in this emerging field[138, 139].

Material limitations
Despite extensive research into biomaterials, current scaffolds face limitations in their ability to accurately mimic the structural complexity and functional diversity of native osteochondral tissue[56]. Hydrogels, while widely used for their ECM-like characteristics, often lack sufficient mechanical strength, which can compromise their integration into load-bearing applications such as cartilage and subchondral bone repair[69]. Composite scaffolds, although offering improved mechanical stability, frequently encounter challenges in maintaining biocompatibility during degradation[68]. The ability to develop materials that effectively balance mechanical strength, bioactivity, and biodegradability remains a pressing need[60].

Moreover, there is a lack of consensus on the optimal combination of materials for osteochondral scaffolds. For example, while natural polymers such as collagen exhibit excellent biocompatibility, their rapid degradation may limit long-term functionality[140]. Conversely, synthetic polymers like polycaprolactone provide durability but may not adequately support cellular attachment and proliferation[141]. This gap underscores the need for further research into hybrid materials that combine the advantages of both natural and synthetic components[60].

Fabrication challenges
Scaffold fabrication methods, including inkjet printing, extrusion-based printing, and laser-assisted bioprinting, face limitations in scalability, reproducibility, and resolution[2]. While inkjet printing excels in precision, its ability to deposit bio-inks with high cell densities is limited, potentially affecting the therapeutic efficacy of the printed scaffolds[69]. Extrusion-based printing offers versatility but often struggles with achieving high-resolution architectures necessary for replicating the intricate osteochondral interface[124]. Laser-assisted bioprinting provides exceptional spatial control but is constrained by the availability of photo-crosslinkable prepolymers and the high costs of equipment[124].

Additionally, the deposition of biological components during printing poses challenges, such as maintaining cell viability and controlling material solidification[69,75]. Soundwave patterning technology has emerged as a potential solution to these issues, but further exploration is required to establish its effectiveness in large-scale scaffold production[75].

Biological interactions
One of the key knowledge gaps in existing research pertains to understanding the interactions between scaffolds and biological systems, particularly the dynamic behavior of cells within printed constructs. While scaffolds aim to provide a conducive environment for tissue regeneration, the lack of standardized protocols to evaluate cellular responses, tissue formation, and scaffold integration limits their clinical applicability[43,48]. For instance, the ability of scaffolds to mimic the osteochondral interface remains variable, with challenges in achieving seamless integration between the cartilage and bone layers[56].

The effects of scaffold degradation products on cellular behavior also require further investigation. In some cases, degradation products may induce inflammatory responses that compromise tissue regeneration[68]. Advanced biomimetic approaches that address these limitations, such as incorporating controlled release systems for bioactive molecules, have shown promise but remain underexplored[69]. A clearer understanding of these shortcomings enables targeted innovation. The following section outlines strategic directions for addressing these bottlenecks and advancing

Table 1 Summary of innovations in 3D printed osteochondral bio-scaffolds based on material type, printing strategy, model used, and translational readiness

Material type	Bioprinting strategy	Application model	Reported innovation	Translational readiness
GelMA + nHA hydrogel	Extrusion-based	*In vitro*, animal	Improved ECM mimicry, layered zonal design	Preclinical feasibility, limited long-term data
PCL/PLGA composites	Melt electrospinning, extrusion	Large animal, cadaveric	Enhanced mechanical strength, zonal stiffness gradients	Reproducible structure; lacks dynamic *in vivo* data
Bioactive glass ink	Inkjet, laser-assisted	*In vitro*	Osteoconductive matrix, micron-scale resolution	Technologically promising; scale-up challenges
Chitosan–collagen blends	Extrusion-based	*In vitro*	Biocompatibility, crosslinkable for customized geometry	Biologically safe; lacks osteoinductive strength
4D smart polymers	Photo-crosslinkable/thermal cues	Preclinical concept models	Stimuli-responsive shape adaptation and integration signaling	Early stage; requires safety and degradation data

ECM: Extracellular matrix; PCL/PLGA: Polycaprolactone/poly (lacto-co-glycolic acid); GelMA: Gelatin methacrylate; nHA: Nano-hydroxyapatite.

translational success. Table 1 illustrates the 3D printed scaffold strategies in Osteochondral TE and their translational limitations.

