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An Overview of the Processes Involved in Producing Bioprinted Materials: Scaffold Development for Musculoskeletal Applications

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Abstract

At the core of tissue engineering and regenerative medicine is the goal of repairing, replacing, or regenerating damaged or diseased cells, tissues, and organs. When an injury occurs, the body's natural healing cycle initiates an inflammatory response, clears damaged debris, and triggers nearby cells to multiply and fill the defect. However, in cases of severe trauma, disease, or large volumetric defects, the body's innate capacity for cellular proliferation and extracellular matrix (ECM) remodeling is often insufficient, resulting in scarring rather than functional tissue. To overcome these limitations, biomedical engineers have developed synthetic, natural, and hybrid biomaterials to create three-dimensional scaffolds that provide temporary architectural frameworks for tissue regeneration. These scaffolds support cell attachment, migration, proliferation, and differentiation while providing appropriate mechanical and structural support. Advances in additive manufacturing, three-dimensional bioprinting, electrospinning, and biomimetic fabrication enable the development of increasingly complex, patient-specific scaffolds with controlled porosity, pore interconnectivity, and degradation characteristics. An ideal scaffold should closely replicate the physiological, structural, and biomechanical properties of the target tissue while promoting vascularization and osteogenesis where ap-

propriate. This review explores current scaffold materials, fabrication techniques, scaffold architectures, and key biomechanical considerations relevant to musculoskeletal tissue engineering, with emphasis on their potential for clinical translation and regenerative applications.

Keywords

Tissue Engineering, Bioprinting, Scaffold Fabrication, Biomaterials, Additive Manufacturing, Musculoskeletal Regeneration, Trauma, Orthopaedic Surgery

1. Introduction

Patients with significant tissue loss following injury, cancer, or deformity-correction surgery may benefit from tissue augmentation using biologically active scaffolds manufactured rather than from a donor. Scaffolds should be biocompatible and possess physicochemical properties that replicate a patient's extracellular matrix, facilitating cell adhesion, proliferation, and differentiation. The triad of a tailored, structurally robust scaffold, cellular augmentation to regenerate bone and cartilage, and signaling molecules is fundamental to tissue engineering strategies [1].

Scaffolds should cause minimal inflammatory response or toxicity to patients. An open, interconnected pore network is a critical design requirement for porous scaffolds to facilitate unrestricted fluid and nutrient delivery to both embedded and developing cells, thereby promoting robust neovascularization. The structure of the implanted tissue must be mechanically robust, with sufficient strength and stiffness to support and promote tissue growth. Programmed biodegradability will facilitate gradual degradation and replacement by new tissue [2].

Advanced manufacturing techniques create scaffolds with tailored pore geometries that mimic the natural extracellular matrix, promoting cellular infiltration and blood vessel formation. Specifically, three-dimensional printing allows for the reproducible fabrication of customizable frameworks designed to repair injured tissues and restore biological function [3]. Bridging the gap in bio-scaffold engineering knowledge fosters essential collaboration between medical practitioners and engineers, driving the innovation of practical clinical treatments. In practice, the guided bone regeneration (GBR) concept isolates the healing site using resorbable or non-resorbable barrier membranes. This structural barrier blocks fast-growing epithelial and connective cells from invading the defect, selectively allowing slower-growing osteogenic cells to proliferate and reconstruct the bone [4] [5]. This article reviews the current practices available to help clinicians treat tissue defects effectively through a narrative review; see **Figure 1** for a flowchart on scaffold development.

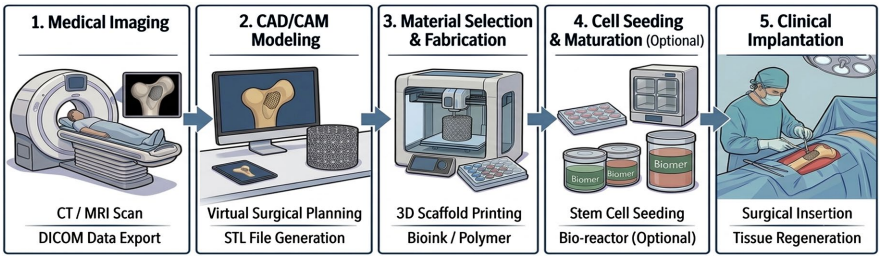

Figure 1. Flowchart for scaffold development (created by R Folkard).

2. Review

2.1. Methods

2.1.1. Search Strategies

A search was conducted in MEDLINE, EMBASE, and PsycINFO. The databases were searched from their inception to April 2025 by an experienced librarian at the institution of the lead author to maximize sensitivity in identifying relevant articles. The main components of the search were "scaffolds" and "outcomes", and the articles were then considered for the relevance of the use of any scaffolds in orthopaedic surgery (see **Appendix** for full search strategy). A qualitative narrative review was undertaken to describe the available processes for manufacturing and producing robust 3D-printed implants to inform those new to this area.

2.1.2. Inclusion and Exclusion Criteria

The eligibility criteria were papers that discussed biological scaffolds or synthetic materials used for reconstruction in surgery, with an emphasis on orthopaedics. Excluded studies were those not reported in the English language, duplicate studies, animal studies, those not reporting on clinical outcomes, and those that did not meet the eligibility criteria (Table 1).

Table 1. Study eligibility.

Criterion	Inclusion Criteria	Exclusion Criteria
Population	• Human patients	• Animal models • *In vitro*/lab-based models
Intervention	• Biological scaffolds • Synthetic materials	• Other repair techniques without scaffolds (e.g., microfracture alone, debridement)
Outcomes	• Clinical outcomes are reported	• Studies lacking functional or clinical data
Study Design	• Non-randomised studies assessable by MINORS criteria • Randomized controlled trials	• Technical notes without clinical data • Review articles or meta-analyses
Language	• English only	• Non-English publications
Timeline & Sources	• MEDLINE, EMBASE, and PsycINFO • From database inception to April 2025	• Studies published after April 2025 • Dissertations or abstracts outside these databases

2.1.3. Screening

EndNote was used for reference management. Duplicate search results were removed. Two researchers participated in both title, abstract, and full-text screening stages (IL, NA), and, where there was uncertainty in study eligibility, a consensus decision was made by at least two screeners. There were 247 articles identified for review of their relevance to orthopaedic surgery and planning. A thematic analysis enabled a qualitative review of the evidence to inform those new to the topic of the principles of scaffolds in current use in orthopaedic surgery.

2.2. Results

Engineered frameworks for bone reconstruction are classified as degradable or non-degradable structures, with biological compatibility categorized as bioactive, bioinert, or bio-tolerant [6] [7]. Synthetic alternatives allow for industrial production and offer tunable properties regarding composition, structure, and degradation kinetics [7]. The materials commonly used in practice are listed in Table 2.

Table 2. Material comparison for tissue engineering.

Material Category	Examples	Key Strengths	Critical Limitations
Natural Polymers	Collagen, Elastin, Alginate, Chitosan	Biomimetic; low immune response; high biocompatibility [6].	Poor mechanical strength; lot-to-lot variability; sterilization issues [6].
Synthetic Polymers	PLA, PGA, PCL, mPCL-TCP	Tunable mechanics & degradation; large-scale production [6].	Lacks biological cues; breakdown by-products may cause inflammation.
Decellularised ECM	Human, Bovine, or Porcine Dermis	Retains native 3D architecture and growth factors [8].	Limited availability; high risk of immunogenicity if not fully processed [8].

A major challenge in regenerative medicine is developing scaffolds that combine biological functionality with structural integrity [1] [2]. Natural biomaterials, which include collagen, elastin, fibrin, alginate, and chitosan, offer excellent biocompatibility and low immunogenicity, yet they frequently suffer from poor mechanical integrity, batch-to-batch variability, and challenging sterilization protocols. Conversely, highly porous synthetic polymer scaffolds can effectively replicate physiological niches, such as the bone marrow microenvironment, to promote stem cell survival and expansion.

While decellularised extracellular matrices (dECM) derived from human, bovine, or porcine dermis successfully replicate native 3D microenvironments at injury sites, their clinical utility is restricted by supply shortages and donor-related challenges. Consequently, there is an urgent need for synthetic alternatives that can be rapidly fabricated for emergency surgical applications [7] [8].

Three-dimensional (3D) bioprinting offers a solution by using computer-aided

design (CAD) to construct complex, patient-specific scaffolds [3]. This biomimetic approach, utilising hydrogel-cell mixtures, has rapidly progressed from basic tissue fabrication to complex, organ-level structures and *in vitro* disease models. Nevertheless, identifying affordable materials that can be processed into layered sheets or flexible filaments under atmospheric conditions remains a hurdle.