From 3D to 4D: Responsive scaffold architectures

Despite rapid advancements, the current body of literature exhibits notable limitations. Many studies rely on inconsistent scaffold characterisation metrics, impeding cross-study comparisons. *In vitro* studies often lack physiologically relevant culture systems, while preclinical trials underreport immune responses or long-term degradation effects. Moreover, the integration of vascularisation strategies within osteochondral scaffolds remains underexplored. The emerging promise of 4D printing—scaffolds capable of dynamic shape transformation under stimuli—faces hurdles related to material reversibility, cell compatibility, and *in vivo* predictability. Similarly, smart biomaterials with biofeedback capabilities remain largely at proof-of-concept stages and require robust long-term safety data. While soundwave-based patterning improves cell viability during deposition, its applicability at scale and cost-efficiency remains to be validated[129].

Addressing the aforementioned knowledge gaps and limitations will require interdisciplinary collaboration across biomaterial science, regenerative medicine, and AM. Additionally, the development of open-access platforms for sharing research data and best practices can facilitate knowledge dissemination and accelerate progress in this field. By investing in advanced biomimetic approaches, refining fabrication techniques, and streamlining regulatory processes, researchers can unlock the full potential of 3D printed scaffolds for osteochondral TE, paving the way for transformative advancements in regenerative medicine. To advance the field, we recommend a shift toward modular scaffold testing pipelines, harmonised outcome metrics (*e.g.*, biomechanical load-bearing thresholds), and interdisciplinary pilot programs combining materials science, stem cell biology, and surgical innovation. Regulatory bodies and academic consortia may further catalyse translation by supporting open-source repositories of scaffold architectures and bioprinting protocols. These recommendations underscore the evolving ecosystem of osteochondral scaffold research—where material science, digital design, and clinical insight converge to reshape the regenerative landscape.

CONCLUSION

3D printing technologies have emerged as a transformative force in osteochondral TE, offering unprecedented opportunities to address complex challenges in tissue repair and regeneration. Through precise fabrication techniques and innovative biomaterials, 3D printed scaffolds have demonstrated the potential to replicate the structural and biological intricacies of native osteochondral tissues. These advancements have enabled the development of biomimetic scaffolds that support tissue integration, cellular adhesion, and ECM formation, while maintaining critical mechanical and biodegradable properties.

Despite these promising developments, several limitations persist. The complexity of creating functional osteochondral scaffolds that seamlessly integrate cartilage and bone remains a significant hurdle. Issues such as scalability, reproducibility, and long-term *in vivo* performance continue to impede the translation of laboratory innovations into clinical applications. Moreover, material limitations, including balancing mechanical stability and bioactivity, as well as regulatory and economic challenges, underscore the need for interdisciplinary collaboration to bridge these gaps.

Innovations such as multi-material printing, graded scaffolds, and advanced bio-inks have opened new avenues for scaffold design and functionality. Future directions, including the exploration of 4D printing, smart biomaterials, and soundwave patterning technologies, hold immense promise for enhancing scaffold efficacy and addressing unresolved challenges. Furthermore, the integration of controlled delivery systems for bioactive molecules and patient-specific scaffold designs could accelerate clinical translation and improve therapeutic outcomes.

In summary, 3D printing has revolutionized the field of osteochondral TE, marking a significant step toward personalized regenerative medicine. Continued research, coupled with collaborative efforts across disciplines, will undoubtedly pave the way for innovative solutions that improve patient outcomes and redefine the future of TE.

FOOTNOTES

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