A 2026 systematic review and meta-analysis of natural versus synthetic biodegradable scaffolds in human soft-tissue reconstruction reported a pooled recurrence risk ratio of 0.30 (95% CI: 0.12 - 0.73) from two studies [9]. However, the underlying study-level data reported in that review were directionally inconsistent with the pooled estimate: Buell *et al.* reported a 5-year recurrence of 38.1% with porcine biologic mesh versus 12.9% with P4HB synthetic mesh [10], while Liu *et al.* reported an 18-month recurrence of 9.26% with biologic mesh versus 1.92% with synthetic polypropylene mesh [11]. Because of this internal inconsistency, the differing clinical indications and follow-up periods, and the broad heterogeneity of scaffold types, the RR 0.30 estimate should not be interpreted as evidence of a universally lower failure rate for natural matrices. Healing time was not significantly different in the meta-analysis [9]. Current research includes photopolymerizable, hydrogel-based systems such as gelatin methacryloyl (GelMA) [12].

This review evaluates current scaffold materials, fabrication techniques, scaffold architectures, and biomechanical considerations relevant to musculoskeletal tissue engineering, explicitly distinguishing acellular additive-manufactured scaffolds, scaffolds cellularised after printing, and cell-laden bioprinting. These workflows impose different constraints on cell viability, sterilization, processing conditions, and regulatory translation.

2.3. Manufacturing & Regulatory Framework

The introduction of 3D printing enables the fabrication of adaptable scaffolds regardless of complexity [7]. In 2026, the regulatory landscape has evolved to accommodate these personalised devices, as summarised in **Table 3**.

Table 3. Custom-made, patient-matched/adapted vs standard devices (UK/EU).

Feature	Custom-Made Device	Patient-Matched/Adapted/ Standard Device
Definition	Specifically made to a written prescription giving specific design characteristics, for the sole use by a particular patient, to meet individual conditions and needs [13] [14].	Not automatically a regulatory category. A mass-produced device that is adapted to a user's requirements is not considered custom-made under the EU MDR [13]; classification depends on the applicable regulatory framework.
Role of 3D Printing	May be used as the manufacturing method, but 3D printing itself does not make a device custom-made [13] [14].	May include patient-specific CAD or adaptation of an existing device; the manufacturing and intended-purpose pathway determine the applicable requirements.

Continued

EU Pathway	Custom-made procedure under MDR Article 52(8) and Annex XIII; class III custom-made implantable devices have additional conformity assessment requirements [13].	Apply the ordinary MDR classification/ conformity-assessment route when the device is not custom-made [13].
Great Britain Pathway	UK MDR 2002 custom-made requirements apply; no UKCA marking is affixed to custom-made devices, but manufacturers must meet the applicable requirements and registration obligations [14].	Apply the relevant UK MDR 2002 route according to the device classification and intended purpose [14].
Responsibility	The manufacturer is responsible for regulatory compliance and required documentation; the authorised prescriber specifies the particular design characteristics within the custom-made definition [13] [14].	The manufacturer remains responsible for the applicable regulatory pathway; clinical professionals retain their professional/clinical responsibilities [14].

Three-dimensional printing is a manufacturing technology rather than a regulatory classification. The regulatory pathway depends on the intended purpose, device characteristics, manufacturing process, and whether the product meets the applicable definition of a custom-made device. In Great Britain, custom-made devices are regulated under the Medical Devices Regulations 2002 (UK MDR 2002), as amended; in Northern Ireland, the EU Medical Devices Regulation (EU) 2017/745 applies to medical devices within its scope [13] [14].

Under Article 2(3) of Regulation (EU) 2017/745, a custom-made device is specifically made to a written prescription that gives specific design characteristics, is intended for the sole use of a particular patient, and meets that patient's individual needs. Mass-produced devices that are adapted to a professional user's or patient's requirements are excluded from the custom-made definition [13]. The EU MDR provides a specific custom-made procedure under Article 52(8) and Annex XIII; class III custom-made implantable devices are subject to additional conformity-assessment requirements [15]. Patient-matched or patient-specific devices should therefore not automatically be described as custom-made: the manufacturing and design pathway must be assessed against the regulatory definitions and applicable classification rules [13].

Manufacturers remain responsible for meeting the applicable regulatory requirements, including the relevant essential requirements, documentation, and registration obligations; custom-made devices do not bear a UKCA mark [14].

2.4. Methods of Fabrication

The orchestration of functional bone tissue regeneration relies heavily on the structural and mechanical fidelity of the underlying scaffold. Current paradigm shifts in tissue engineering have transitioned from conventional scaffolding to sophisti-

cated methodologies, primarily dominated by electrospinning, additive manufacturing, and advanced biomimetic techniques.

2.5. Additive Manufacturing and 3D Printing Modalities

Additive manufacturing (AM) offers unprecedented spatial control over scaffold geometry, allowing the translation of patient-specific anatomical data into physical constructs. Inkjet and binder jetting technologies extrapolate conventional two-dimensional translation into three-dimensional coordinate spaces, adding volumetric height to precisely engineered architectures. This clinical utility was demonstrated by Saijo *et al.*, who successfully fabricated custom-made maxillofacial bone constructs utilizing alpha-tricalcium phosphate (alpha-TCP) powder; the patient-specific implants achieved host integration while reducing intraoperative execution times [16].

Three distinct cellularisation workflows should be distinguished. First, acellular AM produces the scaffold without living cells, allowing fabrication and sterilisation steps to be optimised independently of cell viability. Second, post-print cellularisation introduces cells after fabrication and sterilisation, for example by seeding, hydrogel incorporation, or perfusion, but may be limited by cell penetration and distribution within the printed architecture. Third, cell-laden bioprinting incorporates viable cells into the bio-ink during printing; this can provide spatially controlled cellular placement but imposes additional constraints from shear stress, temperature, photochemistry, or crosslinking, and requires processing conditions compatible with cell survival. These approaches therefore have different requirements for cell viability, sterilisation, processing, storage, and regulatory translation.

Conversely, extrusion-based modalities and direct ink writing (DIW) utilize shear-thinning hydrogel bio-inks—such as alginate, chitosan, and polyethylene glycol (PEG)—to rapidly synthesize bio-ceramics. While DIW represents a highly cost-effective paradigm capable of accommodating both cellularized and acellular matrices, its widespread application is fundamentally constrained by its lower architectural resolution, which typically plateaus at approximately 100 μm [17].

Where high structural porosity and predictable pore morphology are required, fused deposition modelling (FDM) is frequently deployed. FDM melts and extrudes thermoplastic polymers and their corresponding composite matrices (e.g., PCL-TCP, PCL/polyglycolic acid (PGA)) in a layer-by-layer sequence. Although FDM is valued for its economic viability and simplicity, it remains restricted to thermally stable thermoplastics and necessitates temporary support structures. This requirement can introduce geometric inaccuracies, occasionally causing pore exclusion at the complex boundaries of irregular anatomical shapes [17].

For unparalleled structural detailing and mechanical optimisation, selective laser sintering (SLS) and stereolithography (SLA) represent high-fidelity alternatives:

SLS: Utilises a high-energy laser beam to locally fuse powdered ceramics, poly-

mers, and composites (including TCP, hydroxyapatite (HA), and PCL). This allows for the independent modulation of pore size and total porosity, yielding highly complex, thin-walled structures with superior mechanical strength. However, the localised thermal distortion and high processing temperatures warp natural polymers and denature bioactive factors, rendering the synchronous encapsulation of living cells or growth factors impossible during the printing cycle [17].

SLA avoids these thermal constraints by employing photopolymerisation. It delivers high-velocity fabrication of PCL and polyethylene furandicarboxylate (PEF) matrices with exceptional dimensional accuracy (5 - 300 μm) and a smooth surface finish [17]. This high-resolution fidelity makes SLA highly compatible with the uniform encapsulation of cells and bioactive agents. Consequently, it has become a cornerstone in maxillofacial implant manufacturing, generating complex 3D geometries directly derived from patient computed tomography (CT) scan files without the need for traditional moulding or secondary machining [18].

2.6. Micro- and Nanofibrous Scaffolding via Electrospinning

To closely replicate the native extracellular matrix (ECM)—specifically the intricate network of collagen fibers—electrospinning is widely utilised [19] [20]. This electrohydrodynamic technique applies a high-voltage electrostatic field to a polymeric fluid droplet, overcoming its surface tension to induce the formation of a Taylor cone, which elongates into continuous nano- to microfibrous architectures. Utilising polymer blends such as PLGA/PCL, PCL/PEG, and natural silk fibroin, electrospinning yields homogenous fibrous matrices characterised by an ultra-high surface-area-to-volume ratio and remarkable tensile strength [21].

The structural scalability and cost-efficiency of electrospinning are balanced by distinct challenges, including jet instability, processing complexities, and the potential cytotoxicity of residual organic solvents. Nevertheless, its regenerative potential remains profound. For instance, Santos *et al.* engineered electrospun PCL/Chitosan nanofibrous scaffolds functionalised with a bioactive, cell-derived extracellular matrix for osteogenesis. This biomimetic microenvironment significantly accelerated cell proliferation and upregulated osteogenic differentiation, characterised by elevated bone-specific marker gene expression, heightened alkaline phosphatase (ALP) activity, and robust calcium deposition leading to advanced matrix mineralization [22].

2.7. Alternative Scaffolding Strategies: Lyophilization, Leaching, and Biomimetic Systems

Beyond additive technologies, several alternative manufacturing strategies offer distinct structural advantages:

Freeze Drying (Lyophilisation): This process involves dissolving polymers (such as PTFE/PVA combined with graphene oxide nanoparticles), casting the solution into a mould, and subjecting it to controlled freezing and low-pressure sublimation. This yields highly porous structures (up to 90%) with enhanced interconnec-

tivity without requiring a solid porogen [3] [19]. While pore size can be modulated by altering the freeze rate, temperature gradients, and polymer concentration, the resulting pore distribution remains irregular. Furthermore, the reliance on organic solvents, protracted processing times, and high energy consumption limits its industrial efficiency [19].

Solvent-Casting and Particulate Leaching: This approach embeds water-soluble porogens (such as salt particles) within a biodegradable polymer solution. Following solvent evaporation via lyophilisation, the salt is leached out to generate a porous matrix [23]. This method offers straightforward control over total porosity and pore size—as demonstrated by Zimina *et al.*, who developed a PLA/HA composite scaffold with 79% porosity that effectively suppressed adverse tissue ingrowth, limited host inflammatory responses, and enhanced mesenchymal stromal cell (MSC) adhesion compared to pristine PLA [24]. However, particulate leaching inherently suffers from poor inner pore interconnectivity, unpredictable structural thickness, and the retention of toxic solvent residues [3].

Gas-Foaming: This technique circumvents harsh organic solvents by utilising highly pressurised gases to induce nucleation and pore formation within biopolymers like chitosan. It yields porosities up to 85% with pore diameters spanning 30 - 700 μm, though it offers limited mechanical strength and poor pore morphology control [25]. Because pristine chitosan exhibits rapid degradation rates and low osteoinductivity, it is typically combined with reinforcing secondary phases [25].

Bio-printing: Represents the frontier of automated tissue synthesis, combining living autologous or allogeneic cells directly with natural or synthetic hydrogel matrices to yield high cell viability and precise spatial positioning at a sustainable cost. This cell-laden approach should be distinguished from acellular printing followed by post-print cellularization, because the latter permits separate optimization of printing and sterilization before cells are introduced [17].

Regardless of the chosen fabrication pathway, the clinical efficacy of a scaffold is influenced by its structural topology and its interaction with the target tissue. Rather than a universal minimum or optimal pore diameter, pore size should be selected as a tissue-, material-, architecture-, and loading-dependent range, balancing cell migration, vascularization, nutrient transport, mechanical integrity, and degradation behaviour [17] [26].

Crucially, total porosity and pore interconnectivity should be considered together with pore geometry, scaffold orientation, and mechanical loading. An open, interconnected network can support cell migration and transport of nutrients and metabolic waste, but the appropriate architecture depends on the target tissue, material properties, and intended loading conditions [17] [26].

Fabrication may be followed by cellularisation, or cells may be incorporated during printing, depending on the selected workflow. Other 3D techniques include binder jetting, extrusion (FDM), inkjet, powder bed fusion (SLS), sheet lamination, and stereolithography.

2.8. Cellularisation and Scaffold Formats

Scaffold cellularisation can be considered alongside scaffold architecture. Acellular constructs may rely on host-cell recruitment, whereas post-print cellularisation or cell-laden bioprinting introduces defined cell populations. The choice affects sterility, cell viability, spatial distribution, processing conditions, and regulatory translation. Monophasic scaffolds provide a relatively uniform environment and can act as space-maintaining matrices for tissue formation, whereas multiphasic scaffolds contain spatially distinct compartments designed to reproduce different tissue interfaces or gradients. Multiphasic constructs may therefore offer greater biological specificity but introduce additional challenges in interfacial adhesion, manufacturing reproducibility, and mechanical continuity [3] [20] [27].

Monophasic and multiphasic formats can both be combined with biological additives or cellularisation strategies. In monophasic scaffolds, cells may be seeded directly or introduced within a hydrogel, while the scaffold provides space maintenance and structural support [20] [27]. Multiphasic scaffolds use distinct compartments with differing biomechanical properties, chemical composition, or architecture to address interfaces such as bone-ligament or osteochondral junctions [20] [27]. These constructs may recruit endogenous cells or carry pre-cultured cells, but their additional interfaces can create risks of delamination and altered load transfer. Accordingly, fabrication strategy, cellularisation method, and degradation behaviour should be considered together rather than as separate design decisions.

Modern biomaterial design focuses on creating innovative frameworks that actively interact with embedded stem cells to guide their specialization. Synthetic structures that closely mimic native bone architecture improve host integration and match the physical strength of the target tissue. To achieve successful structural and biological performance, especially in major bone injuries, the matrix must feature precise pore sizes, directional pathways, and interconnected channels [27] [28].

2.9. Degradation and Resorption

Degradation behaviour is material-specific and should be matched to the intended tissue-remodelling environment rather than treated as a universal property. Synthetic aliphatic polyesters such as PLA, PGA, and PLGA commonly undergo hydrolytic ester-bond cleavage, whereas many natural polymers, including collagen and other protein- or polysaccharide-based matrices, are susceptible to enzyme-mediated degradation. Actual degradation kinetics also depend on molecular weight, crystallinity, crosslinking, composition, porosity, surface area, local enzymes and fluid environment, sterilisation, and mechanical loading [5].

2.10. Hybrid Scaffolds

Composite or hybrid matrices merge distinct classes of materials to reconstruct

highly intricate tissues, a strategy that effectively overcomes the inherent structural or biological limitations of using any single material alone. For instance, Damaraju *et al.* engineered resilient, three-dimensional fibrous frameworks that closely replicate the structural topology of the native extracellular matrix [29]. This specialized environment successfully guides the multi-lineage differentiation of mesenchymal stem cells (MSCs) and accelerates functional tissue synthesis, making it highly applicable for both articular cartilage restoration and bone repair.

In a parallel approach, Zeng *et al.* modified the surface of mesoporous bioactive glass frameworks with functionalised amino groups. This surface chemistry optimisation significantly enhanced the therapeutic efficacy of hosted MSCs, macrophages, and bone marrow elements, concurrently suppressing localised inflammatory pathways while accelerating osteogenesis [30].

3. Discussion

The creation of a clinically viable framework relies on attracting the necessary cellular populations to a matrix capable of guiding their assembly into structured, functional tissue. Adequate vascular network development within the matrix is essential, as it delivers vital oxygen and nutrients to the embedded cells while effectively removing metabolic waste products. Although matrices engineered with a high surface area and open porosity encourage initial cellular attachment, excessively small pore dimensions restrict cellular migration through the construct [1] [27].

Surgeons increasingly leverage computer-aided design and computer-aided manufacturing (CAD/CAM) protocols to plan interventions and address complex structural defects [7] [21] [28] [31]. Additive manufacturing technologies allow for the production of patient-tailored implants, leading to higher surgical accuracy and better functional recovery. By combining high-resolution medical imaging with three-dimensional bioprinting, engineers can fabricate customised scaffolds. In these workflows, the external geometry, internal pore networks, and overall mechanical performance of the matrix are derived directly from patient-specific data [14].

This engineering pathway begins with diagnostic data collection using magnetic resonance imaging (MRI) and computerised tomography (CT), followed by digital image segmentation, three-dimensional reconstruction, and 3D CAD modelling. This process allows the macro-, micro-, and nano-scale architecture of the implant to be adjusted during fabrication prior to surgical delivery. For instance, creating microporous systems allows the scaffold to double as a localised drug delivery vehicle, while the macroscopic mechanical profile must be tuned to match the host tissue. Such refinements in matrix architecture have successfully enhanced cellular communication and activation, and mastering these pathways remains a key focus for avoiding adverse host tissue reactions [28].

Engineered constructs frequently serve as dual-purpose matrices for cellular and

pharmaceutical delivery. Incorporating bioactive materials—such as multipotent mesenchymal cells, signalling proteins, targeted peptides, or active small molecules—can substantially improve host-implant integration. Strategically co-delivering multiple distinct therapeutics and bioactive compounds can mitigate systemic toxicity and decrease drug dissociation rates. Furthermore, surface modifications can alter the elution profiles of the framework to achieve rapid, sustained, or sequential release. This capability is highly valuable when managing localised infection and inflammation through the targeted delivery of antimicrobial and anti-inflammatory drugs [32].

Synthesised alloplastic materials offer distinct advantages over autologous or allogeneic bone harvesting, which is constrained by limited donor supply, potential immunological rejection, donor site infection, and long-term structural failure. Frequently utilised alloplastic alternatives include hydroxyapatite (HA), biphasic calcium sulphate (BCS), β-tricalcium phosphate (β-TCP), and biphasic calcium phosphate (BCP). Among these, hydroxyapatite (HA) is heavily utilised due to its excellent bioactivity, biocompatibility, lack of systemic toxicity, and osteoconductive properties [33]. However, its clinical application is limited by its inherent brittleness, which prevents it from bearing substantial compressive physiological loads [2].

Despite these benefits, current 3D printing workflows are constrained by elevated financial costs and an extended manufacturing timeline, which typically requires four to six weeks from initial design to final implantation. Because each clinical presentation features distinct anatomical challenges, surgical teams must dedicate substantial preoperative time to reviewing, testing, and preparing the specialized hardware and instruments to anticipate and avoid complications during surgery.

4. Conclusion

Scaffold-based tissue engineering offers a promising solution for reconstructing complex tissue defects where conventional grafting is limited by donor site morbidity, tissue availability, or anatomical complexity. Advances in biomaterials, additive manufacturing, and bioprinting have enabled the development of patient-specific scaffolds with architecture, porosity, and mechanical properties that more closely mimic native tissue. Successful clinical translation depends on balancing biocompatibility, structural integrity, vascularisation, degradation kinetics, and regulatory considerations within a practical manufacturing timeframe. Understanding the strengths and limitations of current scaffold materials and fabrication techniques is essential for both engineers and clinicians. Continued interdisciplinary collaboration is essential for developing clinically viable scaffold systems that improve regenerative outcomes. Clinical translation also requires explicit consideration of whether a construct is acellular, cellularised after manufacture, or cell-laden during printing, because these workflows differ in cell viability, sterilisation, and manufacturing constraints. Regulatory status should be determined from the

intended purpose, device characteristics, and applicable jurisdiction rather than from the use of 3D printing alone.

Declaration of Generative AI and AI-Assisted Technologies in Manuscript Preparation

During manuscript preparation, the authors used Claude (Anthropics) solely for limited language editing of selected sentences to improve clarity. No AI tool was used to generate research content, analyze data, interpret results, or prepare references; the ideas, argument, and intellectual contribution of the paper are entirely original. All AI-assisted suggestions were reviewed, revised where necessary, and approved by the authors, who take full responsibility for the final manuscript.

Author Contributions

IL: Data collection, writing—original draft preparation, review, and editing.

AME: Review and editing.

AV: Study concept and design, review and editing.

AA: Review and editing.

RF: Data curation, review, and editing.

GA: Review and editing.

AG: Review and editing.

NA: Study concept and design, data collection, writing—original draft preparation, review and editing.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix. Search Strategy

Line		Results Returned
1	Scaffolds, Biological, Implants, Bioengineering/	3124
2	(cartilage adj3 (or cartilaginous)).ti,ab.	2972
3	1 or 2	2367
4	exp "Wounds and Injuries"/	1,009,950
5	(trauma or wound or injur*).ti,ab.	1,432,067
6	4 or 5	1,984,491
7	3 and 6	897
8	exp Clinical Decision-Making/	15,647
9	(decision making or decision-making) adj3 (surgical or clinical or medical).ti,ab.	37,554
10	(judgement* or reasoning or importance or relevance or significance) adj3 (surgical or clinical or medical).ti,ab.	226,130
11	exp treatment outcome/	1,246,656
12	(outcome or improv or result or effect or impact*).ti,ab.	17,762,777
13	8 or 9 or 10 or 11 or 12	18,067,279
14	7 and 13	247
15	Limit 14 to English language	247